A RETROSPECTIVE STUDY TO EVALUATE LOW MOLECULAR WEIGHT HEPARIN (LMWH) USAGE AND IDENTIFY RISK FACTORS FOR MAJOR BLEEDING

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ABSTRACT

Evidence from the Western countries suggest that inappropriate dosing of enoxaparin for the treatment of acute coronary syndrome is prevalent and such dosing is associated with adverse outcomes, especially bleeding. However, such data from Asian countries are still lacking. A retrospective cohort study was conducted among all cases of acute coronary syndrome who were admitted to the Ramathibodi Hospital during 2006 – 2009. From a total of 359 patients included in the data analysis, 56.6%, 25.6% and 17.8% of cases were non-ST-elevation myocardial infarction, ST-elevation myocardial infarction and unstable angina, respectively. Based on renal function and body weight, only 42.1% received the recommended dose of enoxaparin. There were 15.6% and 42.3% of cases who received excess dose and lower-than-recommended dose. In the excess dose group, 57.1% had severe renal impairment but still received an unadjusted dose of enoxaparin. Additionally, patients receiving the excess dose tended to be female, were significantly older and had lower body weight. Overall, enoxaparin-associated bleeding was found in 38.7% of cases. Based on GUSTO bleeding criteria, there were 30.9%, 6.6% and 1.2% of mild, moderate, and severe bleeding. Based on TIMI bleeding criteria, there were 34.7%, 3.5% and 1.2% cases of minimal, minor and major bleeding. Based on TACSR bleeding criteria, major bleeding was 8.1%. Compared to patients receiving the recommended dose, excess dose was significantly and independently associated with an increased risk of GUSTO and TIMI overall bleeding (OR, 2.18; 95%CI, 1.18-4.00 and OR, 2.08; 95%CI, 1.13-3.84, respectively). Bleeding was also significantly associated with a stepwise increase in in-hospital mortality as GUSTO and TIMI severity increased. In addition, the length of stay in patients who experienced bleeding was significantly higher compared to patients who did not experience bleeding. For lower-than-recommended dose, the effects were unclear and need further investigation. These results support the assertion that careful attention to the administered dose and development of appropriate corrective actions to promote safe use of enoxaparin is imperative.

KEY WORDS: ENOXAPARIN / LOW MOLECULAR WEIGHT HEPARIN / CUTE CORONARY SYNDROME / BLEEDING

168 pages

การศึกษาแบบย้อนหลังเพื่อประเมินการใช้ยา LOW MOLECULAR WEIGHT HEPARIN (LMWH) และค้นหาปัจจัยเสี่ยงต่อการเกิดอาการเลือดออกชนิดรุนแรง

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บทคัดย่อ

หลักฐานจากประเทศตะวันตกแสดงให้เห็นว่าขนาดยา enoxaparin ที่ไม่เหมาะสมเป็นสิ่งที่พบได้บ่อยและก่อให้เกิดผลเสียโดยตรงต่อผู้ป่วยโรคหลอดเลือดโคโรนารีชนิดเฉียบพลัน โดยเฉพาะเป็นสาเหตุให้เกิดเลือดออก อย่างไรก็ดียังขาดข้อมูลดังกล่าวในคนเอเชีย การศึกษาแบบย้อนหลังนี้จึงมีวัตถุประสงค์เพื่อประเมินการใช้ยา enoxaparin และค้นหาปัจจัยเสี่ยงของการเกิดเลือดออกในผู้ป่วยโรคหลอดเลือดโคโรนารีชนิดเฉียบพลันของโรงพยาบาลรามาธิบดี เก็บข้อมูลผู้ป่วยที่เข้ารับการรักษาตั้งแต่ปี 2549-2551 จำนวน 359 คน จำแนกเป็น ST-elevation myocardial infarction 25.6%, non-ST-elevation myocardial infarction 56.6% และ unstable angina 17.8% ประเมินขนาดยาตามน้ำหนักและการทำงานของไตพบเพียง 42.1% ที่ได้รับขนาดยาเหมาะสม พบขนาดยาสูงเกิน 15.6% และต่ำกว่าคำแนะนำ 42.3% พิจารณากลุ่มขนาดยาสูงเกินพบถึง 57.1% ที่ไม่ได้ปรับขนาดยาตามการทำงานของไตที่บกพร่องรุนแรง นอกจากนี้ยังมีสัดส่วนของเพศหญิงมากกว่า อายุเฉลี่ยมากกว่า และน้ำหนักน้อยกว่า เมื่อเทียบกับกลุ่มที่ขนาดยาเหมาะสม พบเลือดออกที่เกี่ยวเนื่องกับยา enoxaparin 38.7% ความรุนแรง GUSTO ระดับ mild, moderate และ severe พบ 30.9%, 6.6% และ 1.2% ตามลำดับ เกณฑ์ TIMI เป็น minimal, minor และ major พบ 34.7%, 3.5% และ 1.2% ตามลำดับและ TACSR major พบ 8.1% ขนาดยาสูงเกินเสี่ยงต่อเลือดออกโดยรวมเมื่อเทียบกับขนาดยาเหมาะสม อย่างมีนัยสำคัญเมื่อวิเคราะห์หลายตัวแปร (GUSTO: OR, 2.18; 95%CI, 1.18-4.00, TIMI: OR, 2.08; 95%CI, 1.13-3.84) ความเสี่ยงของการเสียชีวิตสัมพันธ์กับความรุนแรงของอาการเลือดออกและระยะเวลานอนโรงพยาบาลสูงกว่า อย่างมีนัยสำคัญเมื่อเทียบกับผู้ที่ไม่มีเลือดออก การศึกษานี้สนับสนุนว่าการเพิ่มความระมัดระวังในการใช้ enoxaparin และพัฒนามาตรการจัดการความเสี่ยงอย่างเป็นระบบเพื่อเพิ่มความปลอดภัยให้กับผู้ป่วยเป็นสิ่งที่ควรสนับสนุนให้มีการดำเนินการอย่างเป็นรูปธรรม

168 หน้า

CONTENTS

CONTENTS(cont.)

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABW	Actual body weight
ACS	Acute coronary syndrome
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAG	Coronary angiography
CHF	Congestive heart failure
CI	Confidence interval
Cr	Creatinine
CrCl	Creatinine clearance
CRUSADE	Can rapid risk stratificationof unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines
C-G	Cockcroft-Gault
DBIL	Direct billirubin
DM	Diabetes mellitus
GFR	Glomerular filtration rate
GIB	Gastrointestinal bleeding
GPI	Glycoprotein IIb/IIIa inhibitor
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
Hb	Hemoglobin
Hct	Hematocrit
HT	Hypertension
H2RA	Histamine-2 receptor antagonist
IBW	Ideal body weight
ICD-10	International statistical classification of diseases and related health problems 10th revision
ICH	Intracranial hemorrhage

LIST OF ABBREVIATIONS (cont.)

INR	International normalized ratio
ISMP	Institute for Safe Medication Practices
IV	Intravenous
LAD	Left anterior descending
LCx	Left cir-cumflex
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
mg	milligram
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
PPI	Proton pump inhibitor
PT	Prothrombin time
PTCA	Percutaneous transluminal coronary angioplasty
RBC	ed blood cell
RCA	Right coronary artery
PR	ulse rate
RR	Relative risk
SC	Subcutaneous
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
TACSR	Thai acute coronary syndrome registry
TBH	Thai Bath
TBIL	Total billirubin
TBW	Total body weight
TIMI	Thrombolysis in Myocardial Infarction
UFH	Unfractionated heparin

LIST OF ABBREVIATIONS (cont.)

UA	Unstable angina
vs	versus
VT	Ventricular tachycardia

CHAPTER I
INTRODUCTION

Low molecular weight heparins (LMWHs) are parenteral anticoagulants derived from unfractionated heparin (UFH) through chemical or enzymatic depolymerization. The LMWHs share a similar mechanism of anticoagulant activity with UFH. However, structural changes of LMWHs to yield products with a smaller chain length has led to agents with less activity against thrombin and enhanced activity against factor Xa. LMWHs have several advantages over UFH. Compared to UFH, LMWHs have been shown to have less proteins and cells binding, higher bioavailability, and more predictable anticoagulant response, thereby making laboratory monitoring unnecessary. LMWHs also have a longer half-life than does UFH, which allows them to be administered conveniently as once or twice daily regimen (1). The expanding use of LMWH was stimulated by their superior pharmacokinetic and pharmacodynamic properties. These advantages have revolutionized management of acute venous thromboembolism by allowing most patients to be treated out of hospital. LMWHs have also greatly simplified in-hospital management of selected patients with venous thromboembolism. LMWH, especially enoxaparin, has been shown to be effective in reducing death or myocardial infarction in patients with acute coronary syndrome (ACS) (2-4). The use of enoxaparin has been supported as class I recommendation for the management of unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) (5) and class IIa recommendation for ST-segment elevation myocardial infarction (STEMI) (6), by the American College of Cardiology/American Heart Association.

Despite this proven efficacy, bleeding complications are still of particular concern. Bleeding, the most common complications of LMWH, can be classified as major, minor, and minimal events. Major bleeding is clinically more important because it often leads to increased morbidity and mortality. The most widely accepted

bleeding classifications are TIMI (Thrombolysis in Myocardial Infarction) and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries).

TIMI bleeding criteria can be classified as major, minor, and minimal events. TIMI major bleeding is defined as intracranial hemorrhage (ICH) or a 5 g/dL decrease in the hemoglobin concentration or 15% absolute decrease in the hematocrit. The definition of TIMI minor bleeding is dependent upon whether the site of bleeding is located or not. If a bleeding site is found, TIMI minor bleeding is defined as a hemoglobin decrease of >3 g/dl or a hematocrit decrease of >10%. If a bleeding site is not found, it is defined as a hemoglobin decrease of >4 g/dl or hematocrit decrease of >12%. Finally, TIMI minimal bleeding is defined as any clinically overt sign of hemorrhage that is associated with a hemoglobin decrease of <3 g/dl or a hematocrit decrease of <9% (7). GUSTO bleeding criteria can be classified as severe, moderate, and mild events. GUSTO severe is defined as intracranial hemorrhage or bleeding with hemodynamic compromise requiring intervention. Moderate bleeding is defined as bleeding requiring blood transfusion not associated with hemodynamic compromise. Lastly, GUSTO mild is defined as bleeding that does not meet criteria for either severe or moderate (8).

The data above suggest that there are some differences between two classifications. First, TIMI is a laboratory-based scale whereas GUSTO is a clinically based scale. In term of morbidity and mortality, bleeding assesses with clinical criteria is more important than assessed with laboratory criteria. Second, the TIMI is more precise and specific while the GUSTO tends to be more subjective. Lastly, TIMI could be limited if hemoglobin or hematocrit values are not obtained (9-11). However, each bleeding classification identified some bleeding events that were missed by the other. As the result, most ACS trials have used a combination of TIMI and GUSTO classifications. On Thai ACS registry, a multi-center prospective project of nationwide registration in Thailand, major bleeding definition is a combination between clinically based and laboratory-based criteria. These criteria 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 hematocrit of greater than 15% (13).

The incidence of major bleeding in patients with ACS have ranged from approximately 1% to 6.5%, depending on the definition of major bleeding, the time of the observation, and the use of concomitant therapies (12). Data from the Global Registry of Acute Coronary Events (GRACE), a multinational, prospective, observational study that collecting data on 'real-life' patient management and outcomes across the full spectrum of ACS, reported that 3.9% ACS patients developed major bleeding. Among 24,045 patients, rates of major bleeding were more frequent in patients with STEMI or NSTEMI than in patients with UA (4.8%, 4.7%, 2.3% in patients with STEMI, NSTEMI, and UA, respectively) (12). In Thailand, the Thai ACS registry which is a national multicenter prospective study in 5,060 patients reported that 6.5% ACS patients developed major bleeding which is higher than the GRACE study. The development of major bleeding was more frequent in patients with STEMI or NSTEMI than in patients with UA (9.5%, 6.6%, and 2.1% in patients with STEMI, NSTEMI, and UA, respectively) (13).

One of the strongest risk factors of bleeding in ACS patients who received enoxaparin therapy is renal impairment (14). This may due to the fact that enoxaparin is primarily cleared by renal excretion. Pharmacokinetics studies of enoxaparin clearly indicated an accumulation of enoxaparin among patients with renal insufficiency. Becker et al (15) conducted a pharmacokinetic study of 445 patients receiving therapeutic dose of enoxaparin for ACS indications. The investigators found that patients with marked renal impairment had higher trough and peak antifactor Xa activity compared with patients with normal renal function. Chow et al (16) performed a multiple-dose pharmacokinetic study of enoxaparin in 18 patients with varying degrees of renal function. A clear linear correlation was established between creatinine clearance (CrCl) and antifactor Xa concentrations ($p<0.0005$).

Data from large randomized controlled trials of enoxaparin in ACS patients indicated that renal insufficiency is an important risk factor for bleeding. Fox et al (17) conducted an analysis to evaluate the effect of decline in renal function on risk of bleeding using data from a randomized, double-blind study in 20,479 patients with STEMI undergoing fibrinolysis. In this study, it was found that rates of major bleeding with enoxaparin progressively increase as renal function declined (1.2%, 2.3%, 3.5% and 5.7% in patients with CrCl>90 mL/min, 60-90 mL/min, 30-60

mL/min, and <30 mL/min, respectively). Spinler et al (18) conducted a post-hoc analysis of two randomized, controlled trials in patients with NSTEMI. Among 6,969 patients, the investigators found that patients with CrCl<30 mL/min were at increased risk for major bleeding compared to those with CrCl>30 mL/min (RR 6.1; 95% CI, 2.47-14.88).

In order to minimize bleeding risk in patients with renal insufficiency, reduced dose of enoxaparin (1 mg/kg once daily) has been proposed and evaluated in several studies. Lachish et al (19) conducted a study testing efficacy and safety of reduced dose of enoxaparin in patients with chronic kidney disease stage 4-5. Results showed that such dosing regimen was safe and antifactor Xa levels did not exceed recommended therapeutic concentrations. Lim et al (20) conducted a meta-analysis of 18 clinical studies involving 4,971 patients to evaluate the risk of bleeding in patients with severe renal insufficiency. While a significantly increased risk of bleeding was found among patients receiving full dose of enoxaparin (OR, 3.88; 95%CI, 1.78-8.45), no increased risk was observed when a reduced dose of enoxaparin was used (OR, 0.58; 95%CI, 0.09-3.78; p=0.23). Consequently, American College of Chest Physicians and College of American Pathologists and the United States Food and Drug Administration has issued a recommendation for enoxaparin dose reduction in patients with severe renal impairment (CrCl<30 mL/min). The dose suggested is 1 mg/kg once daily (1).

Risk of bleeding may be related to renal dysfunction, but also to excess dosing of enoxaparin therapy. LaPointe et al (21) conducted an observational cohort study to determine enoxaparin dose in accordance with the current recommendations in a large, contemporary, community-based NSTEMI population. The investigators also aimed to assess risks of in-hospital major bleeding and death associated with enoxaparin dose. Among 10,687 patients, 2002 patients (18.7%) received an excess dose, 3116 (29.2%) received a lower than-recommended dose, and 5569 (52.1%) received the recommended dose. The proportion of patients with major bleeding was significantly higher in patients who received an excess enoxaparin dose than in those who received the recommended dose (14.2% vs 7.3%; p<0.001). Excess dose compared with recommended dose was independently and significantly associated with an increased risk of major bleeding after adjustment for baseline patient

characteristics, medications, and procedures (OR, 1.47; 95% CI, 1.21-1.80). In addition to renal function and excess dosing, other risk factors including advanced age, stacking of anticoagulant, duration of enoxaparin therapy, the uses of thrombolytic agents or glycoprotein IIb/IIIa receptor blockers, and invasive procedures may also contribute to increased risk of bleeding (14).

Enoxaparin-associated major bleeding may lead to increases in patient suffering, cost of care, hospital stay and mortality. Hence, the Institute for Safe Medication Practices (ISMP) has classified LMWH, including enoxaparin, as high-alert medications which have a heightened risk of causing significant patient harm and should be administered with great care and vigilance (22). Therefore, systematic approach to ensure the patients safety and the quality of care should be implemented in any health care organizations to prevent unwanted and harmful side effects.

Several preventive interventions may minimize the risk of enoxaparin-associated major bleeding and possibly reduce morbidity and mortality. Buckmaster et al (23) conducted a controlled trial in 439 patients with ACS. This study used a retrospective, before-and-after design with concurrent controls, undertaken in two community hospitals. Interventions were active implementation of a user modified clinical pathway coupled with an iterative education program to medical staff versus passive distribution of a similar pathway without user modification or targeted education. Results showed that an implementation of acute chest pain pathway combined with continuous education targeting both junior and senior medical staffs reduced inappropriate use of enoxaparin. A significantly higher proportion of intervention patients at the intervention hospital received appropriate use of enoxaparin therapy overall than historical controls (94% vs. 54%, $P<0.01$) or concurrent controls (94% vs. 68%, $P<0.01$).

Schumock et al (24) conducted a retrospective analysis to assess whether guidelines improve the appropriateness of prescribing, clinical outcomes, and costs associated with the use of LMWHs in community hospitals in the US. The investigators found that an implementation of guidelines resulted in a significant increase in the proportion of anticoagulants that were prescribed appropriately (59.8% vs. 86.9%; $p< 0.01$). There was suggestive evidence, although not statistically significant, that the guidelines resulted in fewer anticoagulant-associated adverse

events (total bleeding RR 0.71) and lower costs (savings of $56.15 per patient per day). Bond et al (25) explored the associations between pharmacist-provided anticoagulation management in hospitalized patients and several major heath care outcomes. The data were retrieved for 717,396 patients treated in 955 US hospitals using National Clinical Pharmacy Services database and Medicare database. In hospitals without pharmacist-provided heparin management, death rates were 11.41% higher, length of stay was 10.05% higher, medicare charges were 6.60% higher, bleeding complications were 3.1% higher and the transfusion rate for bleeding complications was 5.47% higher than in hospitals with pharmacist-provided heparin management. This study clearly indicated the benefits of pharmacist involvement in the management of patients receiving anticoagulants in terms of therapeutic control of anticoagulation, costs, and reduced bleeding complications.

As a result, evidence from the Western countries have shown that almost half the patients treated with enoxaparin did not receive a recommended dose and had worse outcomes, especially those receiving an excess dose. Improved adherence to the recommended dose could substantially improve the safety profile of enoxaparin. However, data on the extent to which enoxaparin was dosed in accordance with the current recommendations in Thailand is currently lacking. Limited data suggested that advanced age may be the risk factor of enoxaparin-associated bleeding. A retrospective cohort study (26) in 50 UA/NSTEMI patients admitted to the Somdejphraphuttalertla hospital and used enoxaparin for treatment were investigated by Pongsawat K. The investigator found that rates of bleeding with enoxaparin are progressively increased with advanced age (81.25% and 64.7% in patients with age$\geq$60 years and age<60 years, respectively). Nevertheless, an analysis did not include patients with severe renal insufficiency which are at high risk for bleeding. In addition, small sample size and no standard bleeding definition are the major limitations of the study.

In conclusion, the purpose of this study is to describe the usage pattern of enoxaparin in hospitalized acute coronary syndrome patients at Ramathibodi Hospital, to determine the incidence of enoxaparin-associated bleeding using internationally standardized criteria, and identify risk factors for enoxaparin-associated bleeding. Information gained from this study may provide important insight which can be used

to perform systematic root cause analysis of enoxaparin-associated major bleeding events and help facilitate the development of appropriate corrective actions to promote safe use of enoxaparin.

CHAPTER II
OBJECTIVES

1 To describe the usage pattern of enoxaparin in patients with acute coronary syndrome

2 To determine the incidence of enoxaparin-associated bleeding using internationally standardized criteria

3 To identify risk factors for enoxaparin-associated bleeding in patients with acute coronary syndrome

CHAPTER III
MATERIALS AND METHODS

Materials

1. Case record form (Appendix A)
2. Patient's medical record

Methods

1. Definitions of terms

The terms used throughout the study were defined as follows:

1.1 Body weight

Body weight was defined as current actual weight that was documented in the medical record on the day of admission. If weight on the day of admission was not found, weight which closest to the day of admission within 1 year was used substitute.

1.2 Height

Height was defined as height that was documented in the medical record.

1.3 Body mass index

Body mass index (BMI) is calculated by dividing the patient's body weight in kilograms by the square of height in meters.

1.4 Creatinine

Creatinine was defined as current creatinine that was investigated in the day of admission or not more than 12 hours after initiation of enoxaparin therapy.

1.5 Creatinine clearance

Creatinine clearance is a method that estimates the glomerular filtration rate (GFR) of the kidney, which is the volume of filtrate made by the kidney per minute. Cockcroft-Gault (C-G) (27) and Modification of Diet in Renal Disease

equations (MDRD) (28) are two widely available formulas in clinical practice. Neither formula was developed or validated in patients with cardiac disease. However, they differ in variables and coefficients. C-G calculates creatinine clearance as

$$CrCl = \frac{[140 - \text{age (year)} \times \text{IBW (kilogram)}]}{72 \times \text{Scr (mg/dl)}}$$

In female, multiply with 0.85

Where, CrCl = creatinine clearance

IBW = ideal body weight

Scr = serum creatinine

IBW (male) = 50 kilogram + 2.3 x (height in inch - 60)

IBW (female) = 45.5 kilogram + 2.3 x (height in inch - 60)

ABW = IBW + 0.4 (TBW - IBW)

Where, ABW = adjusted body weight, TBW = total body weight

If patient's actual body weight was less than the ideal body weight, the actual body weight was used. In each patient who has the body weight more than 20% above their ideal body weight (IBW), the adjusted body weight (ABW) was used in place of IBW. In elderly patients (Age more than or equal to 65 years) who have the creatinine less than 1 mg/dl, creatinine of 1 mg/dl was used. As the results, C-G formula should be used height value to calculate ideal body weight.

The MDRD formula estimates GFR as (ml/min/1.73 m^2 of body surface area) = 186 x (serum creatinine in mg/dl)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female gender).

The MDRD equation is recommended by the National Kidney Foundation as more accurate for estimating GFR (29-30). The C-G formula is recommended by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the Food and Drug Administration and is easier to calculate at the bedside (5,31). In ACS patients, Melloni et al (32) conducted an analytical study in NSTEMI patients to compare C-G and MDRD formula for estimating GFR and determined in-hospital outcomes and the association between antithrombotic dose adjustment and bleeding by each formula. Among 2,778 patients treated with enoxaparin, excess dose based on C-G occurred in 18.4% (n = 511), and excess dose by MDRD occurred in 12.6% (n = 351). The adjusted ORs of in-hospital major

bleeding for enoxaparin excess based on C-G and MDRD were 1.54 (95% CI 1.04 to 2.28) and 1.50 (95% CI 1.06 to 2.14), respectively. These results suggested that C-G formula may slightly be a better method to estimate GFR in ACS patients, despite the fact that the two formulas are highly correlated ($r = 0.89$; $p < 0.0001$). Based on the above information, creatinine clearance will be estimated using C-G formula in this study. If height value was less than 60 inch or height was not found in medical record, the MDRD formula was used.

1.6 Bleeding complications

Bleeding severity was defined according to three classifications.

1.6.1 Thai Acute Coronary Syndrome Registry major bleeding classification (TACSR) (13)

TACSR major bleeding is defined as 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 hematocrit of greater than 15%.

1.6.2 The Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) classification (8)

GUSTO bleeding can be classified into three categories: severe, moderate, and mild.

Severe bleeding is defined as intracerebral or if bleeding that resulted in substantial hemodynamic compromise requiring treatment.

Moderate bleeding is defined as bleeding requiring blood transfusion not associated with hemodynamic.

Mild bleeding is defined as bleeding that does not meet criteria for either severe or moderate.

1.6.3 The Thrombolysis In Myocardial Infarction (TIMI) classification (7)

TIMI bleeding can be classified into three categories: major, minor, and minimal.

Major bleeding is defined as a reduction of hemoglobin of 5 g/dl or more (or >15% in hematocrit) or intracranial bleeding.

Minor bleeding is dependent upon whether the site of bleeding is located or not. If a bleeding site is found, TIMI minor bleeding is defined as a hemoglobin decrease of >3 g/dl or a hematocrit decrease of >10%. If a bleeding site is not found, it is defined as a hemoglobin decrease of >4 g/dl or hematocrit decrease of >12%.

Minimal bleeding is defined as any clinically overt sing of hemorrhage associated with a < 3 g/dl decrease in the haemoglobin concentration or < 9% decrease in haematocrit.

1.7 Enoxaparin-associated bleeding

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

1.8 Recommended dose

On the basis of product labeling, the recommended enoxaparin dose is 1 mg/kg every 12 hours for patients with a CrCl of 30 mL/min or greater and 1 mg/kg every 24 hours for patients with a CrCl less than 30 mL/min. Therefore, the recommended daily dose of enoxaparin is 2 mg/kg for patients with a CrCl of 30 mL/min or greater and 1 mg/kg for patients with a CrCl less than 30 mL/min. The patient's recorded body weight was used for this calculation. CrCl was estimated using the C-G or MDRD formulas.

Recommended dose of enoxaparin was defined as an initial prescribing daily dose that did not vary from the recommended dose by more than 10 mg/day (21). These definitions were established to allow for a small variation for rounding in the recommended dose.

1.9 Out of the recommended dose

Out of the recommended dose was defined as prescribing daily doses that vary from the recommended dose by more than 10 mg/day. Within out of the recommended dose group, there were two subgroups as follows.

1.9.1 Excess dose

Excess dose was defined as an initial prescribing daily dose that was more than 10 mg above the recommended dose. This definition has been validated to accurately predict risk of bleeding in a large registry of patients with ACS (21).

1.9.2 Lower-than recommended dose

Lower-than recommended dose was defined as a prescribing daily dose that was more than 10 mg less than the recommended dose (21).

1.10 Proportion of patients receiving recommended dose

Percentage of recommended dose was calculated by the number of patients who received recommended dose divided by the number of total patients multiplied by 100.

1.11 Proportion of patients receiving excess dose

Percentage of excess dose was calculated by the number of patients who received excess dose divided by the number of total patients multiplied by 100.

1.12 Proportion of patients receiving lower-than recommended dose

Percentage of low dose was calculated by the number of patients who received lower dose divided by the number of total patients multiplied by 100.

1.13 Proportion of paients having TACSR major bleeding

Percentage of TACSR major bleeding was calculated by the number of patients who had TACSR major bleeding divided by the number of total patients multiplied by 100.

1.14 Proportion of patients having GUSTO severe bleeding

Percentage of GUSTO severe bleeding was calculated by the number of patients who had GUSTO severe bleeding divided by the number of total patients multiplied by 100.

1.15 Proportion of patients having GUSTO moderate bleeding

Percentage of GUSTO moderate bleeding was calculated by the number of patients who had moderate bleeding divided by the number of total patients multiplied by 100.

1.16 Proportion of patients having GUSTO mild bleeding

Percentage of GUSTO mild bleeding was calculated by the number of patients who had mild bleeding divided by the number of total patients multiplied by 100.

1.17 Proportion of patients having TIMI major bleeding

Percentage of TIMI major bleeding was calculated by the number of patients who had TIMI major bleeding divided by the number of total patients multiplied by 100.

1.18 Proportion of patients having TIMI minor bleeding

Percentage of TIMI minor bleeding was calculated by the number of patients who had TIMI minor bleeding divided by the number of total patients multiplied by 100.

1.19 Proportion of patients having TIMI minimal bleeding

Percentage of TIMI minimal bleeding was calculated by the number of patients who had TIMI minimal bleeding divided by the number of total patients multiplied by 100.

1.20 Length of stay

Length of stay (LOS) was calculated by subtracting day of admission from day of discharge. However, patients entering and leaving a hospital on the same day have a length of stay of one. Patients who died in the hospital were excluded from this calculation.

1.21 Cost of care

Cost of care was directly taken from the hospital charges database. The cost represented total cost of care during the corresponding admission period.

2. Study design

This study is designed as a retrospective cohort study.

3. Ethical approval

This study protocol was approved by the Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital on March, 2009.

4. Study population

The aim of this study is to describe the usage pattern of enoxaparin in real-world clinical practice. All patients who were hospitalized over the time period were enrolled in an analysis. Thus, the sample size was not calculated.

4.1 Inclusion criteria

Patients with $\geq$ 18 years of age, who were hospitalized at the Ramathibodi Hospital with the diagnosis of acute coronary syndrome and had ever received one or more doses of enoxaparin.

4.2 Exclusion criteria

Patients were excluded according to the following criteria:

4.2.1 Patients with platelet count $\leq$ 50,000 cells/mL

4.2.2 Pregnancy

4.2.3 Patients with Burn

4.2.4 Patients with hemophilia A or B, von Willebrand' s disease, hereditary hemorrhagic telangiectasis, idiopathic thrombocytotic papura, thrombocytopenia, dengue hemorrhagic fever, antithrombin III deficiency

4.2.5 Enoxaparin dose, dosing interval, date of birth, serum creatinine, or weight values are missing

5. Period of study

Patient database covering a period of 2006-2009 serves as a pool population. Data collection and analysis were commenced from March to December 2009.

6. Steps of investigation

6.1 The population in this study was hospitalized patients age $\geq$ 18 years who had ever received enoxaparin since 2006 to 2009 with the diagnosis of acute coronary syndrome according to The International Statistical Classification of Diseases and Related Health Problems 10^{th} Revision (ICD-10). They identify using the computerized database. In the case of multiple admissions, the latest admission record that was available was used.

6.2 Thirty patients preliminary analysis was performed to develop case record form.

6.3 The researcher-developed case record form was used to collect patient demographic variables, detail information on doses of enoxaparin during hospital stay, renal function, concomitant medications, and bleeding events. To conceal this patient information, the locked form was used.

6.4 The conversion of paper into electronic documents was performed by researcher and using a computerized checking to ensure the correctness of data conversion.

6.5 The recorded initial prescribing dose and dosing interval were used to determine the total amount of enoxaparin administered in one day (prescribing daily dose). The current creatinine was used to estimate CrCl. The recommended daily dose of enoxaparin was calculated for each patient. The prescribing daily dose was compared with the recommended dose. After that, patients was classified to three groups: recommended dose, excess dose, or lower-than recommended dose.

6.6 Bleeding complication was reviewed from each medical record. The event will be collected for data analysis if it occurred during enoxaparin therapy or within 24 hours after discontinuation. Detailed information of the event was collected

and analyzed. Severity of bleeding was assessed and categorized according to TACSR, GUSTO and TIMI classifications. For patients who experienced more than one bleeding episode, only the most severe bleeding was considered.

6.7 Multivariate logistic regression was used to identify risk factors of enoxaparin-associated bleeding. Steps of investigation were summarized in Figure 1.

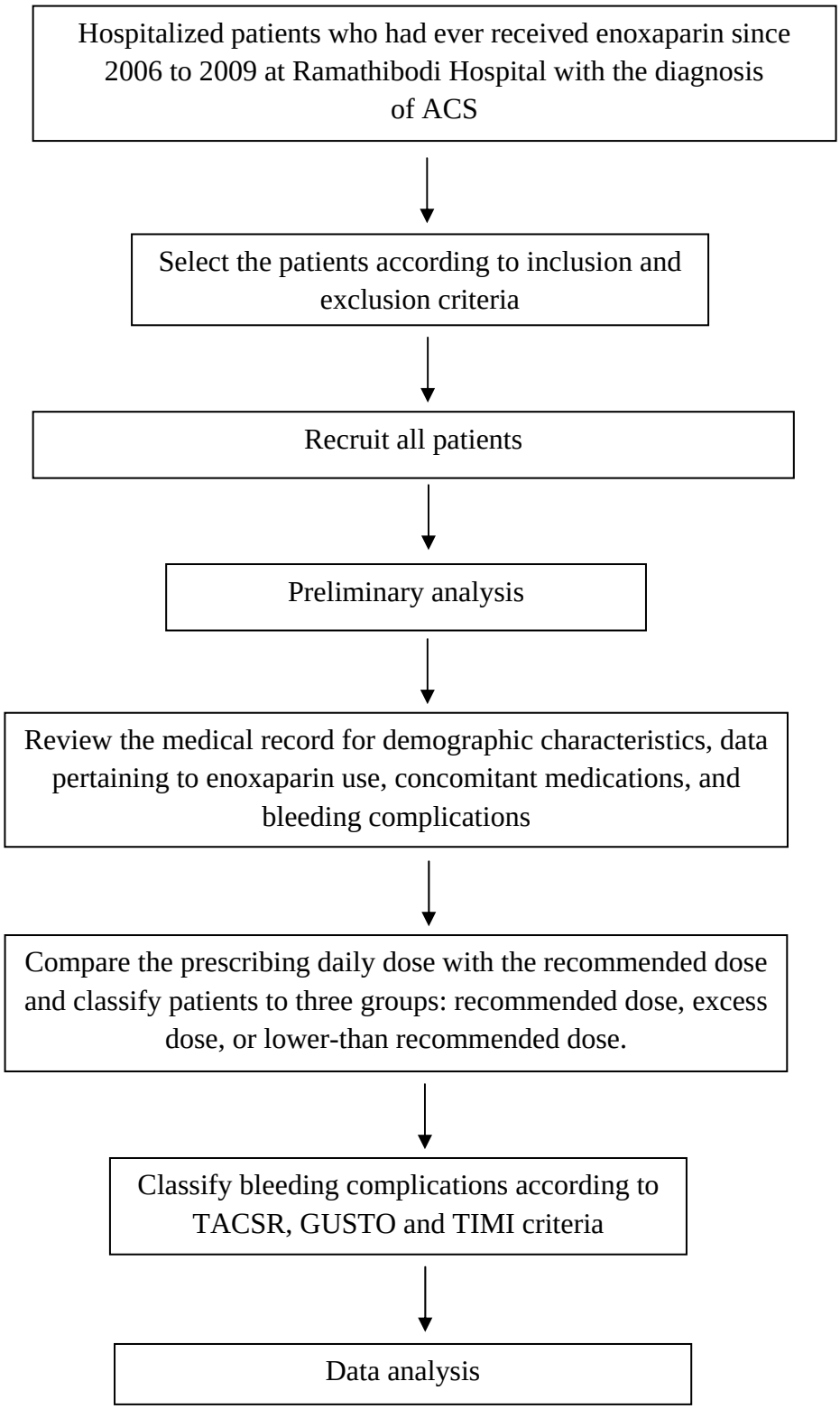

Figure 1. Steps of investigation

7. Data collections

7.1 Demographic characteristics

Date of birth, gender, body weight, height, congestive heart failure at admission, early invasive or conservative treatment, history of previous bleeding and comorbid diseases (diabetes mellitus, hypertension, previous stroke) were collected. The laboratory results including creatinine, hemoglobin, hematocrit, platelet count since enoxaparin therapy to 24 hours after discontinue therapy, admission date, and discharge date were collected.

7.2 Data pertaining to enoxaparin usage

Indication, prescribing dose, actual receiving dose, dosing interval, number of enoxaparin dose, and duration of enoxaparin therapy were collected.

7.3 Concomitant medications

Concomitant medications that may affect bleeding risk were documented including warfarin, antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitor (PPIs), histamine-2 receptor antagonists, glycoprotein IIb/IIIa inhibitors, and thrombolytic agents.

7.4 Bleeding complications

Sign and symptom of bleeding, area or organ, a fall in hemoglobin levels and hematocrit levels, antifactor Xa, hemodynamic status, vasopressor usage, units of blood transfusion, and outcome (death or alive) were collected.

8. Data analysis

8.1 Descriptive analysis

An analysis was developed for the overall patient population and for subgroups of patients with STEMI, NSTEMI, and UA. Patient characteristics were reported by descriptive statistics. Continuous variables including age, weight, BMI, length of stay, duration of enoxaparin therapy, accumulative dose of enoxaparin, and CrCl were reported as mean (standard deviation). Categorical variables including

gender, indication, concomitant medications, history of previous bleeding, CHF at admission, coronary artery angiography (CAG), percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) were reported as number and percentage. In addition, assessment of renal function before enoxaparin prescription was reported in number and percentage.

The aims of this analysis are to describe the usage pattern of enoxaparin and

determine the incidence of enoxaparin-associated bleeding using TACSR, GUSTO and TIMI criteria. The recorded initial enoxaparin dose and dosing interval were used to determine the total amount of enoxaparin prescribed in one day (initial prescribing daily dose). The current creatinine was used to estimate CrCl by C-G or MDRD equations. The recommended daily dose of enoxaparin was calculated for each patient. The prescribing daily dose was compared with the recommended dose. Then, patients were classified into three groups including excess dose, lower-than recommended dose, and recommended dose.

Descriptive statistic was used to report the number and percentage of patients in each group. Patient characteristics between dosing groups were compared. Mean and standard deviation were reported for continuous variables and percentages were reported for categorical variables. Kolmogorov-Smirnov was to test the normality of these values. For normal distribution, Student's t-test and chi-square test were used. If the data are non-normal distribution, the Mann-Whitney U-test was used. P-value less than 0.05 was considered statistically significant for all tests.

Enoxaparin-associated bleeding was defined as bleeding that occurred during enoxaparin therapy or following discontinuation of enoxaparin therapy within 24 hours prior to bleeding event.

For bleeding analysis, patients who participated in other clinical trial were excluded. Bleeding complications were categorized according to three classifications. The first was GUSTO classification which classifies bleeding into three categories: severe, moderate, and mild. The second was TIMI classification which classifies bleeding into three categories: major, minor, and minimal. The third was TACSR major bleeding criteria. Total bleeding was defined as all enoxaparin-associated

bleeding occurrences. For patients who experienced more than one bleeding episode, only the most severe episode was considered.

8.2 Risk factor analysis

The aim of this analysis is to identify risk factors of enoxaparin-associated bleeding. Univariate and multivariate logistic regression analysis were used to identify risk factors of enoxaparin-associated bleeding. Factors in these analyses included age, female gender, BMI, creatinine, CrCl, enoxaparin dose status, duration of enoxaparin therapy, accumulative dose of enoxaparin, CHF at admission, concomitant medications (warfarin, dual antiplatelet agents, NSAIDs, GPIs, thrombolysis and PPIs). The risks of these events were reported by the odds ratio (OR) presented with its 95% confidence interval.

8.3 Association between bleeding severity and length of stay

Descriptive statistic was used to report mean and standard deviation of LOS for each bleeding severity. Kolmogorov-Smirnov was to test the normality of these values. For normal distribution, Student’s t-test was used for compare mean LOS between patients who experienced bleeding and patients who were not experienced bleeding. If the data are non-normal distribution, the Mann-Whitney U-test was used. P-value less than 0.05 was considered statistically significant.

CHAPTER IV
RESULTS

Acute coronary syndrome patients who were older than 18 years who were hospitalized and received enoxaparin between January 1, 2006, and February 1, 2009 were identified from the computerized database. For patients who experienced more than one admission, only the most recent admission was considered. All inpatient medical records coded with ACS under 1-385 were retrospectively reviewed. Of these, 26 patients were excluded from the data analysis because the following reasons: creatinine value was missing in 1 patient, information on weight were missing in 6 patients, enoxaparin dose were missing in 6 patients, enoxaparin dosing interval were missing in 8 patients, and 5 patients were not diagnosed to have ACS (miss coding). Finally, data for 359 patients were evaluated for the study. This retrospective cohort study was conducted between April 24, 2009 and July 16, 2009 at the Medical Records and Statistics Department, Ramathibodi Hospital. The results of this study were presented as follows:

I. Patient characteristics
II. Enoxaparin dosing
III. Bleeding complications, risk factors, and outcomes
IV. Exploratory analysis

I. Patient characteristics

Patient characteristics and enoxaparin usage are presented in Table 1. From a total of 359 patients included in the data analysis, 56.5%, 25.6% and 17.8% of cases were NSTEMI, STEMI and UA, respectively. The average age is 66.8 years. A

total of 240 (66.8%) patients were found to have renal impairment (CrCl less than 50 ml/min).

Furthermore, 39.3% (n=141) were severe renal impairment (CrCl less than 30 ml/min). There were 217 (60.5%) patients who received conservative treatment and 142 (39.5%) who received early invasive treatment. Mean duration of enoxaparin therapy is 3.8 days and mean accumulative dose is 354.3 mg. A total of 346 (96.4%) patients received aspirin, 339 (94.4%) received clopidogrel, 333 (92.8%) received dual antiplatelet therapy, 44 (12.3%) received GPIs, and 21 (5.8%) received thrombolysis. In-hospital mortality rate is 8.9% (n=32). Data on length of stay (LOS) followed non-parametric distribution, with median LOS of 6 days and mean LOS of 10 days. The proportion of renal function assessment at admission is 99.72%.

Table 1. Patient characteristics, enoxaparin usage, and outcome

Characteristics	All Patients (n=359)	Patients by ACS Groups		
		STEMI (n=92)	NSTEMI (n=203)	UA (n=64)
Age (years)	66.8 (11.9)	62.1 (12.1)	68.4 (11.6)	68.1 (11.0)
Female	120 (33.4%)	19 (20.6%)	79 (38.9%)	22 (34.4%)
Weight (kg)	63.9 (11.72)	64.4 (12.8)	63.6 (10.6)	64.3 (13.6)
BMI (kg/m^2)	24.7 (3.54)	24.5 (3.9)	24.8 (3.4)	24.8 (3.4)
CrCl (ml/min)	40.4 (24.52)	51.9 (26.0)	36.0 (23.3)	38.0 (20.9)
CHF at admission	162 (45.1%)	37 (40.2%)	101 (49.7%)	24 (37.5%)
History				
Bleeding	53 (14.76%)	11 (11.96%)	31 (15.27%)	11 (17.19%)
Stroke	54 (15.0%)	11 (12.0%)	34 (16.7%)	9 (14.1%)
Diabetes	179 (49.9%)	35 (38.0%)	120 (59.1%)	24 (37.5%)
Hypertension	270 (75.2%)	54 (58.7%)	169 (83.2%)	47 (73.4%)
CAG	199 (55.4%)	73 (79.3%)	102 (50.2%)	24 (37.5%)
LOS (median)	6	6	6	6
LOS (mean)	10.1 (10.5)	10.4 (11.8)	10.3 (10.4)	9.0 (8.4)
Death	32 (8.9%)	12 (13.0%)	17 (8.37%)	3 (4.7%)

Table 1. Patient characteristics, enoxaparin usage, and outcome (cont.)

Characteristics	All Patients (n=359)	Patients by ACS Groups		
		STEMI (n=92)	NSTEMI (n=203)	UA (n=64)
Treatment				
Conservative	217 (60.5%)	32 (34.8%)	135 (66.5%)	50 (78.1%)
Invasive	142 (39.5%)	60 (65.2%)	68 (33.5%)	14 (21.9%)
PCI	114 (31.7%)	56 (60.9%)	53 (26.1%)	5 (7.8%)
CABG	31 (8.6%)	6 (6.5%)	16 (7.9%)	9 (14.1%)
Enoxaparin usage				
Duration (days)	3.8 (3.5)	3.6 (4.4)	3.9 (3.3)	3.81 (2.9)
Accumulative dose (mg)	354.3 (294.9)	344.9 (342.1)	353.5 (274.9)	370.4 (287.7)
Concomitant Medications				
Aspirin	346 (96.4%)	85 (92.4%)	198 (97.5%)	63 (98.4%)
Clopidogrel	339 (94.4%)	86 (93.5%)	196 (96.5%)	57 (89.1%)
Dual antiplatelet	333 (92.8%)	84 (91.3%)	192 (94.6%)	57 (89.1%)
Warfarin	23 (6.4%)	5 (5.4%)	14 (6.9%)	4 (6.2%)
GPI	44 (12.3%)	30 (32.6%)	12 (5.9%)	2 (3.1%)
Thrombolysis	21 (5.8%)	21 (22.8%)	0	0
NSAIDs	4 (1.1%)	0	1 (0.5%)	3 (4.7%)
PPI	283 (78.8%)	77 (83.7%)	155 (76.3%)	51 (79.7%)
H_2RA	7 (1.9%)	2 (2.1%)	3 (1.5%)	2 (3.1%)

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAG, coronary angiogram; CHF, congestive heart failure; CrCl, creatinine clearance; GPI, glycoprotein IIb/IIIa inhibitor; H_2RA, histamine-2 receptor antagonist; LOS, length of stay; NSAIDs, non-steroidal anti-inflammatory drugs; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

II. Enoxaparin dosing

The differences between prescribing dose and the recommended dose are presented in Figure 2. There were 151 patients (42.1%) who received recommended dose. There were 152 (42.3%) and 56 patients (15.6%) who received lower-than-recommended doses and excess doses, respectively. Among patients who received excess doses, 32 patients (57.1%) had severe renal impairment (CrCl less than 30 ml/min) and did not received renally adjusted dose.

There were some differences between dosing group. Patients who received an excess dose were older (mean age 72.42 years vs 68.03 years, p=0.02), more likely to have severe renal impairment (69.64% vs 47.68%, p<0.01), with lower body weight (mean weight 55.75 kg vs 60.22 kg, p=0.01), and more often women (53.57% vs 31.79%, p<0.01) compared with patients who received the recommended dose. Patients who received a lower-than-recommended dose were younger (mean age 63.42 years vs 68.03 years, p<0.01), more likely to have adequate renal function (19.74% vs 47.68%, p<0.01), with larger body weight (mean weight 70.64 kg vs 68.03 kg, p<0.01) compared with patients who received recommended dose. Characteristics of patients with excess, lower-than-recommended, and recommended enoxaparin doses are presented in Table 2.

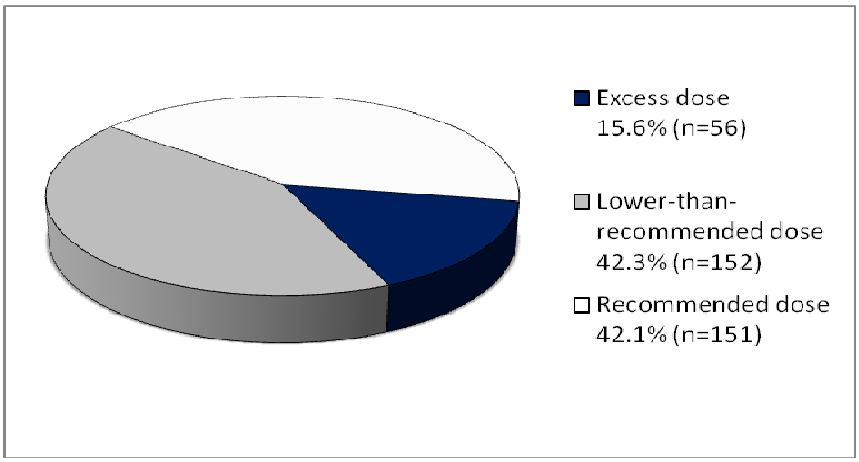

Figure 2. The proportion of patients receiving the excess, lower-than-recommended, and recommended enoxaparin doses

Table 2. Characteristics of patients with excess, lower-than-recommended, and recommended enoxaparin doses

Characteristics[a]	Enoxaparin dosing		
	Recommended Dose (n=151)	**Excess Dose (n=56)**	**Low Dose (n=152)**
Age	68.03 (12.18)	72.42* (10.96)	63.42*** (11.05)
Weight	60.22 (6.83)	55.75** (11.04)	70.64*** (12.29)
BMI	23.56 (2.43)	20.38*** (1.71)	26.31*** (3.62)
Female	31.79	53.57***	27.63
CHF	50.33	42.86	40.79
Renal function			
CrCl	35.67 (23.27)	33.19 (19.35)	47.84*** (25.56)
CrCl<30	47.7	69.6***	19.7***
Diagnosis			
STEMI	21.8	23.2	30.3
NSTEMI	60.3	54.4	53.3
UA	17.9	21.4	16.4
History			
Bleeding	12.6	19.6	15.1
Stroke	15.2	14.3	15.1
DM	50.3	46.4	50.7
HT	70.9	78.6	78.3

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CHF, congestive heart failure; CrCl, creatinine clearance; DM, diabetes mellitus; HT, hypertension; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina. [a] Data are given as mean (SD) for continuous variables and percentage for categorical variables. *p=0.02, **p=0.01, ***p<0.01 compared with the recommended dose.

III. Bleeding, risk factors, and outcomes

3.1 Characteristics and incidences of bleeding

Among 359 patients, 13 were excluded from bleeding and risk factors analysis because the following reasons: 11 patients participated in antiplatelet trials, one patient did not received enoxaparin, and one patient whose medical record was missing. Lastly, data for 346 patients were evaluated in this analysis.

Bleeding characteristics were listed in Table 3. Hematuria, gastrointestinal bleeding, and blood-stained sputum were the three most common symptoms. Among patients with a bleeding event, 25 patients received blood transfusion, 4 patients became hemodynamically unstable and one patient suffered from intracranial hemorrhage.

Table 3. Bleeding characteristics

Bleeding characteristics	No. (%)
Hematuria	31 (23.1)
Gastrointestinal bleeding	25 (18.8)
Blood-stained sputum	24 (17.9)
Hematoma	21 (15.7)
Ecchymosis	19 (14.3)
Groin bleeding	7 (5.2)
Bleeding per gum	2 (1.5)
Intracranial hemorrhage	1 (0.7)
Pericardial effusion	1 (0.7)
Internal jugular bleeding	1 (0.7)
Bruise	1 (0.7)
Epistaxis	1 (0.7)
Total	**134 (38.7)**

From a total of 346 patients, 146 patients (42.2%) experienced bleeding during hospitalization but only 134 patients were judged to have enoxaparin-associated bleeding (38.7%). Using an internationally standardized classification, incidence of patients with GUSTO mild, moderate, and severe bleeding was 30.9% (n=107), 6.6% (n=23), and 1.2% (n=4), respectively. With regard to TIMI bleeding, 34.7% (n=120), 3.5% (n=12) and 1.2% (n=4) of patients experienced TIMI minimal bleedings, TIMI minor bleedings, and TIMI major bleedings. Based on TACSR criteria, 8.1% (n=28) of patients experienced major bleeding events. Patient case series of enoxaparin associated major/severe bleeding are presented in Appendix B. Patient case summaries of enoxaparin associated bleeding are presented in Appendix C.

Bleeding severity by enoxaparin dosing groups are given in Table 4. There was a stepwise increase in bleeding event as enoxaparin dosing increased. However,

no statistically significant association between incidences of GUSTO severe bleeding, TIMI major bleeding, or TACSR major bleeding and enoxaparin dose were found. Bleeding severity by ACS groups are given in Table 5. The results showed a stepwise increase in bleeding occurrence as severity of disease increased. Nevertheless, no statistically significant association between incidences of GUSTO severe bleeding, TIMI major bleeding, or TACSR major bleeding and ACS groups were found.

Table 4. Bleeding severity by enoxaparin dosing groups

Bleeding Severity	All patients (N=346)	Patients by enoxaparin dosing groups[a]		
		Excess dose (N=54)	Recommended dose (N=145)	Lower-than recommended dose (N=147)
Overall bleeding	134 (38.73%)	28 (51.85%)	58 (40.00%)	48 (32.65%)
ICH	1 (0.29%)	1 (1.85%)	-	-
TACSR criteria				
Major	28 (8.09%)	6 (11.11%)	14 (9.66%)	8 (5.44%)
GUSTO criteria				
Severe	4 (1.16%)	1 (1.85%)	1 (0.69%)	2 (1.36%)
Moderate	23 (6.65%)	5 (9.26%)	12 (8.28%)	6 (4.08%)
Mild	107 (30.92%)	22 (40.74%)	45 (31.03%)	40 (27.21%)
TIMI criteria				
Major	4 (1.16%)	1 (1.85%)	2 (1.38%)	1 (0.68%)
Minor	12 (3.47%)	3 (5.56%)	6 (4.14%)	3 (2.04%)
Minimal	120 (34.68%)	24 (44.44%)	51 (35.17%)	45 (30.61%)

Abbreviations: GUSTO, global use of strategies to open occluded coronary arteries; ICH, intracranial hemorrhage; TACSR, Thai acute coronary syndrome registry; TIMI, thrombolysis in myocardial infarction. [a] Data are given as percentage.

Table 5. Bleeding severity by acute coronary syndrome groups

Bleeding Severity	All patients (N=346)	Patients by ACS groups[a]		
		STEMI (N=87)	NSTEMI (N=196)	UA (N=63)
Overall bleeding	134 (38.73%)	44 (50.57%)	73 (37.24%)	17 (26.98%)
ICH	1 (0.29%)	-	1 (0.51%)	-
TACSR criteria				
Major	28 (8.09%)	5 (5.75%)	16 (8.16%)	7 (11.11%)
GUSTO criteria				
Severe	4 (1.16%)	1 (1.15%)	2 (1.02%)	1 (1.59%)
Moderate	23 (6.65%)	4 (4.60%)	14 (7.14%)	5 (7.94%)
Mild	107 (30.92%)	39 (44.83%)	57 (29.08%)	11 (17.46%)
TIMI criteria				
Major	4 (1.16%)	1 (1.15%)	1 (0.51%)	2 (3.17%)
Minor	12 (3.47%)	6 (6.90%)	5 (2.55%)	1 (1.59%)
Minimal	120 (34.68%)	38 (43.68%)	68 (34.69%)	14 (22.22%)

Abbreviations: ACS, acute coronary syndrome; GUSTO, global use of strategies to open occluded coronary arteries ; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; TACSR, Thai acute coronary syndrome; TIMI, thrombolysis in myocardial infarction; UA, unstable angina.

[a] Data are given as percentage.

To evaluate the duration of exposure to enoxaparin therapy and bleeding, we analyzed and reported numbers of day of enoxaparin usage prior to bleeding events, which is shown in Table 6. For TACSR major bleedings, GUSTO severe bleedings, and TIMI major bleedings, the duration of exposure were 1.89$\pm$1.37 days, 1.75$\pm$0.95 days, and 1.75$\pm$0.95 days, respectively. For GUSTO moderate and TIMI minor bleedings, such duration were 2.30$\pm$1.29 and 2.58$\pm$2.19 days, respectively.

Table 6. Duration of exposure to enoxaparin therapy and bleeding

Bleeding Types	Mean number of days of enoxaparin usage prior to bleeding events[a] (±S.D.)
TACSR criteria	
Major (n=28)	1.89 (1.37)
GUSTO criteria	
Severe bleeding (n=4)	1.75 (0.95)
Moderate bleeding (n=23)	2.30 (1.29)
TIMI criteria	
Major bleeding (n=4)	1.75 (0.95)
Minor bleeding (n=12)	2.58 (2.19)

Abbreviations: GUSTO, global use of strategies to open occluded coronary arteries; TACSR, Thai acute coronary syndrome registry; TIMI, thrombolysis in myocardial infarction. [a] Data are given as mean (SD).

3.2 Risk factors of bleeding

Table 7 and table 8 summarized all findings from univariate logistic regression analysis. Table 7 listed results of all factors included in the regression analysis while table 8 displayed only factors that were found to be significantly associated with bleeding according to bleeding definition and ranked by order of magnitude.

GUSTO Bleeding

Factors found to be significantly associated with GUSTO overall bleeding were glycoprotein IIb/IIa inhibitors usage (OR, 4.21; 95% CI, 2.04-8.63), an excess dose of enoxaparin (OR, 1.89; 95% CI, 1.05-3.39), proton pump inhibitors usage (OR, 1.81; 95% CI, 1.02-3.19), renal impairment as defined by CrCl less than 60 ml/min (OR, 1.75; 95% CI, 1.08-2.67), and female gender (OR, 1.70; 95% CI, 1.08-2.67, respectively).

For a combination of severe and moderate bleeding events, moderate and severe renal impairment as defined by CrCl < 60 ml/min (OR, 2.98; 95% CI, 1.01 – 8.85) and CrCl < 30 ml/min (OR, 5.88; 95% CI, 2.31 – 14.99) significantly increased risk of such bleedings. For analysis of each individual degree of GUSTO bleeding, we found no significant impact from any factors, which was most likely a result of limited number of events in each category.

TIMI Bleeding

Findings from TIMI bleeding were quite similar to GUSTO bleeding with small variations. Factors found to be significantly associated with TIMI overall bleeding were glycoprotein IIb/IIa inhibitors usage (OR, 4.69; 95% CI, 2.25 – 9.79), proton pump inhibitors usage (OR, 1.86; 95% CI, 1.05 – 3.29), an excess dose of enoxaparin (OR, 1.83; 95% CI, 1.02-3.39), renal impairment as defined by CrCl less than 60 ml/min (OR, 1.70; 95% CI, 1.05 – 2.74), female gender (OR, 1.63; 95% CI, 1.04 – 2.56) and duration of enoxaparin therapy (OR, 1.07;95% CI, 1.01 – 1.14).

For a combination of major and minor bleeding events, only glycoprotein IIb/IIa inhibitors usage was found to significantly increase the risk of such bleeding. Similar to our results from GUSTO bleeding, analysis of each individual degree of TIMI bleeding showed no significant impact from any factors.

TACSR

In contrast to GUSTO and TIMI bleeding, moderate and severe renal impairment as defined by CrCl < 60 ml/min (OR, 3.13; 95% CI, 1.06-9.24) and CrCl < 30 ml/min (OR, 6.21; 95% CI, 2.45-15.76) were the only two factors associated with bleeding by TACSR definition. Other factors such as glycoprotein IIb/IIIa inhibitors usage, excess dose of enoxaparin, proton pump inhibitor usage, female gender, duration of enoxaparin therapy were not found to have significant influence on TACSR bleeding.

Overall, renal impairment appeared to be the most consistent factor influencing the increased risk of bleeding by all analysis. Usage of glycoprotein IIb/IIIa inhibitors and excess dose of enoxaparin also showed a strong impact on the risk of bleeding. These findings were consistent with pathophysilogical and pharmacological aspects of the study population and drug properties, respectively.

Table 7. Overall results of univariate analysis to identify risk of bleeding[a]

Risks	GUSTO			TIMI			TACSR
	Severe (N=4)	Severe + Moderate (N=27)	Overall (N=134)	Major (N=4)	Major + Minor (N=16)	Overall (N=136)	Major (N=28)
Enoxaparin usage							
Excess Dose	1.82 (0.19 – 17.81)	1.61 (0.62 – 4.20)	1.89* (1.05 – 3.39)	1.81 (0.19 – 17.81)	1.87 (0.58 – 6.02)	1.83* (1.02 – 3.39)	1.53 (0.59 – 3.98)
Duration of therapy (days)	0.35 (0.10 – 1.21)	1.03 (0.93 – 1.14)	1.07 (1.00 – 1.14)	1.06 (0.86 – 1.31)	1.01 (0.88 – 1.16)	1.07* (1.01 – 1.14)	1.05 (0.96 – 1.15)
Accumulative dose (mg)	0.99 (0.98 – 1.00)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)
Patient characteristics							
CrCl (cont.)	1.00 (0.96 – 1.04)	0.96 (0.94 – 0.98)	0.99 (0.98 – 1.00)	1.01 (0.97 – 1.04)	0.99 (0.96 – 1.01)	0.99 (0.98 – 1.00)	0.96 (0.94 – 0.98)
CrCl < 60 ml/min	0.48 (0.07 – 3.46)	2.98* (1.01 – 8.85)	1.75* (1.08 – 2.82)	0.48 (0.07 – 3.46)	1.48 (0.47 – 4.69)	1.70* (1.05 – 2.74)	3.13* (1.06 – 9.24)
CrCl < 30 ml/min	0.49 (0.05 – 4.73)	5.88* (2.31 – 14.99)	1.41 (0.91 – 2.18)	0.49 (0.05 – 4.73)	1.95 (0.71 – 5.37)	1.42 (0.91 – 2.20)	6.21* (2.45 – 15.76)
Female	0.63 (0.06 – 6.15)	1.87 (0.85 – 4.11)	1.70* (1.08 – 2.67)	-	0.86 (0.29 – 2.54)	1.63* (1.04 – 2.56)	1.73 (0.79 – 3.77)
Age (cont.)	0.94 (0.86 – 1.03)	1.01 (0.98 – 1.05)	1.00 (0.98 -1.02)	0.97 (0.89 – 1.05)	0.99 (0.95 – 1.03)	1.00 (0.98 – 1.02)	1.01 (0.98 – 1.05)
Age>65 years	0.26 (0.03 – 2.50)	1.36 (0.61 – 3.07)	0.94 (0.61 – 1.46)	0.26 (0.03 – 2.50)	1.00 (0.37 – 2.77)	0.89 (0.58 – 1.38)	1.23 (0.56 – 2.71)
Weight (cont.)	1.01 (0.94 – 1.10)	1.00 (0.97 – 1.04)	0.98 (0.96 – 1.00)	1.06 (0.99 – 1.13)	1.00 (0.95 – 1.04)	0.98 (0.96 – 1.00)	1.01 (0.98 – 1.05)
HF at admission	0.39 (0.04 – 3.81)	1.31 (0.60 – 2.87)	1.47 (0.95 – 2.27)	1.19 (0.17 – 8.56)	0.92 (0.33 – 2.53)	1.47 (0.95 – 2.27)	1.41 (0.65 – 3.06)
Concomittant medications							
PPI	0.77 (0.08 – 7.54)	7.31 (0.97 – 54.81)	1.81* (1.02 – 3.19)	0.77 (0.08 – 7.54)	4.04 (0.52 – 31.10)	1.86* (1.05 – 3.29)	3.60 (0.83 – 15.55)
Dual Antiplatelets	0.22 (0.02 – 2.16)	0.38 (0.12 – 1.22)	1.29 (0.53 – 3.09)	0.07 (0.01 – 0.51)	0.29 (0.08 – 1.11)	1.32 (0.55 – 3.17)	0.40 (0.13 – 1.27)
Warfarin	-	0.55 (0.07 – 4.22)	0.33 (0.11 – 1.00)	5.09 (0.51 – 51.12)	2.21 (0.47 – 10.42)	0.32 (0.11 – 0.98)	1.15 (0.25 – 5.18)
GPI	2.67 (0.27 – 26.28)	1.41 (0.46 – 4.32)	4.21* (2.04 – 8.63)	2.67 (0.27 – 26.28)	5.40* (1.84 – 15.80)	4.69* (2.25 – 9.79)	1.35 (0.44 – 4.11)
Thrombolysis	-	-	0.77 (0.31 – 1.98)	-	1.03 (0.13 – 8.22)	0.76 (0.30 – 1.93)	-
NSAIDs	-	-	0.52 (0.05 – 5.08)	-	-	0.51 (0.05 – 4.96)	-

Abbreviations: cont, continuous; CrCl, creatinine clearance; GUSTO, use of strategies to open occluded coronary arteries; HF, heart failure; PPI, proton pump inhibitor; GPI, glycoprotein IIb/IIIa inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; TACSR, Thai acute coronary syndrome registry; TIMI, thrombolysis in myocardial infarction. [a]Data presented with OR and its 95% CI. *Statistical significant.

Table 8. Factors significantly associated with bleeding (univariate analysis) ranked by order of magnitude for each bleeding definition

Bleeding severity	Variables	OR (95% CI)	P-value
GUSTO			
Overall bleeding (n=134)	GPI	4.21 (2.04-8.63)	< 0.01
	Excess dose of enoxaparin	1.89 (1.05-3.39)	0.03
	PPI	1.81 (1.02-3.19)	0.04
	CrCl < 60 ml/min	1.75 (1.08-2.82)	0.02
	Female	1.70 (1.08-2.67)	0.02
Severe + moderate (n=27)	CrCl < 30 ml/min	5.88 (2.31-14.99)	< 0.01
	CrCl < 60 ml/min	2.98 (1.01-8.85)	0.03
TIMI			
Overall bleeding (n=136)	GPI	4.69 (2.25 – 9.79)	< 0.01
	PPI	1.86 (1.05 – 3.29)	0.03
	Excess dose of enoxaparin	1.83 (1.02 – 3.39)	0.04
	CrCl < 60 ml/min	1.70 (1.05 – 2.74)	0.03
	Female	1.63 (1.04 – 2.56)	0.03
	Duration of enoxaparin therapy	1.07 (1.01 – 1.14)	0.03
Major + minor (n=16)	GPI	5.40 (1.84-15.80)	< 0.01
TACSR			
Major (n=28)	CrCl<30 ml/min	6.21 (2.45-15.76)	< 0.01
	CrCl<60 ml/min	3.13 (1.06-9.24)	0.02

Abbreviations: CrCl, creatinine clearance; GPI, glycoprotein IIb/IIIa inhibitors; GUSTO, global use of strategies to open occluded coronary arteries; OR, odd satio; PPI, proton pump inhibitors; TACSR, Thai acute coronary syndrome registry; TIMI, thrombolysis in myocardial infarction.

An excess dose compared with the recommended dose was significantly and independently associated with an increased risk of all bleeding after adjustment for patient characteristics, duration of enoxaparin therapy, and concomitant medications (GUSTO adjusted OR, 2.18; 95%CI, 1.18-4.00 and TIMI adjusted OR, 2.08; 95%CI, 1.13-3.84). The unadjusted and adjusted risks of bleeding are given in Table 8. For analysis of each individual degree of GUSTO and TIMI bleeding, we

found no statistically significant associations between each bleeding category and enoxaparin dose, which was most likely a result of limited number of events in each category.

Table 9. Unadjusted and adjusted risks of bleeding by excess enoxaparin dose compared with recommended dose

Excess dose	GUSTO overall bleeding (n=134)	TIMI overall bleeding (n=136)
Unadjusted OR	1.89* (1.05-3.39)	1.83* (1.02-3.29)
Adjusted[a] OR	2.18* (1.18-4.00)	2.08* (1.13-3.84)

[a]Adjusted for baseline characteristics, duration of therapy, and concomitant medications. *Statistical significance.

Among patients with appropriate enoxaparin dose, there were some differences between once daily and twice daily dose group. Despite receiving renally adjusted dose, we found that bleeding risk in patients with severe renal impairment were significantly higher than patients without severe renal impairment. Once daily dose administration was significantly and independently associated with an increased risk of TACSR major, GUSTO severe and moderate, and GUSTO moderate bleeding after adjustment for patient characteristics, and concomitant medications (adjusted OR, 8.69; 95% CI 1.74-43.39, adjusted OR, 7.91; 95% CI 1.56-40.12, adjusted OR, 7.14; 95% CI 1.38-36.89). Unadjusted and adjusted risks of bleeding among appropriated dose group are given in Table 9.

Table 10. Unadjusted and adjusted risks of bleeding between patients with severe renal impairment receiving renally adjusted once daily dosing versus patients with normal renal function receiving twice daily dosing

Odd Ratios: OD vs BID dosing	TACSR major	GUSTO severe and moderate	GUSTO moderate
Unadjusted OR	7.32* (1.58-34.02)	6.60* (1.41-30.94)	5.90* (1.24-27.97)
Adjusted[a] OR	8.69* (1.74-43.39)	7.91* (1.56-40.12)	7.14* (1.38-36.89)

Abbreviations: CI, confidence interval; OR, odds ratio; [a]Adjusted for patient characteristics, and concomitant medications. *Statistical significance.

3.3 Risk factors of in-hospital death

Table 10 shows risk factors of in-hospital death from univariate analysis. There are a statistically significant stepwise increase in in-hospital death as GUSTO and TIMI severity increased. There are significantly higher risk of in-hospital death in patients who experienced GUSTO severe bleeding, GUSTO moderate bleeding, TIMI major bleeding, TIMI minor bleeding, TIMI minimal bleeding, and TACSR major bleeding (OR, 35; 95% CI, 3.52-348.07, OR, 7.29; 95% CI, 2.70 -19.08, OR, 35; 95% CI, 3.52-348.07, OR, 12.92; 95% CI, 3.87-43.12, OR, 2.70, 95% CI 1.26-5.78, OR, 12.50; 95% CI, 5.15-30.34, respectively) compared to patients who did not experience bleeding. In addition, patients who had severe renal impairment, creatinine more than 2 mg/dl, older than 65 years, and experienced CHF at admission were at significantly higher risk of in-hospital death (OR, 3.63; 95% CI, 1.66-7.98, OR 4.91; 2.29-10.49, OR, 3.01; 1.26-7.19, OR, 2.37, 95% CI, 1.10-5.11, respectively). However, there was no statistically significant association with risk of in-hospital death between use of an excess dose or lower-than-recommended dose compared with the recommended dose (OR, 1.32; 95% CI, 0.51-3.38 and OR, 0.61; 95% CI, 0.28-1.34, respectively).

Table 11. Risk factors of in-hospital death (univariate analysis)

Characteristics	Number of deaths/Total Number	% in-hospital Mortality	OR (95% CI)	P-value
Age				
Age ≤ 65 years	8 / 161	5.0	1.00	
Age > 65 years	24 / 198	12.2	3.01 (1.26-7.19)*	< 0.01*
CHF at admission				
No CHF	12 / 197	6.1	1.00	
With CHF	20 / 162	12.3	2.37 (1.10-5.11)*	0.02*
Renal function				
Normal (CrCl ≥ 60 ml/min)	2 / 71	2.8	1.00	
Creatinine > 2 mg/dl	17 / 75	22.7	4.91 (2.29-10.49)*	< 0.01*
CrCl < 60 ml/min	30 / 288	10.4	2.22 (0.88 – 5.57)	0.07
CrCl < 30 ml/min	22 / 140	15.7	3.63 (1.66-7.98)*	< 0.01*
Enoxaparin dose				
Recommended dose	15 / 145	10.34	1.00	
Excess dose	6 / 54	11.1	1.32 (0.51-3.38)	0.57
Low dose	9 / 147	6.1	0.61 (0.28-1.34)	0.21
GUSTO Bleeding				
No	5 / 212	2.4	1.00	
Yes	25 / 134	18.7	9.49 (3.54-25.50)*	< 0.01*
GUSTO severe	3 / 4	75.0	35 (3.52-348.07)*	< 0.01*
GUSTO moderate	8 / 23	34.8	7.29 (2.70-19.08)*	< 0.01*
GUSTO mild	14 / 107	13.1	2.10 (0.98-4.47)	0.06
TIMI Bleeding				
No	4 / 210	1.9	1.00	
Yes	26 / 136	19.1	12.17 (4.14-35.76)*	< 0.01*
TIMI major	3 / 4	75.0	35 (3.52-348.07)*	< 0.01*
TIMI minor	6 / 12	50.0	12.92 (3.87-43.12)*	< 0.01*
TIMI minimal	17 / 120	14.2	2.70 (1.26-5.78)*	0.01*
TACSR major bleeding				
No	18 / 318	5.7	1.00	
Yes	12 / 18	42.9	12.50 (5.15-30.34)*	< 0.01*

Abbreviations: CHF, congestive heart failure; CrCl, creatinine clearance; GUSTO, global use of strategies to open occluded coronary arteries;TACSR, Thai acute coronary syndrome registry; TIMI, thrombolysis in myocardial infarction. *Statistical significance

3.4 Bleeding severity and length of stay

Table 11 displays length of stay by bleeding severity. Each GUSTO bleeding event and TIMI bleeding event significantly increased LOS (mean LOS 12.31 days vs 8.27, median LOS 7 days vs 6 days, p<0.01 for GUSTO bleeding and mean LOS 9.66 days vs 8.27 days, median 7 days vs 6 days, p<0.01 for TIMI bleeding) compared with patients who did not experience bleeding. Focusing on bleeding severity, each TACSR major bleeding episode significantly increased LOS (mean LOS 19.44 days vs 8.27 days, median LOS 14.5 vs 6 days, p<0.01). There was only one patient who was alive after GUSTO severe and TIMI major bleeding occurrence. Therefore, association between severe (or major) bleeding and length of stay can not be evaluated. However, each GUSTO moderate, TIMI minor, and TIMI minimal bleeding event significantly increased LOS (mean LOS 20.40 days vs 8.27 days, median 18 days vs 6 days, p=0.02 for GUSTO moderate bleeding; mean LOS 19.80 days vs 8.27 days, median LOS 13 days vs 6 days, p<0.01 for TIMI minor bleeding; mean LOS 11.96 days vs 8.27 days, median 6 days and 6 days for TIMI minimal bleedng, p=0.01, respectively).

Table 12. Length of stay by bleeding severity[a]

Bleeding severity	Bleeding		No bleeding	
	Mean (SD)	Median	Mean (SD)	Median
TACSR criteria				
Major*	19.44 (17.93)	14.5	8.27 (7.93)	6
GUSTO criteria				
Severe	5	5	8.27 (7.93)	6
Moderate**	20.40 (18.13)	18	8.27 (7.93)	6
Mild	11.09 (12.09)	6	8.27 (7.93)	6
Overall*	12.31 (13.34)	7	8.27 (7.93)	6
TIMI criteria				
Major	11	11	8.27 (7.93)	6
Minor*	19.80 (12.52)	13	8.27 (7.93)	6
Minimal*	11.96 (13.39)	6	8.27 (7.93)	6
Overall*	9.66 (10.28)	7	8.27 (7.93)	6

Abbreviations: GUSTO, global use of strategies to open occluded coronary arteries; TACSR, Thai acute coronary syndrome registry; TBH, Thai Bath; TIMI, thrombolysis in myocardial infarction. [a]Data are given in days. *p<0.01, **p=0.02 compared with no bleeding.

IV. Exploratory analysis

Since there were high incidences of enoxaparin underdosing in our study, we conducted additional analysis to investigate the effects of the lower-than recommended dose in this population.

4.1 Effects of lower-than recommended dose

We compare major cardiovascular events, readmission, and length of stay in recommended dose and lower-than recommended dose group. Within the lower-than recommended dose, there were four subgroups as follows.

- L1: Patients who received a daily dose that was 10 to 30 mg less than the recommended dose.
- L2: patients who received a daily dose that was 30 to 60 mg less than the recommended dose.
- L3: patients who received a daily dose that was 60 to 90 mg less than the recommended dose.
- L4: patients who received a daily dose that was 90 mg less than the recommended dose.

There are no statistically significant difference in incidence of cardiovascular events (recurrent ischemia, revascularization, all cause death, death from ACS) and readmission from ACS within 30 days in patients received lower-than recommended dose (all subgroups) compared with patients who received the recommended dose. Composite endpoints combining cardiovascular events and readmission were also not different between lower-than recommended dose subgroups and the recommended dose group. However, mean length of stay (LOS) in L3 and L4 groups are statistically significant less than patients who received the recommended dose (mean LOS 5.71 ± 2.89; $p<0.01$ and 4.75 ± 2.75; $p=0.02$ versus 9.97 ± 10.34, respectively). Major cardiovascular events, readmission, and length of stay in recommended dose group and lower-than recommended dose group are presented in Table 12.

Table 13. **Major cardiovascular events, readmission, and length of stay in lower-than recommended dose subgroup and recommended dose.**

	Outcomes	L1 (n=92)	L2 (n=36)	L3 (n=15)	L4 (n=4)	Recommended dose (n=145)
1.	Recurrent ischemia	5 (5.4%)	0	0	0	3 (2.1%)
2.	Revascularization	0	0	0	0	1 (0.7%)
3.	All-cause death	7 (7.6%)	1 (2.8%)	1 (6.7%)	0	15 (10.3%)
4.	Dead from ACS	0	0	0	0	2 (1.4%)
5.	Readmission from ACS within 30 days	1 (1.1%)	1 (2.8%)	1 (6.7%)	0	3 (2.1%)
6.	Length of stay (days)	9.71 (10.96)	7.83 (7.11)	5.71* (2.89)	4.75** (2.75)	9.97 (10.34)
Composite endpoints						
	1+2	5 (5.4%)	0	0	0	3 (2.1%)
	1+2+3	11 (11.9%)	1	1	0	18 (12.4%)
	1+2+4	5 (5.4%)	0	0	0	5 (3.4%)
	1+2+3+5	12 (13.0%)	2	2	0	21 (14.5%)
	1+2+4+5	6 (6.5%)	1	1	0	8 (5.5%)

Abbreviation: ACS, acute coronary syndrome; L1, a daily dose that was 10 to 30 mg less than the recommended dose; L2, a daily dose that was 30 to 60 mg less than the recommended dose; L3, a daily dose that was 60 to 90 mg less than the recommended dose; L4, a daily dose that was 90 mg less than the recommended dose. [a] Data are given as mean (SD) for continuous variables and number (percentage) for categorical variables. *p<0.01, **p=0.02, compared with the recommended dose.

CHAPTER V
DISCUSSION

This study is the first and largest study of enoxaparin usage and bleeding complications in Thai ACS patients to date. We compiled the data from a tertiary care university hospital center, which received the largest number of ACS patients in Thailand. Our findings reflect the safety of enoxaparin use in a tertiary care center in Thailand.

Our study has several important findings. First, we have shown that approximately 1 of 6 patients who received enoxaparin for treatment of ACS received a dose that was in excess of current dosing recommendations. Compared with Western population using data from CRUSADE national quality improvement initiative (21), approximately 1 of 5 NSTEMI patients received an excess enoxaparin dose. Thus, the issue of excess dose at this tertiary care center is comparable to the Western world. On the other hand, we demonstrated that almost half of Thai ACS patients were administered lower-than recommended enoxaparin dose. This incidence of enoxaparin underdose is higher than the Western population (42.3% vs 29.2%) (21). Interestingly, more than half of patients who received an excess dose had severe renal impairment, in which increasing dosing interval from every 12 hours to every 24 hours is recommended. With regard to weight measurement, in real life, actual weight measurement is often not performed when orders are written. Therefore, approximations may cause underdosing of heavy patients and overdosing of thinner patients.

Second, we found that both GUSTO severe and TIMI major bleeding proportions in this study were low compared with those reported from large, randomized, placebo-controlled trials (1.2% for this study and range from 1% to 6.5% for landmark studies) (12, 33, 35). The most likely reasons are a high incidence of underdosing and infrequent use of glycoprotein IIb/IIIa inhibitors and thrombolysis in

our study population. In addition, early detection of the signs of bleeding which led to early corrective measures may minimize risk of major bleeding.

For Thailand, a different bleeding definition called TACSR was used which is based on the Thai Acute Coronary Syndrome Registry (13). This definition focused on only major bleeding which, in detail, is different from both GUSTO and TIMI. In a recent report from Thai ACS Registry, TACSR major bleeding rate among 5,537 NSTE-ACS Thai patients was 5.9% (36). Using TACSR major bleeding definition, we found higher rate of bleeding (8.1%) among our study population. This is most likely a result of a much more complicated patients in our study population compared to the Thai ACS Registry, especially high incidence of severe renal impairement. Another notable factor was frequent blood transfusion found in our study. Since blood transfusion is listed as one of the TACSR bleeding criteria, higher frequency of blood transfusion would lead to higher incidence of bleeding based on TACSR criteria. This however may not reflect true incidence of bleeding since a number of patients may be anemic at baseline, blood transfusion may therefore be an attempt to correct such abnormal baseline findings.

For comparative purpose with Western registry, CRUSADE (21) may be the best comparator to our study. Despite higher incidence of renal impairment, underdosing and infrequent use of glycoprotein IIb/IIIa inhibitors and thrombolysis in our study population, incidence of TACSR major bleeding in our study is comparable to CRUSADE (8.1% versus 8.8%).

Lastly, our findings were congruent with published reports on the association between excess enoxaparin dose and bleeding. Excess enoxaparin dose is significantly and independently associated with higher risk of in-hospital bleeding. Furthermore, bleeding is financially costly and associated with worse patient outcomes with longer hospital stay and higher mortality.

Our study has important implications for both clinical care and clinical research. Despite a near 100% ordering of creatinine test, a significant number of patients whose renal function were severely impaired, still received an unadjusted dose of enoxaparin. With excess dosing, there were unnessary loss of healthcare resources and associated with poor patient outcomes. As a result, measures to improve enoxaparin dosing accuracy should be instituted. Dosing guides on standard order

forms, computerized verify order entry systems, clinical pharmacists on rounds, and multidisciplinary teams are potential ways to improve this dosing accuracy.

There are two interesting topics for future investigations. First, despite renally adjusted dose, bleeding risk in patients with severe renal impairment remains higher than patients without severe renal impairment. However, these may be exacerbated by an impairment in hemostasis in uremic patients or improper anticoagulant dosage. Further investigations to understand the reasons are needed. Second, we saw large number of patients receiving under-dose of enoxaparin. Exploratory analysis and composite endpoints analysis have not shown any significance increased in an incidence of cardiovascular events or readmission from ACS within 30 days. However, it is not a primary outcome in this investigation. Additional studies are needed to investigate an effect of lower-than recommended enoxaparin dose in Thai ACS patients.

Study limitations

Our study has some limitations. First, only an initial daily dose of enoxaparin was evaluated. Subsequent dosing adjustments made after the initial dose were delivered or alterations in dosing interval for enoxaparin were not considered. Second is an inhomogeneous population of ACS patients included in this study (NSTEMI, STEMI, and UA). We chose not to subdivide the patients into subgroups because of the limited size of our sample. Third, we conducted only a univariate analysis on risk factors for in-hospital mortality. Therefore, this result may be affected by confounding factors and need further evaluation by multivariate analysis. Lastly, results of this study may not reflect the prevailing patterns of care in Thailand. Enoxaparin dosing and bleeding are from a single institution, they may not be representative of other hospitals.

Despite these limitations, information gained from this study may serve as a strong reminder to all healthcare professionals that inappropriate use of enoxaparin, a high alert drug with narrow therapeutic index, can lead to adverse outcomes. Therefore, caution must be excerised when using this drug, especially in certain subgroups of patients. In addition, dosage adjustment based on renal function and

body weight are two simple yet underemployed strategies to reduce the risk of bleeding. The investigators strongly believe that information from the study may help facilitate the development of appropriate corrective actions to promote safe and effective use of enoxaparin in Thailand.

Conclusions

Among patients suffering from ACS and treated with enoxaparin, only 42% of patients received the appropriate dose of enoxaparin according to prescribing guideline. Excess dosing of enoxaparin (15.6%) was relatively common. The most common causes of excess dosing was the lack of dosage adjustment according to renal function and body weight. Up to 42.3% received lower-than-recommended doses. Impacts of such practice on clinical outcome should be further investigated. Compared with the data from Western countries, we found similar rate of excess dose but much higher rate of underdosing.

Overall, up to 38.7% of patients experienced enoxaparin-associated bleeding. Using GUSTO and TIMI criteria, two internationally stabdardized bleeding classifications, the majority of bleeding events in our study population were considered to be mild. There were limited numbers of events that are considered of high clinical importance (1.2% and 6.7% for GUSTO severe and moderate bleedings and 1.2% and 3.5% of TIMI major and minor bleedings). For Thailand's standard definition using TACSR criteria, 8.1% of our study population experienced TACSR major bleeding. Nevertheless, such bleeding rates may be understated since up to 42.3% of our study population received underdosing of enoxaparin.

Our findings were consistent with published reports on risk factors of bleeding in ACS patients. There was a stepwise increase in bleeding rates as enoxaparin dosing increased. An excess dose of enoxaparin is associated to increase overall bleeding. Additionally, renal impairement, low body weight, female gender, proton pump inhibitors, and glycoprotein IIb/IIIa inhibitors usage were found to associate with increased bleeding risk.

In addition, we also found that excess dose of enoxparin significantly increased risk of bleeding and increased length of hospital stay. We also found a

stepwise increase for in-hospital mortality with increasing severity of bleeding events. In addition, we found that age > 65 years, presence of CHF on admission and presence of renal impairment were significantly associated with increased risk of in-hospital death. However, we found no significant association between enoxaparin dosing and in-hospital death.

In conclusion, inappropriate dosing of enoxaparin in the setting of ACS may be common. Such inappropriate dosing, especially excess dose, can lead to adverse clinical outcomes. Measures to ensure appropriate dosing of this drug should be instituted nationwide to promote safe and effective use of enoxaparin in the setting of ACS in Thailand.

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APPENDICES

APPENDIX A
CASE RECORD FORM

ID_____

Inclusion Criteria	**Y/N**
Age > 18 years	
ACS	
Received enoxaparin	
Exclusion Criteria	Y/N
Platelet count < 50,000 cells/ml	
Pregnancy	
Burn	
Hemophilia A, B	
Von Willebrand's disease	
Thrombocytopenia	
Hereditary hemorrhagic telangiectasis	
Idiopathic thrombocytotic papura	
Dengue hemorrhagic fever	
Dengue hemorrhagic fever	
Patient's data point is missing	
Enoxaparin dose	
Enoxaparin interval frequency	
Date of birth	
Serum creatinine	
Weight within one year	

Case Summary

Admission Date ____/____/____ Discharge Date ____/____/____

CC: _____

HPI: _____

PMH: _____

MH: _____

FH&SH: _____

PE: _____

ALL: _____

Hospital Course: _____

_____

_____

_____

_____

Dx _____

ID_____

General Information

❑ UA, Dx Date__/__/__ ❑ NSTEMI, Dx Date__/__/__ ❑ STEMI, Dx Date__/__/_

Enoxaparin Dose

Prescribing Dose

Start Date____/____/____ Time_____ Stop Date____/____/____Time_____

Date										
Time										
Dose										
Frequency										

Actual Receiving Dose

Start Date____/____/____ Time_____ Stop Date____/____/____ Time_____

Date										
Time										
Dose										
Frequency										

Factors That May Affect To Enoxaparin Dose

Date of birth ____/____/____ Gender ❑ Male

❑ Female

Date										
Ht (cm)										
Wt (kg)										
Cr (mg/dl)										

ID_____

Factors That May Affect To Bleeding Risk

History	Y/N	
Bleeding		
Stroke		
DM		
HT		
Current Disease		
CHF at admission		
Procedure		
CAG		
PCI		
CABG		

Concomitant Medications (Actual Receiving)

Warfarin ❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

Aspirin ❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

Clopidogrel ❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

NSAIDs: _____

❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

PPIs, H2RA:_____

❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

GPI: _____

❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

Thrombolysis: _____

❑No ❑Yes, Start___/___/___Time____ Stop___/___/___ Time_____

ID_____

Bleeding Complication

Was the bleeding site identified ❑No ❑Yes, date ____/____/____ time _____

Medical term of bleeding ❑ICH ❑_____

Laboratory results

Date	Admit									
Hb/Hct										
AST/ALT										
TBIL/DBIL										
ALP/GGT										
PT/INR										
SBP/DBP										
PR										
Anti-Xa										

Treatment

Blood Transfusion ❑No ❑Yes

Date										
Time										
Type										
Unit										

Vasopressor ❑No ❑Yes

Date										
Time										
Medications										
Dose										

Outcome

❑Death ❑ Alive

APPENDIX B
MAJOR/SEVERE BLEEDING CASE SERIES

Case 1: TACSR Major Bleeding
ID 005: GIB

A 88-year-old man was admitted to Ramathibodi Hospital and diagnosed with non-ST elevation acute myocardial infarction (NSTEMI), heart failure (HF), and acute-on-top of chronic renal failure. His medical history was remarkable for hypertension, dyslipidemia, coronary heart disease, chronic kidney disease, and benign prostrate hypertrophy. He did not have a history of any bleeding disorder or coagulopathies.

At admission, his weight was 63 kg and his height was 1.65 m, representing a body mass index of 23.1 kg/m^2. Initial laboratory data yielded creatinine: 3.3 mg/dl, AST: 86 IU/l, ALT: 73 IU/l, haemoglobin: 9.6 g/dl, hematocrit: 28%, platelets: 252,000/cu mm, prothrombin time: 12.8 s, INR: 1.1. His creatinine clearance was 13.2 ml/min. He was treated with aspirin, clopidogrel, and the recommended dose of enoxaparin which was administered 60 mg subcutaneously every 24 hours. No coronary angiography was performed.

Twenty two hours after the second dose of enoxaparin, he had melena stool. Fecal occult blood test was confirmed. At this point, his hemoglobin was 8.9 g/dl and hematocrit was 27.2%. He remained on enoxaparin. On the fourth day, he had 2 melena stools. Hemoglobin and hematocrit were checked immediately and noted to be decreased. Hemoglobin and hematocrit were 8 g/dl and 23.4%, respectively. His blood pressure and heart rate were stable. Enoxaparin was then stopped. He was given blood transfusion with 2 units of packed red cells. In the following day, his hemoglobin and hematocrit levels returned to normal. He clinically improved in hospital and was discharged home one week later.

Case 2: GUSTO Severe Bleeding and TACSR Major Bleeding
ID 056 Gross Hematuria

A 65-year-old man with a background of diabetes, hypertension, dyslipidemia, and triple vessel disease presented with NSTEMI with HF. He did not have a history of any bleeding disorder or coagulopathies. His weight was 71.2 kg and his height was 1.6 m, representing a body mass index of 27.8 kg/m^2. He has recently been discharged from the hospital 2 days ago. Last admission, he was identified to have NSTEMI with

HF. He denied coronary artery bypass graft (CABG) surgery and had received subcutaneous enoxaparin for five days.

Initial laboratory data yielded creatinine: 1.9 mg/dl, hemoglobin: 15 g/dl, hematocrit: 44.5%, platelets: 291,000/cu mm. His creatinine clearance was 34.3 ml/min. He was treated with aspirin, clopidogrel and lower-than-recommended dose of enoxaparin which was administered 60 mg subcutaneously every 12 hours.

Five hours after the third dose of enoxaparin, he had blood in urine. After gross hematuria, he was in cardiovascular collapse with a blood pressure of 60/- mmHg. Intravenous fluids loading and dopamine drip was then started, resulting in an increase in the patient's blood pressure. Enoxaparin was then stopped. He remained on antiplatelet agents. Post-bleeding hemoglobin and hematocrit values were not found in his medical record and database. However, no blood transfusion was given.

Three day later, the cardiologist performed a coronary angiography. Angiography revealed a progressively obstructive coronary artery disease. His hemoglobin and hemoglobin after CAG were 13.5 mg/dl and 39.2%, respectively. He clinically improved in hospital and was discharged home one week later. Elective CABG surgery was performed the next admission.

Case 3: GUSTO Severe Bleeding/TACSR Major Bleeding/TIMI Major Bleeding
ID 175 ICH

A 72-year-old man was admitted secondary to NSTEMI with obstructive pneumonitis. His medical history included diabetes, hypertension, dyslipidemia, benign prostrate hypertrophy, coronary artery disease (post-CABG). In additional, he had advanced stage cancer with lymph node, esophagus, lung, and bone metastasis. He had a history of allergy to clopidogrel.

At admission, his weight was 51 kg and his height was 1.68 m. His body mass index was 18.1kg/m^2. Initial laboratory data yielded creatinine: 0.8 mg/dl, haemoglobin: 11.6 g/dl, hematocrit: 33.6%, platelets: 149,000/cu mm, prothrombin time: 11.4 s, INR: 0.95. His creatinine clearance was 58.2 ml/min. He was treated with aspirin and enoxaparin 60 mg subcutaneously every 12 hours which was higher than recommended 1 mg/kg dose. No coronary angiography was performed.

Eight hours after the fifth dose of enoxaparin, he became drowsy with right hemiplegia. Emergency brain computed tomography (CT) was done and showed a large multiseptation intraparenchymal hematoma and subarachnoid hemorrhage with left herniation, subfalcine herniation and 1.5-midline shift to right. He was intubated and ventilated. Enoxaparin and aspirin were then stopped. A full blood count showed hemoglobin: 10 g/dl, hematocrit: 30%, INR: 1.01. He was given 8 units of packed red cells and 4 units of fresh frozen plasma. His relatives declined brain surgery and resuscitation. He died 5 hours later and an autopsy was not performed. The cause of death in his medical certificate was intracranial hemorrhage from brain metastasis and anticoagulant.

Case 4: GUSTO Severe Bleeding/TACSR Major Bleeding/TIMI Major Bleeding
ID 192 Pericardial effusion

A 53-year-old man presented with syncope. At admission, his blood pressure was 70/50 mmHg and pulse rate was 123/min. His past medical history was remarkable for diabetes, hypertension, and dyslipidemia. He was a heavy smoker. His weight was 73 kg and his height was 1.69 m. (body mass index of 25.6 kg/m^2). Initial laboratory data yielded creatinine: 1.3 mg/dl, AST: 53 IU/l, ALT: 70 IU/l, hemoglobin: 14.2 g/dl, hematocrit: 42.2%, platelets: 470,000/cu mm, prothrombin time: 10.1 s, INR: 0.89. His creatinine clearance was 60.5 ml/min. He did not have a history of any bleeding disorder or coagulopathies.

In the emergency department, his electrocardiogram (ECG) showed ST-segment elevation with elevation of cardiac markers. Emergency cardiac catheterization was performed and revealed double vessel disease of left anterior descending artery and left cir-cumflex with large clot at proximal of left anterior descending artery. Percutaneous transluminal coronary angioplasty (PTCA) was performed successfully and led to re-opening of the left anterior descending. Eptifibatide (glycoprotein IIb/IIIa inhibitors) was administered intravenously at an initial 6.8 ml bolus and then was continued at 12 ml/hr for 24 hours. He was given a bolus injection of heparin 5,000 units followed by enoxaparin 60 mg subcutaneous every 12 hour which was lower-than recommendation.

Twelve hours after the first dose of enoxaparin, he was developed gingival and 50 ml of groin bleeding. His hematocrit level decreased to 34%. He had persistent chest pain and electrocardiogram showed ST depression. Twenty seven hours later, he was in cardiogenic shock with a blood pressure of 60/- mmHg. Echocardiogram demonstrated akinesia of anterior wall, thing of anteroapical wall, and pericardial effusion 0.5-0.7 cm. After that, he had gross hematuria. At this point, hematocrit level decreased to 24%. Dressler's syndrome was suspected. A dopamine drip was started. Eptifibatide and enoxaparin were then stopped. Follow-up echocardiogram showed an increased of pericardial effusion to 1.35 cm. Pericardial drainage was done to remove 50 ml of blood within pericardium. After that, he had several episodes of ventricular tachycardia (VT). Despite active resuscitation, he passed away.

Case 5: TACSR Major Bleeding
ID 082 Gross Hematuria

A 84-year-old man was referred to Ramathibodi Hospital for coronary angiography. At private hospital, he was diagnosed to have ischemic heart disease and heart failure. He was treated with furosemide, nitroglycerine, morphine, dobutamine, and ceftriaxone. His past medical history was remarkable for diabetes, hypertension, dyslipidemia, chronic kidney disease, benign prostate hypertrophy, and gout. He did not have a history of any bleeding disorder or coagulopathies. His weight was 87 kg. His height was not recorded in medical record. Laboratory data at Ramathibodi

yielded creatinine: 4.9 mg/dl, AST: 124 IU/l, ALT: 56 IU/l, haemoglobin: 9.2 g/dl, hematocrit: 28%, platelets: 79,000/cu mm, prothrombin time: 13.2 s, INR: 1.15. His creatinine clearance was 6.9 ml/min.

Four hour after arrival at Ramathibodi Hospital, he developed cardiac arrest. A cardiopulmonary resuscitation was done for 10 minutes. He was intubated and ventilated. After that, he developed upper gastrointestinal bleeding. Hematocrit was found to be 27%. He received 2 units of packed red cell, resulting in an increase of hematocrit to 30%. Dopamine and lansoprazole were started.

Emergency cardiac catheterization showed severe triple vessel disease (99% LCx, 99% LAD, CTO RCA). He had cardiac arrest during cardiac catheterization. Percutaneous transluminal coronary angioplasty (PTCA) was attempted to left circumflex. He was given a bolus injection of heparin 4,000 units followed by enoxaparin 60 mg subcutaneous every 24 hour which was lower-than recommendation. At this point, he was diagnosed to have STEMI, heart failure, acute renal failure, metabolic acidosis, and septicemia due to coagulase-negative Staphylococcus.

Fortheen hours after the second dose of enoxaparin, he had gross hematuria, fresh blood in sputum, and melena stool (50 ml). His hematocrit was decreased to 27%. He was given replacement with 4 units of packed red cells and remained on enoxaparin for five days. In the following week, he had high grade fever and was diagnosed to have ventilator-associated pneumonia with acute renal failure. He died from supraventricular tachycardia 1 day later. An autopsy was not performed.

Case 6: TACSR Major Bleeding
ID 031 Blood-Stained Sputum

A 79-year-old male patient was admitted to the hospital with typical chest pain and diagnosed to have unstable angina with heart failure. His medical history included diabetes, hypertension, and chronic kidney disease. His weight was 62 kg. His height was not recorded in medical record. He did not have a history of any bleeding disorder or coagulopathies.

Initial laboratory data yielded creatinine: 2.8 mg/dl, AST: 43 IU/l, ALT: 51 IU/l, haemoglobin: 10.2 g/dl, hematocrit: 30.4%, platelets: 224,000/cu mm, prothrombin time: 12.6 s, INR 1.09. His creatinine clearance was 10.0 ml/min. He was treated with aspirin, clopidogrel and enoxaparin 60 mg subcutaneously every 24 hours which was considered to be an appropriate. No coronary angiography was performed.

One hour after the third dose of enoxaparin, he had episodes of bloody sputum. His blood pressure and heart rate were stable. He received 2 units of packed red cells because his hematocrit level fell to 26% and remained on enoxaparin for five days. His clinical status continued to be improved and was discharged home 2 days later.

Case 7: TACSR Major Bleeding
ID 096 Blood-Stained Sputum

A 82-year-old woman was referred to Ramathibodi Hospital. She was diagnosed with NSTEMI and myasthenic crisis precipitated by pneumonia. Her past medical history was remarkable for diabetes, hypertension, dyslipidemia, and myasthenia gravis. She did not have a history of any bleeding disorder or coagulopathies. Her weight was 65 kg and her height was 1.5 m, her body mass index was 28.9 kg/m^2.

Laboratory data at Ramathibodi yielded creatinine: 1.5 mg/dl, AST: 52 IU/l, ALT: 40 IU/l, haemoglobin: 10.2 g/dl, hematocrit: 29.8%, platelets: 241,000/cu mm, prothrombin time: 12.5 s, INR: 1.04. Her creatinine clearance was 20.4 ml/min. Her NSTEMI was treated with aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 24 hour which was appropriate. No coronary angiography was performed.

Twenty two hours after the third dose of enoxaparin, she had fresh blood in sputum and bruise at left forearm. Hemoglobin level was found to be 9.7 g/dl and hematocrit level was found to be 28.6%. Prothrombin time and INR were normal. Her blood pressure and heart rate were stable. One unit of packed red cell was given. Her clinical status continued to be improved and was discharged home one week later.

Case 8: TACSR Major Bleeding
ID 167 Hematoma

A 74-year-old woman was diagnosed to have NSTEMI. Her past medical history was remarkable for hypertension and ischemic heart disease. She did not have a history of any bleeding disorder or coagulopathies. Her weight was 63.2 kg and her height was 1.57, representing a body mass index of 25.7 kg/m^2.

Laboratory data yielded creatinine: 1.2 mg/dl, AST: 210 IU/l, ALT: 137 IU/l, haemoglobin: 10.8 g/dl, hematocrit: 31%, platelets: 341,000/cu mm, prothrombin time: 11.5 s, INR: 1.01. Her creatinine clearance was 26.9 ml/min. She was treated with aspirin, clopidogrel, and enoxaparin 40 mg subcutaneous every 12 hour which was higher than recommended once daily dose.

In the third day of enoxaparin therapy, she had injection-site hematoma (5 cm.). Her hemoglobin was 12.1 g/dl and her hematocrit was 34.5%. She remained on enoxaparin and changed the injection-site. In the fourth day, her hemoglobin was found to be 8.9 g/dl and hematocrit was found to be 26.2%. Gastrointestinal bleeding was suspected, but fecal occult blood testing was negative. However, her blood pressure and heart rate were stable. Two units of packed red cell were given. Enoxaparin and aspirin were then stopped. Proton pump inhibitor was started. No gastroduadenal was performed. In the sixth day, coronary angiography revealed no significant stenosis. Her clinical status continued to be improved and was discharged home three days later.

Case 9: TACSR Major Bleeding
ID 013 Hematuria and Ecchymosis

A 48-year-old man presented with hematoma at left leg, abdomen, and INR 4.34. His past medical history was remarkable for SLE, hypertension, cirrhosis, triple vessel disease with poor LVEF, and ischemic stroke which controlled with warfarin and cilastazol. He has recently been discharged from the hospital 8 days ago. Last admission, he was identified to have STEMI and received conservative treatment with enoxaparin for five days. His weight was 56.3 kg, and his height was 1.67 m, representing a body mass index of 20.2 kg/m^2.

In the ninth day of this admission, he developed STEMI with hospital acquired pneumonia. At this point, Laboratory data yielded creatinine: 0.8 mg/dl, hemoglobin: 11.3 g/dl, hematocrit: 33.6%, platelets: 97,000/cu mm, prothrombin time: 32.4 s, INR: 2.19. His creatinine clearance was 63.1 ml/min. Warfarin was then stopped. He was treated with clopidogrel, cilastazol, and enoxaparin 60 mg subcutaneous every 12 hours which considered to be an appropriate. No coronary angiography was performed.

In the second day of enoxaparin therapy, he had blood in urine. Urinalysis confirmed hematuria with RBC>100. His blood pressure and heart rate were stable. He remained on enoxaparin. In the fourth day of enoxaparin therapy, he had new progressive ecchymosis inside part of the arm. A full blood count showed hemoglobin: 8.2 g/L, hematocrit: 24.7%, prothrombin time: 20.4 s, INR: 1.72, and anti-Xa: 0.4. He was given replacement with 2 units of packed red cells, resulting in an increase of hematocrit to 34.3%. One week later, he developed sepsis with respiratory failure. Despite active resuscitation, he passed away. An autopsy was not performed.

Case 10: TACSR Major Bleeding and TIMI Major Bleeding
ID 087 Blood-Stained Sputum

A 59-year-old man was diagnosed to have unstable angina (UA) and heart failure. His past medical history was remarkable for diabetes, hypertension, chronic kidney disease, triple vessel disease (80% RCA, 70% LAD, CTO LCx). He denied for CABG. He did not have a history of any bleeding disorder or coagulopathies. His weight was 110 kg and his height was 1.72 m, representing a body mass index of 37.2 kg/m^2.

Laboratory data yielded creatinine: 1.5 mg/dl, AST: 15 IU/l, ALT: 29 IU/l, hemoglobin: 15.5 g/dl, hematocrit: 47.2%, platelets: 266,000/cu mm. His creatinine clearance was 29.3 ml/min. He was administered aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 12 hour which is in recommended dose for his UA. Four hours after admission, he was developed cardiac arrest. Cardiopulmonary resuscitation was done. He then went into a deep coma with cardiac arrhythmia, aspiration pneumonia, and acute renal failure. He did not recover from coma and remains in a

persistent vegetative state. He was intubated and ventilated. At this point, enoxaparin was reduced to 40 mg subcutaneous every 24 hours.

12 hours after the second dose of enoxaparin, he had large quantities bloody sputum and hematuria. His hematocrit was checked and found to be 30.8% decreased compared to the admission value of 47.2%. Additional laboratory values included creatinine: 4.4 mg/dl, AST: 78 IU/l, ALT: 64 IU/l, prothrombin time 20.2 sec, INR 1.75. The following week, he was developed ventricular tachycardia and passed away.

Case 11: TACSR Major Bleeding
ID 126 GIB

A 65-year-old woman was referred to Ramathibodi Hospital for coronary angiography. She was diagnosed to have NSTEMI with congestive heart failure and cardiogenic shock. At private hospital, she was administered dopamine, aspirin, clopidogrel, and 2 doses of enoxaparin 40 mg subcutaneous every 12 hours. Her past medical history was remarkable for diabetes, hypertension, dyslipidemia, coronary artery disease post-PCI, and poor LVEF (25%). She did not have a history of any bleeding disorder or coagulopathies. Her weight was 46 kg and her height was 1.5 m, representing a body mass index of 20.4 kg/m^2.

At Ramathibodi, laboratory data yielded creatinine: 1.5 mg/dl, AST: 120 IU/l, ALT: 211 IU/l, haemoglobin: 11.6 g/dl, hematocrit: 35.5%, platelets: 241,000/cu mm, prothrombin time: 11.2 s, INR: 0.98. Her creatinine clearance was 21.3 ml/min. She was treated with aspirin, clopidogrel, and enoxaparin 40 mg subcutaneous every 12 hour which was higher than recommended once daily dose. She remained on intravenous dopamine.

Five hours after the first dose of enoxaparin, she developed coffee grounds nasogastric aspirate. Her hemoglobin was found to be 9.9 g/dl and her hematocrit was found to be 30%. No gastroduadenal was performed. Enoxaparin and antiplatelet drugs remained on until the time of CAG. Four day later, angiography revealed double vessel disease with long segment occlusion of the right coronary artery. Percutaneous transluminal coronary angioplasty (PTCA) was attempted and success to re-open the right coronary artery. Eptifibatide, glycoprotein IIb/IIIa inhibitor, was administered intravenously 7 ml/hr for 24 hours. After PCI, she remained on enoxaparin. Ten hours after the seventh dose of enoxaparin, she had hematuria and blood-stained sputum. She received 2 units of packed red cells because his hematocrit level fell to 26%. In the following day, her hemoglobin and hematocrit levels returned to normal. Her blood pressure and heart rate was stable. Her clinical status continued to be improved and was discharged home one week later.

Case 12: TACSR Major Bleeding
ID 176 GIB

A 69-year-old man was diagnosed to have STEMI and heart failure. His past medical history was remarkable for diabetes, hypertension, chronic kidney disease stage. He was waiting for an arteriovenous fistula (AVF) placement. He did not have a history of any bleeding disorder or coagulopathies. His weight was 51.7 kg. His height was not found in medical record.

Laboratory data yielded creatinine: 7.2 mg/dl, AST: 25 IU/l, ALT: 36 IU/l, hemoglobin: 11.2 g/dl, hematocrit: 34.6%, platelets: 107,000/cu mm. His creatinine clearance was 3.4 ml/min. He received conservative treatment for STEMI because he had a contraindication to thrombolytic therapy. He was administered aspirin, clopidogrel, and enoxaparin 40 mg subcutaneous every 24 hours which was lower-than-recommendation.

Fourteen hours after the first dose of enoxaparin, he had 5 melena stools. Fecal occult blood tests were confirmed. His blood pressure and heart rate were stable. He received 2 units of packed red cells because his hematocrit level fell to 26%. He remained on enoxaparin and antiplatelet agents. Intravenous lansoprazole was then started. No gastroduadenal endoscopy was performed. One week later, he developed sepsis with metabolic acidosis and recurrent myocardial infarction. Despite continuing attempts at resuscitation, he died.

Case 13: TACSR Major Bleeding
ID 200 GIB

A 59-year-old woman was diagnosed to have NSTEMI and heart failure. Her past medical history was remarkable for diabetes, hypertension, dyslipidemia, triple vessel disease post-CABG, and heart failure. He did not have a history of any bleeding disorder or coagulopathies. Her weight was 52 kg and her height was 1.5 m, representing a body mass index of 23.1 kg/m^2.

Laboratory data yielded creatinine: 1.9 mg/dl, AST: 14 IU/l, ALT: 29 IU/l, hemoglobin: 9.9 g/dl, hematocrit: 28.2%, platelets: 287,000/cu mm. Her creatinine clearance was 16.6 ml/min. She was treated with aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 24 hours which was appropriate.

One hour after the second dose of enoxaparin, she was developed haematemesis and subsequently black tarry stools. Fecal occult blood tests were confirmed. At this point, her hemoglobin was found to be 8.2, and her hematocrit was found to be 23.8%. Her blood pressure and heart rate were stable. Enoxaparin was then stopped. Oral double dose of proton pump inhibitor was then started. She was given replacement with 2 units of packed red cells, resulting in an increase of hematocrit to 36%. No gastroduadenal endoscopy was performed. Her clinical status continued to be improved and was discharged home three days later.

Case 14: TACSR Major Bleeding
ID 205 GIB

A 69-year-old woman presented with severe abdominal pain with blood pressure drops to 90/60 mmHg. Her past medical history was remarkable for diabetes, hypertension, and osteoporosis. She did not have a history of any bleeding disorder or coagulopathies. In additional, she had history of NSAIDs self-medication. Her weight was 50 kg. Her height was not found in medical record.

She was diagnosed to have perforated peptic ulcer with cardiogenic shock. After the emergency surgery to closure the perforation, she was given replacement with 11 units of packed red cells, resulting in an increase of hematocrit level to normal. One day after surgery, she developed STEMI with hyperkalemia, atrial fibrillation, and multiple organism septicemia. Norepinephrine was then started. At this point, laboratory data yielded creatinine: 2.2 mg/dl, AST: 17 IU/l, ALT: 28 IU/l, hemoglobin: 11.3 g/dl, hematocrit: 30.4%, platelets: 72,000/cu mm, prothrombin time 17.4 sec, INR 1.5. His creatinine clearance was 13.6 ml/min. She received conservative treatment because her contraindication to thrombolytic therapy. She was administered enoxaparin 60 mg subcutaneous every 24 hours which was appropriate without antiplatelet agent.

After the second dose of enoxaparin, she had coffee grounds nasogastric aspirate. A full blood count showed hemoglobin: 9.7 mg/dl, hematocrit: 27.4%. She was given replacement with 4 units of packed red cells. No gastroduadenal endoscopy was performed. Intravenous esomeprazole was then started. She remained on enoxaparin. Four day later, she died from progressive sepsis and multiple organ failure. An autopsy was not performed.

Case 15: TACSR Major Bleeding
ID 218 Blood-Stained Sputum

A 77-year-old woman was referred to Ramathibodi Hospital for coronary angiography. Her past medical history was remarkable for diabetes. She did not have a history of any bleeding disorder or coagulopathies. Her weight was 52.4 kg and her height was 1.55 m, representing a body mass index of 21.8 kg/m^2. At primary hospital, she was diagnosed to have NSTEMI with heart failure, respiratory failure, and hematuria. She was administered enoxaparin 60 mg subcutaneous every 12 hours, dobutamine, furosemide, aspirin, clopidogrel, amiodarone, and bisoprolol.

At Ramathibodi Hospital, laboratory data yielded creatinine: 1.8 mg/dl, AST: 62 IU/l, ALT: 74 IU/l, haemoglobin: 8.7 g/dl, hematocrit: 29.9%, platelets: 108,000/cu mm, prothrombin time: 11.9 s, INR: 1.03. Her creatinine clearance was 16.8 ml/min. Angiography revealed triple vessel disease with occlusion at left main coronary artery. Percutaneous transluminal coronary angioplasty (PTCA) was attempted and success to re-open right coronary artery and left anterior descending. She was administered

aspirin and clopidogrel. Enoxaparin 40 mg subcutaneous every 24 hours which was lower-than-recommendation was administered until the time of CAG.

Four hours after the first dose of enoxaparin, she developed bloody sputum. Hemoglobin was found to be 8.3 g/dl and hematocrit was found to be 25.8%. She was given replacement with 2 units of packed red cells, resulting in an increase of hematocrit to 28%. In the sixth day, percutaneous transluminal coronary angioplasty (PTCA) was attempted and success to re-open left cir-cumflex and left main coronary artery. After PCI, she developed acute renal failure. The renal replacement therapy was started. Her clinical status continued to be improved and was discharged home one week later.

Case 16: TASR Major Bleeding
ID 222 Hematuria

A 82-year-old woman was referred to Ramathibodi Hospital for coronary angiography. Her past medical history was remarkable for hypertension, dyslipidemia, and osteoporosis. Her weight was 60 kg. Her height was not found in medical record. She did not have a history of any bleeding disorder or coagulopathies. At primary hospital, she was diagnosed to have NSTEMI with heart failure and cardiogenic shock. She was administered isosorbide dinitrate and bronchodilator.

At Ramathibodi, laboratory data yielded creatinine: 2.2 mg/dl, AST: 46 IU/l, ALT: 38 IU/l, haemoglobin: 12.4 g/dl, hematocrit: 36.9%, platelets: 277,000/cu mm, prothrombin time: 12.2 s, INR: 1.07. Her creatinine clearance was 13.1 ml/min. She was administered aspirin and clopidogrel. Enoxaparin 60 mg subcutaneous every 24 hours which considered to be an appropriate was administered until the time to CAG. Angiography revealed triple vessel disease with severe occlusion at left main coronary artery. Percutaneous transluminal coronary angioplasty (PTCA) was attempted but failed to re-open the coronary artery.

Fourteen hours after received enoxaparin, she developed hematuria and fresh blood in sputum. Her hematocrit was found to be 28%. She was given replacement with 2 units of packed red cells, resulting in an increase of hematocrit to 31%. Three day later, she developed atrial fibrillation, hypotension, and cardiogenic shock. Her relatives were declined resuscitation. She died three hour later. An autopsy was not performed.

Case 17: TACSR Major Bleeding
ID 223 Blood-Stained Sputum

A 70-year-old man was referred to Ramathibodi Hospital for coronary angiography. His past medical history was remarkable for diabetes, hypertension, and chronic kidney disease. His weight was 74.5 kg. His height was not found in medical record. He did not have a history of any bleeding disorder or coagulopathies. At

primary hospital, he was diagnosed to have UA with heart failure. He was administered enoxaparin 40 mg subcutaneous every 12 hours, aspirin, clopidogrel, dopamine, and furosemide.

At Ramathibodi, laboratory data yielded creatinine: 3.3 mg/dl, AST: 25 IU/l, ALT: 39 IU/l, haemoglobin: 11.1 g/dl, hematocrit: 32%, platelets: 140,000/cu mm, prothrombin time: 16 s, INR: 1.38. His creatinine clearance was 11.4 ml/min. He was administered aspirin and clopidogrel. Enoxaparin 60 mg subcutaneous every 24 hours which was lower-than-recommendation was administered until the time to CAG.

Three hours after the first dose of enoxaparin, she was developed blood-stained sputum. Hemoglobin was found to be 9.2 g/dl and hematocrit was found to be 28.7%. Subcutaneous enoxaparin was replaced by intravenous heparin. No blood transfusion was given. The following day, enoxaparin was initiated at same dose. After that, he was developed several episodes of bloody sputum. His hematocrit was found to be 25%. He was given replacement with 2 units of packed red cells, resulting in an increase of hematocrit to 30.2%. In the sixth day, coronary angiography was performed. Angiography revealed triple vessel disease. Percutaneous transluminal coronary angioplasty (PTCA) was attempted to re-open the left main coronary artery and left anterior descending. After that, he was developed acute renal failure with pneumonia and septicemia. He died 15 days later. An autopsy was not performed.

Case 18: TACSR Major Bleeding
ID 274 GIB

A 76-year-old man presented with syncope. His past medical history was remarkable for chronic anemia, diabetes, hypertension, and severe aortic stenosis. His weight was 60.6 kg and his height was 1.76 m, representing a body mass index of 19.7 kg/m^2.

Laboratory data yielded creatinine: 1.9 mg/dl, AST: 18 IU/l, ALT: 28 IU/l, hemoglobin: 7.9 g/dl, hematocrit: 24%, platelets: 214,000/cu mm. His creatinine clearance was 28.5 ml/min. He was diagnosed to have NSTEMI secondary to anemia. He denied coronary angiography. He was treated with aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 24 hours which was appropriate.

Four hour after the first dose of enoxaparin, he was developed haematemesis and subsequently black tarry stools. Fecal occult blood tests were confirmed. His blood pressure and heart rate were stable. He was given replacement with 4 units of packed red cells, resulting in an increase of hematocrit to 32%. Intravenous proton pump inhibitor was then started. No gastroduadenal endoscopy was performed. She remained on enoxaparin for five days. Her clinical status continued to be improved and was discharged home six days later.

Case 19: TACSR Major Bleeding
ID 289 GIB

A 54-year-old man presented with typical chest pain during hemodialysis. His past medical history was remarkable for hypertension, dyslipidemia, fatty liver, end stage renal failure, and triple vessel disease. He was waiting for CABG and remained on hemodialysis twice weekly. His weight was 67 kg and his height was 1.65 m, representing a body mass index of 24.6 kg/m^2.

Laboratory data yielded AST: 2 IU/l, ALT: 38 IU/l, hemoglobin: 12.2 g/dl, hematocrit: 35.8%, platelets: 162,000/cu mm, prothrombin time 11.4 sec, INR 1.00. He was diagnosed to have NSTEMI and was administered aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 24 hours which considered to be an appropriate.

In the seventh day of enoxaparin therapy, he developed lower gastrointestinal bleeding. Fecal occult blood tests were confirmed. His blood pressure and heart rate were stable. Hemoglobin was found to be 9.1 g/dl and hematocrit was found to be 26.5%. He was given replacement with 3 units of packed red cells, resulting in an increase of hematocrit to 34%. Antiplatelet agents were then stopped. Intravenous proton pump inhibitor was then started and he remained on enoxaparin until the time to CABG. His clinical status continued to be improved and was discharged home one week after CABG.

Case 20: TACSR Major Bleeding
ID 346 Blood-Stained Sputum

A 82-year-old woman was referred to Ramathibodi Hospital. Her past medical history was remarkable for diabetes, hypertension, and ischemic heart disease. He did not have a history of any bleeding disorder or coagulopathies. Her weight was 60.9 kg and her height was 1.54 m, representing a body mass index of 25.7 kg/m^2. At primary hospital, she was diagnosed to have acute coronary syndrome and received isosorbide dinitrate.

At Ramathibodi Hospital, laboratory data yielded creatinine: 1.7 mg/dl, AST: 39 IU/l, ALT: 38 IU/l, haemoglobin: 9.9 g/dl, hematocrit: 30.6%, platelets: 174,000/cu mm. Her creatinine clearance was 17.6 ml/min. She was administered aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 24 hours which was appropriate.

Five hours after the first dose of enoxaparin, she was developed blood-stained sputum. Hemoglobin was found to be 8.9 g/dl and hematocrit was found to be 26.8%. She was administered 2 units of packed red cell. Enoxaparin was then stopped. The following day, his hematocrit returned to 31%. Enoxaparin was initiated with reduced dose to 40 mg subcutaneous every 24 hours. She developed several episodes of bloody sputum. She was given replacement with 2 units of packed red cells, resulting in an increase of hematocrit to normal. In the eleventh day, coronary angiography was

performed. Angiography revealed triple vessel disease with left main disease. Percutaneous transluminal coronary angioplasty (PTCA) was attempted but failed to re-open the coronary artery. After CAG, he developed acute renal failure, atrial fibrillation, septicemia, and died 20 days later. An autopsy was not performed.

Case 21: GUSTO Severe Bleeding/TACSR Major Bleeding
ID 360 GIB

A 43-year-old woman presented with sudden dyspnea and respiratory distress. Her past medical history was remarkable for diabetes, hypertension, coronary artery disease with functional class III, and end stage renal disease. She did not have a history of any bleeding disorder or coagulopathies. She was waiting for renal replacement therapy and has recently been discharged from the hospital 5 days ago. Last admission, she was identified to have with fluid overload and received intravenous furosemide.

This admission, her weight was 69 kg and her height was 1.58 m, representing a body mass index of 27.7 kg/m^2. Initial laboratory data yielded creatinine: 9.3 mg/dl, AST: 39 IU/l, ALT: 26 IU/l, hemoglobin: 23 g/dl, hematocrit: 36.4%, platelets: 293,000/cu mm. Her creatinine clearance was 2.8 ml/min. She was diagnosed to have fluid overload with UA and pneumonia. She was intubated and ventilated. Hemodialysis was then started. She was treated with aspirin and clopidogrel, and enoxaparin 60 mg subcutaneously every 24 hours which was appropriate. She denied coronary angiography.

Three hour after the first dose of enoxaparin, she developed coffee grounds nasogastric aspirate (200 ml). Her hematocrit was checked immediately and noted to be decreased to 26%. Enoxaparin and antiplatelet agents were then stopped. Intravenous omeprazole was then started. Two hour after bleeding, her blood pressure was dropped to 70/43 mmHg. She had decreasing pulse oximeter blood oxygen saturation. Her relatives were declined for resuscitation. She died 1 hour later. An autopsy was not performed.

Case 22: TACSR Major Bleeding
ID 362 Blood-Stained Sputum

A 48-year-old woman was referred to Ramathibodi Hospital. Her past medical history was remarkable for diabetes, hypertension, dyslipidemia, coronary artery disease, ischemic stroke, and bipolar disorder. She did not have a history of any bleeding disorder or coagulopathies. Her weight was 90 kg and her height was 1.6 m, representing a body mass index of 35.2 kg/m^2. At primary hospital, she was diagnosed to have NSTEMI with lithium overdose, septicemia, and acute renal failure.

At Ramathibodi Hospital, laboratory data yielded creatinine: 1.6 mg/dl, AST: 41 IU/l, ALT: 42 IU/l, haemoglobin: 9.6 g/dl, hematocrit: 28.8%, platelets: 329,000/cu

mm. prothrombin time 12.7 s, INR 1.10. Her creatinine clearance was 21.1 ml/min. She was administered aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 12 hours which was higher than recommended once daily dose. No coronary angiography was performed.

One hour after the first dose of enoxaparin, she developed hematoma at left forearm. Five hours after the second dose, she had blood-stained sputum. A full blood count showed hemoglobin: 8.4, hematocrit: 24.6%. Her blood pressure and heart rate were stable. Enoxaparin and antiplatelet agents were then stopped. She was given replacement with 1 unit of packed red cells. Her clinical status continued to be improved and was discharged home four week later.

Case 23: TACSR Major Bleeding
ID 368 GIB

A 61-year-old man was diagnosed to have NSTEMI with heart failure. His past medical history was remarkable for diabetes, hypertension, chronic kidney disease, chronic anemia, and double vessel disease post-PCI to Left cir-cumflex . His weight was 87 kg and his height was 1.7 m, representing a body mass index of 30.1 kg/m^2.

Initial laboratory data yielded creatinine: 2.7 mg/dl, hemoglobin: 9 g/dl, hematocrit: 27%, platelets: 333,000/cu mm, prothrombin time 11.8, INR 1.03. His creatinine clearance was 14.8 ml/min. He was treated with aspirin, clopidogrel, and enoxaparin administered 60 mg subcutaneously every 24 hours which was lower-than recommendation. No coronary angiography was performed.

Two hour after the first dose of enoxaparin, he developed fresh blood (50 ml) and coffee grounds nasogastric aspirate (170 ml). His hematocrit was checked immediately and noted to be decreased to 26%. Enoxaparin and antiplatelet agents were then stopped. Intravenous omeprazole was then started. He was given replacement with 1 unit of packed red cells. The following day, he received 2 units of packed red cell because his hematocrit level fell to 23%. Blood pressure and heart rate were stable. Gastroduodenal endoscopy was performed and revealed 2 small clean based gastric ulcers. His clinical status continued to be improved and was discharged home five days later.

Case 24: TACSR Major Bleeding
ID 394 GIB

A 72-year-old man was referred to Ramathibodi hospital. His weight was 58 kg and his height was 1.6 m, representing a body mass index of 22.7 kg/m^2. His past medical history was remarkable for diabetes and coronary artery disease. He did not have a history of any bleeding disorder or coagulopathies. He has recently been discharged from the hospital 1 week ago. Last admission, He was identified to have

triple vessel disease and percutaneous transluminal coronary angioplasty (PTCA) was attempted to re-open the left anterior descending.

At private hospital, he presented with chest pain. Angiography revealed stent thrombosis at mid left anterior descending. The balloon dilatation was performed and eptifibatide was initiated. He was diagnosed to have subacute stent thrombosis with cardiogenic shock and heart failure. In additional, his echocardiogram showed clot in LV. Warfarin was initiated and he developed upper gastrointestinal bleeding one day before refer to Ramathibodi Hospital.

At Ramathibodi Hospital, laboratory data yielded creatinine: 2.0 mg/dl, AST: 256 IU/l, ALT: 90 IU/l, haemoglobin: 9.1 g/dl, hematocrit: 26.5%, platelets: 450,000/cu mm. prothrombin time 27.5 sec, INR 2.18. His creatinine clearance was 26.9 ml/min. Warfarin was then stopped. He was given replacement with 2 units of packed red cells, resulting in an increase in hematocrit to 35%. He was treated with aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 12 hours which was higher than recommended once daily dose.

After the second dose of enoxaparin, he was developed coffee grounds nasogastric aspirate. Hematocrit was found to be 27.5%. Enoxaparin was then stopped. Intravenous lansoprazole was then started. He was given replacement with 2 units of packed red cells. No gastroduadenal endoscopy was performed. The following day, hemotocrit level returned to normal. His clinical status continued to be improved and was discharged home 2 weeks later.

Case 25: TACSR Major Bleeding
ID 421 GIB

A 81-year-old man was diagnosed to have COPD with acute exacerbation. His past medical history was remarkable for diabetes, chronic kidney disease, ischemic cardiomyopathy with poor LVEF (20%), and atrial fibrillation controlled with warfarin. His weight was 63.2 kg and his height was 1.55 m, representing a body mass index of 26.3 kg/m^2.

In the second day, he developed UA with heart failure. At this point, laboratory data yielded creatinine: 2.6 mg/dl, AST: 25 IU/l, ALT: 26 IU/l, hemoglobin: 10.6 g/dl, hematocrit: 31.7%, platelets: 152,000/cu mm, prothrombin time 17.9 sec, INR 1.5. His creatinine clearance was 14.6 ml/min. He was administered aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 24 hours which was appropriate.

Ten hours after the first dose of enoxaparin, he was developed bleeding via endotracheal tube. Enoxaparin and antiplatelet drugs were then stopped. The following day, he had bleeding per gum, hematoma at tongue, and fresh blood in sputum. A full blood count showed hemoglobin: 9.3 mg/dl, hematocrit: 27.1%, prothrombin time 20.7 sec, and INR 1.71. He was given replacement with 2 units of fresh fresh plasma. Two days later, he developed ventricular tachycardia and cardiac arrest. A cardiopulmonary resuscitation was done. He then went into a deep coma with acute

renal failure and ischemic hepatitis. His relatives denied hemodialysis and he died 4 days later. An autopsy was not performed.

Case 26: TASR Major Bleeding
ID 466 Hematoma

A 77-year-old man was referred to Ramathibodi Hospital for coronary angiography. His weight was 70 kg and his height was 1.58 m, representing a body mass index of 28 kg/m^2. His past medical history was remarkable for diabetes hypertension, and dyslipidemia. He did not have a history of any bleeding disorder or coagulopathies.

At Ramathibodi Hospital, laboratory data yielded creatinine: 0.7 mg/dl, AST: 54 IU/l, ALT: 43 IU/l, haemoglobin: 10.9 g/dl, hematocrit: 31%, platelets: 458,000/cu mm. prothrombin time 11.5 sec, INR 1.0. His creatinine clearance was 71.8 ml/min. He was diagnosed to have NSTEMI. Angiography revealed 95% occlusion at left anterior descending with large clot in left main coronary artery. Percutaneous transluminal coronary angioplasty (PTCA) was attempted to re-open the left anterior descending. Eptifibatide was administered intravenously at an initial 6.2 ml bolus and then was continued at 11 ml/hr for 24 hours. Post-CAG hematocrit was 30%. He was administered aspirin, clopidogrel, and enoxaparin 60 mg subcutaneous every 12 hours which was lower-than-recommendation.

After the third dose of enoxaparin, he developed bleeding and hematoma (1x1 inch) both groin. A full blood count showed hemoglobin: 8.3 mg/dl, hematocrit: 23.2%. He was given replacement with 3 units of packed red cells. The following day, his hematocrit level returned to normal. His clinical status continued to be improved and was discharged home three days later.

Case 27: TACSR Major Bleeding/TIMI Major Bleeding
ID 261 GIB

A 65-year-old man with hypertrophic obstructive cardiomyopathy was admitted to Ramathibodi Hospital for alcohol septal ablation. His weight was 63 kg and his height was 1.7 m, representing a body mass index of 21.8 kg/m^2. He did not have a history of any bleeding disorder or coagulopathies.

During the procedure, he developed cardiac arrhythmia, anterior wall myocardial infarction, complete heart block and pulmonary edema. He was intubated and ventilated. A dopamine drip was initiated. At this point, laboratory data yielded creatinine: 1.7 mg/dl, AST: 100 IU/l, ALT: 41 IU/l, hemoglobin: 15.3 g/dl, hematocrit: 46.6%, platelets: 134,000/cu mm, prothrombin time 14.3 s, INR 1.19. His creatinine clearance was 37.1 ml/min. He was given aspirin and enoxaparin 60 mg subcutaneous every 12 hours which considered to be an appropriate.

Three hours after the first dose, he was developed blood-stained sputum. He remained on enoxaparin. Eleven hours after the forth dose of enoxaparin, he was developed coffee grounds nasogastric aspirate and melena stool (200 ml). His hemoglobin was found to be 10.1 g/dl and hematocrit was found to be 29.9%. Enoxaparin was reduced to 60 mg subcutaneous every 24 hours and remained on for two days. Intravenous omeprazole was then started. He was given replacement with 1 unit of packed red cell. The following day, his hematocrit was found to be 32.5%. His clinical status continued to be improved and was discharged home five days later.

Case 28: TACSR Major Bleeding
ID 233 GIB

A 55-year-old man presented with typical chest pain. His past medical history was hypertension, dyslipidemia, chronic kidney disease , and triple vessel disease. He was waiting for CABG and did not have a history of any bleeding disorder or coagulopathies. His weight was 71.5 kg and his height was 1.67 m, representing a body mass index of 25.8 kg/m^2. He has recently been discharged from the hospital 2 week ago. Last admission, he was identified to have UA and atrovastatin induced rhabdomyolysis. At date discharged, his hematocrit was 40%.

This admission, laboratory data yielded creatinine: 2.2 mg/dl, AST: 43 IU/l, ALT: 97 IU/l, haemoglobin: 9.6 g/dl, hematocrit: 28.4%, platelets: 249,000/cu mm. His creatinine clearance was 19.2 ml/min. He was diagnosed to have anemia induced UA and was given replacement of 2 units of packed red cells, resulting in an increase of hematocrit to 30%. Fecal occult blood tests and ultrasound for abdominal hematoma were negative. Thus, he was administered aspirin, clopidogrel and enoxaparin 60 mg subcutaneous every 12 hours which was higher than recommended once daily dose.

Six hour after the second dose of enoxaparin, he was developed melena stool. His hematocrit was found to be 26.4%. His blood pressure and heart rate were stable. Enoxaparin and antiplatelet agents were then stopped. Proton pump inhibitor was changed from oral to intravenous route. He was given replacement of 2 units of packed red cells. Gastroduadenal endoscopy was unremarkable. His clinical status continued to be improved and was discharged home two weeks later.

APPENDIX C
BLEEDING CASE SUMMARY

1. Enoxaparin excess dose group

No.	ID	Sex	Age (years)	Diagnosis	Weight (kg)	CrCl (ml/min)	Bleeding severity	
							GUSTO	TIMI
1	3	Male	86	NSTEMI	65.5	27.3	Mild	Minimal
2	11	Female	80	UA	53	32.8	Mild	Minimal
3	28	Female	70	NSTEMI	75.7	22.8	Mild	Minimal
4	38	Female	84	NSTEMI	70	26.3	Mild	Minimal
5	116	Male	83	NSTEMI	67	18.6	Mild	Minimal
6	125	Male	78	STEMI	48.5	35.9	Mild	Minimal
7	127	Female	89	STEMI	40.6	28.7	Mild	Minimal
8	160	Male	57	NSTEMI	81	17.2	Mild	Minimal
9	161	Female	81	UA	43	29.3	Mild	Minimal
10	177	Female	78	NSTEMI	47	29.5	Mild	Minimal
11	183	Female	50	STEMI	52	81.2	Mild	Minimal
12	204	Male	80	STEMI	48	49.9	Mild	Minor
13	206	Male	82	STEMI	54	29.8	Mild	Minimal
14	230	Male	72	STEMI	49	42.1	Mild	Minimal
15	240	Male	70	STEMI	62	17.2	Mild	Minor
16	262	Male	47	NSTEMI	54	99.6	Mild	Minimal
17	265	Male	67	NSTEMI	52	101.9	Mild	Minimal
18	272	Female	84	NSTEMI	51	14.6	Mild	Minimal
19	273	Female	86	NSTEMI	50	20.2	Mild	Minimal
20	275	Male	74	NSTEMI	61	28.1	Mild	Minimal
21	418	Female	71	NSTEMI	56	21.0	Mild	Minimal
22	462	Female	80	UA	38	12.5	Mild	Minimal

2. Enoxaparin recommended dose group

No.	ID	Sex	Age (years)	ACS groups	Weight (kg)	CrCl (ml/min)	Bleeding severity	
							GUSTO	TIMI
1	17	Female	71	UA	58	43.4	Mild	Minimal
2	29	Male	55	STEMI	69	23.6	-	Minor
3	37	Female	64	UA	59	44.4	Mild	Minimal
4	65	Male	82	NSTEMI	60	34.5	Mild	Minimal
5	88	Female	48	NSTEMI	59	38.0	Mild	Minimal
6	98	Male	83	NSTEMI	58	39.3	Mild	Minimal
7	109	Male	63	NSTEMI	52	7.1	Mild	Minimal
8	111	Female	73	NSTEMI	61	15.0	Mild	Minimal
9	123	Female	90	NSTEMI	50	25.9	Mild	Minimal
10	147	Female	80	STEMI	61	42.4	Mild	Minimal
11	155	Female	64	NSTEMI	59	55.2	Mild	Minimal
12	159	Male	58	STEMI	59	71.2	Mild	Minimal

No.	ID	Sex	Age (years)	ACS groups	Weight (kg)	CrCl (ml/min)	Bleeding severity	
							GUSTO	TIMI
13	165	Female	81	STEMI	45	29.3	Mild	Minor
14	173	Male	61	STEMI	62	62.4	Mild	Minimal
15	180	Male	86	NSTEMI	59	8.8	Mild	Minimal
16	185	Male	62	STEMI	59	71.0	Mild	Minimal
17	189	Male	77	STEMI	56	39.9	Mild	Minor
18	198	Male	45	STEMI	56	82.8	Mild	Minimal
19	208	Male	76	STEMI	64	7.5	Mild	Minimal
20	237	Male	63	STEMI	50	18.4	Mild	Minimal
21	239	Female	63	NSTEMI	51	1.9	Mild	Minimal
22	286	Male	79	STEMI	67	14.1	Mild	Minimal
23	307	Male	50	STEMI	62	95.9	Mild	Minimal
24	310	Male	64	NSTEMI	65	28.9	Mild	Minimal
25	317	Female	48	STEMI	58	74.4	Mild	Minimal
26	321	Male	81	STEMI	63	46.9	Mild	Minimal
27	323	Male	72	STEMI	56	22.9	Mild	Minimal
28	329	Female	72	NSTEMI	56	33.5	Mild	Minimal
29	338	Male	83	NSTEMI	62	14.1	Mild	Minimal
30	366	Female	60	NSTEMI	59	34.7	Mild	Minimal
31	372	Female	69	NSTEMI	66	16.1	Mild	Minimal
32	377	Male	56	NSTEMI	65	59.7	Mild	Minimal
33	379	Male	79	NSTEMI	61	30.0	Mild	Minimal
34	380	Female	55	NSTEMI	60	83.9	Mild	Minimal
35	386	Male	57	NSTEMI	63	60.5	Mild	Minimal
36	408	Female	79	NSTEMI	57	32.8	Mild	Minimal
37	409	Female	58	STEMI	62	66.3	Mild	Minimal
38	413	Male	74	NSTEMI	61	9.6	Mild	Minimal
39	440	Male	52	NSTEMI	65	2.0	Mild	Minimal
40	448	Male	69	UA	57	20.8	Mild	Minimal
41	458	Male	38	NSTEMI	63	37.9	Mild	Minimal
42	459	Female	55	NSTEMI	63	57.9	Mild	Minimal
43	468	Female	67	NSTEMI	50	6.1	Mild	Minimal
44	469	Female	67	NSTEMI	46	21.3	Mild	Minimal
45	477	Male	45	STEMI	60	98.9	Mild	Minimal

3. Enoxaparin lower-than-recommended dose group

No.	ID	Sex	Age (years)	ACS groups	Weight (kg)	CrCl (ml/min)	Bleeding severity	
							GUSTO	TIMI
1	25	Male	76	NSTEMI	64	17.9	Mild	Minimal
2	40	Male	47	STEMI	76	39.9	Mild	Minimal
3	58	Female	86	UA	42	36.5	Mild	Minimal
4	59	Male	66	NSTEMI	77	15.4	Mild	Minimal
5	76	Female	61	UA	70	39.1	Mild	Minimal
6	91	Male	80	NSTEMI	66	39.6	Mild	Minimal
7	114	Female	57	NSTEMI	71	39.6	Mild	Minimal
8	129	Female	76	NSTEMI	54	19.2	Mild	Minor
9	144	Female	72	NSTEMI	70	12.8	Mild	Minimal
10	169	Female	71	NSTEMI	54	3.4	Mild	Minimal

No.	ID	Sex	Age (years)	ACS groups	Weight (kg)	CrCl (ml/min)	Bleeding severity	
							GUSTO	TIMI
11	172	Male	50	STEMI	70	45.1	Mild	Minimal
12	178	Male	65	STEMI	71	41.3	Mild	Minimal
13	186	Male	65	STEMI	48	33.3	Mild	Minimal
14	193	Male	67	NSTEMI	68	36.6	Mild	Minimal
15	194	Male	47	NSTEMI	80	49.3	Mild	Minimal
16	216	Male	72	NSTEMI	74	56.6	Mild	Minimal
17	228	Male	62	NSTEMI	80	53.3	-	Minor
18	242	Male	59	UA	69	74.2	Mild	Minimal
19	245	Female	53	NSTEMI	68	73.0	Mild	Minimal
20	249	Male	44	STEMI	83	75.3	Mild	Minimal
21	251	Male	79	STEMI	47	44.3	Mild	Minimal
22	257	Male	48	STEMI	72	46.0	Mild	Minimal
23	258	Male	65	STEMI	67	56.4	Mild	Minimal
24	268	Male	61	STEMI	73	69.5	Mild	Minimal
25	271	Female	63	NSTEMI	53	38.8	Mild	Minimal
26	279	Male	79	NSTEMI	52	14.1	Mild	Minimal
27	284	Male	72	STEMI	79	36.6	Mild	Minimal
28	302	Female	58	STEMI	55	52.4	Mild	Minimal
29	325	Male	55	NSTEMI	68	44.8	Mild	Minimal
30	339	Male	87	UA	69	32.1	Mild	Minimal
31	358	Male	49	NSTEMI	66	104.2	Mild	Minimal
32	375	Male	63	NSTEMI	70	55.7	Mild	Minimal
33	395	Male	48	STEMI	76	73.9	Mild	Minimal
34	397	Male	46	STEMI	71	48.0	Mild	Minimal
35	401	Male	50	STEMI	73	62.5	Mild	Minimal
36	403	Female	71	STEMI	40	37.9	Mild	Minimal
37	424	Male	53	NSTEMI	72	47.1	Mild	Minimal
38	435	Female	53	NSTEMI	83	35.6	Mild	Minimal
39	441	Male	68	STEMI	75	53.6	Mild	Minimal
40	456	Female	66	NSTEMI	93	73.3	Mild	Minimal
41	470	Female	63	NSTEMI	68	51.9	Mild	Minimal

APPENDIX D

STATISTICAL ANALYSIS USING STATA

1. Patient characteristics

1.1 ID: summarize to check the number of patients

```
use "D:\Original\Gen.dta"
sum
keep id
sort id
save "D:\ID_total_359.dta"
```

1.2 Diagnosis: get the number (%) of patients with UA, NSTEMI, and STEMI

```
use "D:\Original\Gen.dta"
sum
keep id dx
tab dx
sort id
save "D:\Dx.dta"
```

1.3 Age: creates age and summarize mean of age according to the diagnosis

```
use "D:\Original\FDose.dta"
gen datebirth=mdy(mob ,dob, yob)
gen dateadmit=mdy(moa ,doa, yoa)
gen agedate=abs(dateadmit-datebirth)
gen ageyr=agedate/365.25
gen age=round(ageyr, 1)
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum age
save "D:\Age.dta"
sort id
merge id using "D:\Dx.dta"
tab _merge
drop _merge
sum age if dx==0
sum age if dx==1
sum age if dx==2
```

1.4 Gender: summarize proportion of gender according to the diagnosis

```
use "D:\Original\FDose.dta"
keep id gender
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
tab gender
sort id
save "D:\Gender.dta"
merge id using "D:\Dx.dta"
tab _merge
drop _merge
tab gender if dx==0
tab gender if dx==0
tab gender if dx==0
```

1.5 Weight: Creates weight and summarize mean of weight

```
use "D:\Original\FDose.dta"
drop if wt==0
gen dateadmit=mdy( moa ,doa, yoa)
gen datefactor=mdy( month ,date, year)
gen wt_dif_date= datefactor-dateadmit
drop if  wt_dif_date>365.25
drop  dob mob yob doa moa yoa dodc modc yodc gender ht cr date
month year dateadmit datefactor wt_dif_date
sum wt
sort id
save "D:\Weigth.dta"
merge id using "D:\Dx.dta"
tab _merge
drop _merge
sum wt if dx==0
sum wt if dx==1
sum wt if dx==2
```

1.6 Body mass index: Creates body mass index variable and summarize mean of weight according to the diagnosis

```
use "D:\Original\FDose.dta"
keep if ht!=0
sum ht
gen ht_metre=ht/100
sum ht_metre
gen sqht_metre= ht_metre^2
sum sqht_metre
gen bmi=wt/sqht_metre
sum bmi
```

```
sort id
save "D:\BMI.dta"
merge id using "D:\Dx.dta"
tab _merge
drop _merge
sum bmi if dx==0
sum bmi if dx==1
sum bmi if dx==2
```

1.7 Length of stay

```
use "D:\Original\FDose.dta"
keep id doa moa yoa dodc modc yodc
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
gen dateadmit=mdy( moa ,doa, yoa)
gen datedc=mdy( modc ,dodc, yodc)
drop doa moa yoa dodc modc yodc n minn
gen los=datedc-dateadmit
sum los
save "D:\LOS.dta"
```

1.8 Creatinine

1.8.1 Creates 1st date prescribing order

```
use "D:\Original\Dose.dta"
drop if order==0
drop if selection==1
drop if cont==0
gen datepres=mdy( month ,date, year)
sort id
by id:egen indexdate= min(datepres)
keep if datepres==indexdate
gen tim=length(time)
gen timmm=substr(time,1,1) if tim==4
sort timmm
replace timmm=substr(time,1,2) if tim==5
sort timmm
gen ntime=real(timmm)
sort id ntime
by id: gen n=_n
keep if n==1
drop date month year time order off cont selection indexdate tim
timmm ntime n
gen fdaydose= dose* frequency
drop dose
```

```
sum cr
sort id
save "D:\1stday_pres_dose.dta"
```

1.8.2 Select creatinine on the 1st date prescribing

```
use "D:\Original\FDose.dta"
drop dob mob yob dodc modc yodc gender ht wt
drop if cr==0
gen datefactor=mdy( month ,date, year)
sort id
merge id using "D:\1stday_pres_dose.dta"
gen datedif_cr=(datefactor-datepres)
drop doa moa yoa date month year _merge
keep if datedif_cr<1
sort id
by id:egen ndate=max( datedif_cr)
keep if  ndate== datedif_cr
drop datedif_cr ndate
sum cr
sort id
save "D:\1stday_pres_Cr.dta"
merge id using "D:\Dx.dta"
tab _merge
drop _merge
sum cr if dx==0
sum cr if dx==1
sum cr if dx==2
```

1.9 Creatinine clearance

1.9.1 CG-creatinine clearance calculation

```
use “D:\Original\FDose.dta”
*Patient AGE at admission
sort id
merge id using “D:\Age.dta”
tab _merge
drop _merge

*Gen DATE factor (datedif)
gen datefactor=mdy( month ,date, year)
gen datedif=abs(datefactor-dateadmit)
*Height & Weight
gen htinch=ht/2.54
drop if wt==0
drop if htinch<=60
keep if datedif<=365.25
```

```
*Calculate IBW
replace gender=50 if gender==0
replace gender=45.5 if gender==1
gen ibw=gender+2.3*(htinch-60)
gen adjbw=ibw+0.4*(wt-ibw)
gen wtdif=0.2*ibw
gen ibwcal=ibw
replace ibwcal=wt if wt<ibw
replace ibwcal=adjbw if (wt-ibw)>wtdif

*Gen Sex Factor for CG-CrCl
replace gender=1 if gender==50
replace gender=0.85 if gender==45.5
drop dob mob yob doa moa yoa dodc modc yodc cr ht date month year
datebirth dateadmit agedate ageyr htinch ibw adjbw wtdif datedif
sort id
merge id using “D:\1stday_pres_Cr.dta”
drop if ibwcal==.
drop datefactor datepres _merge

*CALCULATE CG-CrCl
gen cg_crcl=((140- age)*ibwcal)/(72* cr)
drop ibwcal
sort id
save “D:\CG_CrCl.dta”
```

1.9.2 MDRD-creatinine clearance calculation

```
use “D:\Original\Fdose.dta”
gen datebirth=mdy( mob ,dob, yob)
gen dateadmit=mdy( moa ,doa, yoa)
gen datefactor=mdy( month ,date, year)
gen agedate=abs(dateadmit-datebirth)
gen ageyr=agedate/365.25
gen age=round(ageyr, 1)
replace gender=0.742 if gender==1
replace gender=1 if gender==0
drop agedate ageyr
sort id
merge id using “D:\1stday_pres_dose.dta”
gen difdate= datefactor- datepres
drop dob mob yob doa moa yoa dodc modc yodc ht wt date month year
datebirth _merge
drop if cr==0
keep if difdate<1
sort id
by id: egen ndate=max(difdate)
keep if ndate==difdate
drop dateadmit ndate
```

```
gen supcr=cr^(-1.154)
gen supage=age^(-0.203)
gen mdrd_crcl=(186* supcr* supage* gender)/1.73
drop datefactor datepres difdate supcr supage
sum mdrd_crcl
sort id
save “D:\MDRD_CrCl.dta”
```

1.9.3 Creatinine clearance <end>

```
use “D:\CG_CrCl.dta”
sort id
merge id using “D:\MDRD_CrCl.dta”
tab _merge
drop _merge
gen endcrcl= cg_crcl
replace endcrcl= mdrd_crcl if  endcrcl==.
sum endcrcl
sort id
save "D:\endCrCl_359.dta"
merge id using "D:\Dx.dta"
tab _merge
drop _merge
sum cr if dx==0
sum cr if dx==1
sum cr if dx==2
```

1.10 History: bleeding, stroke, DM, HT, and CHF at admission

```
use "D:\Original\FBleed.dta"
sum
tab hxbleed
tab stroke
tab dm
tab ht
tab chf
sort id
merge id using "D:\Dx.dta"
tab _merge
drop _merge
tab hxbleed if dx==0
tab hxbleed if dx==1
tab hxbleed if dx==2
tab stroke if dx==0
tab stroke if dx==1
tab stroke if dx==2
tab dm if dx==0
tab dm if dx==1
tab dm if dx==2
tab dm if ht==0
```

```
tab dm if ht==1
tab dm if ht==2
tab chf if dx==0
tab chf if dx==1
tab chf if dx==2
```

1.11 CAG

```
use "D:\Original\MedPro.dta"
*restrict CAG
keep if medpro==1
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop _merge
sort id
save "D:\CAG.dta"
```

1.12 PCI

```
use "D:\Original\MedPro.dta"
keep if medpro==2
keep id medpro
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
rename medpro pci
sum
keep id pci
sort id
save "D:\PCI.dta"
```

1.13 CABG

```
use "D:\Original\MedPro.dta"
keep if medpro==3
keep id medpro
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
rename medpro cabg
sum
keep id cabg
sort id
save "D:\CABG.dta"
```

1.14 Conservative treatment

```
use "D:\PCI.dta"
sort id
merge id using "D:\CABG.dta"
tab _merge
drop _merge
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop _merge
replace pci=0 if pci==.
replace cabg=0 if cabg==.
gen contx=1 if pci==0 & cabg==0
replace contx=0 if contx==.
tab contx
sort id
merge id using "D:\Dx.dta"
tab _merge
drop _merge
tab contx if dx==0
tab contx if dx==1
tab contx if dx==2
```

1.15 Duration of enoxaparin therapy (days)

```
use "D:\Original\Dose.dta"
keep if order==0
keep id date month year time
gen dateact=mdy( month ,date, year)
sort id
by id: egen mindate=min(dateact)
by id: egen maxdate=max(dateact)
keep if dateact== mindate | dateact==maxdate
sum
drop mindate maxdate
gen tim=length(time)
gen timm=substr(time,1,1) if tim==4
sort timm
replace timm=substr(time,1,2) if tim==5
sort timm
gen ntime=real(timm)
sort id dateact ntime
by id: gen n=_n
by id: egen minn=min(n)
by id: egen maxn=max(n)
keep if n==minn | n==maxn
sum
keep id dateact
sort id
```

```
bysort id:gen n=_n
reshape wide dateact, i(id)j(n)
sum
replace dateact2= dateact1+1 if  dateact2==.
gen difdate=dateact2-dateact1
sum difdate
sort id
save "D:\DurationEnoxTher_actual_day.dta"
```

1.16 Accumulative dose of enoxaparin

```
use "D:\Original\Dose.dta"
*Restrict only actual receiving dose
keep if order==0
drop date month year time frequency order off cont selection
sum dose

*Summarize to check the number of patients
sort id
bysort id:gen n=_n
reshape wide dose,i(id)j(n)

*Sort data according to id
*Changing the shape of the data from long to wide
replace dose2=0 if dose2==.
replace dose3=0 if dose3==.
replace dose4=0 if dose4==.
replace dose5=0 if dose5==.
replace dose6=0 if dose6==.
replace dose7=0 if dose7==.
replace dose8=0 if dose8==.
replace dose9=0 if dose9==.
replace dose10=0 if dose10==.
replace dose11=0 if dose11==.
replace dose12=0 if dose12==.
replace dose13=0 if dose13==.
replace dose14=0 if dose14==.
replace dose15=0 if dose15==.
replace dose16=0 if dose16==.
replace dose17=0 if dose17==.
replace dose18=0 if dose18==.
replace dose19=0 if dose19==.
replace dose20=0 if dose20==.
replace dose21=0 if dose21==.
replace dose22=0 if dose22==.
replace dose23=0 if dose23==.
replace dose24=0 if dose24==.
replace dose25=0 if dose25==.
replace dose26=0 if dose26==.
```

```
replace dose27=0 if dose27==.
replace dose28=0 if dose28==.
replace dose29=0 if dose29==.
replace dose30=0 if dose30==.
replace dose31=0 if dose31==.
replace dose32=0 if dose32==.
replace dose33=0 if dose33==.
replace dose34=0 if dose34==.
gen acenox= dose1+ dose2+ dose3+ dose4+ dose5+ dose6+ dose7+
dose8+ dose9+ dose10+ dose11+ dose12+ dose13+ dose14+ dose15+
dose16+ dose17+ dose18+ dose19+ dose20+ dose21+ dose22+
dose23+ dose24+ dose25+ dose26+ dose27+ dose28+ dose29+
dose30+ dose31+ dose32+ dose33+ dose34

*Creates a new variable called acenox (enoxaparin accumulative dose)
*and set it equal to the summary of enoxaparin actual receiving dose
sum acenox
save "D:\Accumulative_Dose_Enox.dta"
```

1.17 Concomitant medications

1.17.1 Aspirin

```
use "D:\Original\MedPro.dta"
keep if medpro==5
gen daterc=mdy( month , date,  year)
drop date month year time on medpro
sort id
by id: egen startd=min(daterc)
by id: egen stoptd=max(daterc)
keep if daterc==startd | daterc==stoptd
sum
drop startd stoptd
sort id daterc
bysort id:gen n=_n
reshape wide daterc, i(id)j(n)
rename daterc1 startasa
rename daterc2 stopasa
sum
replace stopasa= startasa if stopasa==.
gen difdate=stopasa-startasa
sum difdate
sort id
save "D:\ASA_Receiving_Date.dta"
```

1.17.2 Clopidogrel

```
use "D:\Original\MedPro.dta"
drop time on date month year
keep if medpro==6
```

```
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro clo
replace clo=1 if clo==5
replace clo=0 if clo==.
tab clo
sort id
save "D:\Concomed_Clopi.dta"
```

1.17.3 Dual antiplatelet therapy

1.17.3.1 ID patients receiving aspirin

```
use "D:\Original\MedPro.dta"
keep if medpro==5
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
rename medpro asa
keep id asa
sort id
save "D:\ID_rcv_asa.dta"
```

1.17.3.2 ID patients receiving clopidogrel

```
use "D:\Original\MedPro.dta"
keep if medpro==6
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
rename medpro clo
keep id clo
sort id
save "D:\ID_rcv_clo.dta"
```

1.17.3.3 ID patients receiving dual antiplatelet agents

```
use "D:\ID_rcv_asa.dta"
merge id using "D:\ID_rcv_clo.dta"
tab _merge
```

```
replace _merge=0 if _merge==1 | _merge==2
tab _merge
rename _merge dual
sort id
merge id using "D:\Original\Gen.dta"
tab _merge
tab dual
replace dual=0 if dual==.
keep id dual dx
tab dual if dx==0
tab dual if dx==1
tab dual if dx==2
replace dual=1 if dual==3
tab dual
drop dx
sort id
save "D:\Dual_Antiplt.dta"
```

1.18 Warfarin

```
use "D:\Original\MedPro.dta"
drop time on date month year
keep if medpro==4
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro warfarin
replace  warfarin=1 if warfarin==4
replace  warfarin=0 if warfarin==.
tab warfarin
sort id
save "D:\Concomed_War.dta"
```

1.19 Glycoprotein IIb/IIIa antagonists

```
use "D:\Original\MedPro.dta"
drop time on date month year
keep if medpro==10
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
```

```
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro gpi
replace gpi=1 if gpi==10
replace gpi=0 if gpi==.
tab gpi
sort id
save "D:\Concomed_GPI.dta"
```

1.20 Thrombolysis

```
use "D:\\Original\MedPro.dta"
drop time on date month year
keep if medpro==11
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro thr
replace thr=1 if thr==10
replace thr=0 if thr==.
tab thr
sort id
save "D:\Concomed_THR.dta"
```

1.21 NSAIDs

```
use "D:\Original\MedPro.dta"
drop time on date month year
keep if medpro==7
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro nsaid
replace nsaid=1 if nsaid==7
replace nsaid=0 if nsaid==.
tab nsaid
sort id
```

```
save "D:\Concomed_NSAID.dta"
```

1.22 Proton pump inhibitors

```
use "D:\Original\MedPro.dta"
drop time on date month year
keep if medpro==8
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro ppi
replace ppi=1 if ppi==8
replace ppi=0 if ppi==.
tab ppi
sort id
save "D:\Concomed_PPI.dta"
```

1.23 Histamine$_2$ antagonist

```
use "D:\Original\MedPro.dta"
drop time on date month year
keep if medpro==9
sort id
by id: gen n=_n
by id: egen minn=min(n)
keep if n==minn
sum
sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop n minn _merge
rename medpro h2ra
replace h2ra=1 if h2ra==8
replace h2ra=0 if h2ra==.
tab h2ra
sort id
save "D:\Concomed_H2RA.dta"
```

2. Enoxaparin dosing

2.1 Evaluated dose

2.1.1 Dose from CG-CrCl

```
use "D:\CG_CrCl.dta"
```

```
gen rec_fq=2 if cg_crcl>=30
replace rec_fq=1 if cg_crcl<30
gen rec_day_dose=wt*rec_fq
gen difdose=fdaydose-rec_day_dose
gen anlyz_cg=0 if difdose<=10 | difdose>=-10
replace  anlyz_cg=1 if difdose<-10
replace  anlyz_cg=2 if difdose>10
tab anlyz_cg
sort id
save "D:\AnalyzedDose_CG.dta"
keep id cg_crcl anlyz_cg
sort id
save "D:\AnalyzedDose_CG_forMergeMDRD.dta"
```

2.1.2 Evaluated dose from MDRD-CrCl

```
use "D:\MDRD_CrCl.dta"
sort id
merge id using "D:\Weigth.dta"
gen rec_fq=2 if mdrd_crcl>=30
replace rec_fq=1 if mdrd_crcl < 30
gen rec_day_dose= wt*rec_fq
gen difdose=fdaydose-rec_day_dose
drop gender cr age _merge
gen anlyz_md=0 if  difdose<=10 | difdose>=-10
replace anlyz_md=1 if difdose<-10
replace anlyz_md=2 if difdose>10
tab anlyz_md
sort id
save "D:\\AnalyzedDose_MDRD.dta"
```

2.1.3 Evaluated dose <end>

```
use "D:\\AnalyzedDose_MDRD.dta"
sort id
merge id using "D:\AnalyzedDose_CG_forMergeMDRD.dta"
gen anlyz_sum=anlyz_cg
replace anlyz_sum=anlyz_md if anlyz_cg== .
tab anlyz_sum
save "D:\AnalyzedDose_MDRDplusCG_359.dta"
```

2.2 Characteristics of Patients with Excess, Lower-Than-Recommended, and Recommended Enoxaparin Doses

2.2.1 Student t-test

```
use "D:\AnalyzedDose_MDRDplusCG_359.dta"
tab anlyz_sum
sort id
merge id using "D:\Age.dta"
tab _merge
```

```
drop _merge
sum
sort id
merge id using "D:\Weigth.dta"
tab _merge
drop _merge
sum
sort id
merge id using "D:\endCrCl_359.dta"
tab _merge
drop _merge
sum
sort id
merge id using "D:\BMI.dta"
tab _merge
drop _merge
sum

*Excess dose
gen overdose=1 if anlyz_sum==2
replace overdose=0 if anlyz_sum==0
tab overdose
sdtest age, by(overdose)
ttest age, by(overdose)
sdtest wt, by(overdose)
ttest wt, by(overdose) unequal
sdtest bmi, by(overdose)
ttest bmi, by(overdose)
sdtest ncrcl, by(overdose)
ttest ncrcl, by(overdose)
drop overdose

*Under dose
gen underdose=1 if anlyz_sum==1
replace underdose=0 if anlyz_sum==0
tab underdose
sdtest age, by(underdose)
ttest age, by(underdose)
sdtest wt, by(underdose)
ttest wt, by(underdose) unequal
sdtest bmi, by(underdose)
ttest bmi, by(underdose) unequal
sdtest ncrcl, by(underdose)
ttest ncrcl, by(underdose)
```

2.2.2 Chi-2

```
use "D:\Analyze_Dose_CGplusMDRD_359.dta"
```

```
sort id
merge id using "D:\Age.dta"
tab _merge
drop _merge
sort id
gen agegrp=1 if age>=65
replace agegrp=0 if agegrp==.
tab agegrp

sort id
merge id using "D:\endCrCl_359.dta"
tab _merge
drop _merge
gen renalgr2=1 if ncrcl<30
replace renalgr2=0 if renalgr2==.
tab renalgr2

sort id
merge id using "D:\Dx.dta"
tab _merge
drop _merge
tab dx
gen dx_ua=dx
replace dx_ua=1 if dx==0
replace dx_ua=0 if dx==1
replace dx_ua=0 if dx==2
tab dx_ua
gen dx_nstemi=dx
replace dx_nstemi=0 if ndx==2
tab dx_nstemi
gen dx_stemi=dx
replace dx_stemi=1 if dx==2
replace dx_stemi=0 if dx==1
tab dx_stemi

sort id
merge id using "D:\Gender.dta"
tab _merge
drop _merge
tab gender

sort id
merge id using "D:\Original\FBleed.dta"
tab _merge
tab hxbleed
tab stroke
tab dm
tab ht
```

```
tab chf

*Analyze Excess VS Rec
tab anlyz_sum
*anlyz_sum=0=recommended dose; 1= underdose; 2=overdose
replace anlyz_sum=. if anlyz_sum==1
replace anlyz_sum=1 if anlyz_sum==2
tab agegr if anlyz_sum==0
tab agegr if anlyz_sum==1
tab anlyz_sum agegrp, chi2
tab renalgr2 if anlyz_sum==0
tab renalgr2 if anlyz_sum==1
tab renalgr2 anlyz_sum, chi2
tab dx_ua if anlyz_sum==0
tab dx_ua if anlyz_sum==1
tab dx_ua anlyz_sum, chi2
tab dx_nstemi if anlyz_sum==0
tab dx_nstemi if anlyz_sum==1
tab dx_nstemi anlyz_sum, chi2
tab dx_stemi if anlyz_sum==0
tab dx_stemi if anlyz_sum==1
tab dx_stemi anlyz_sum, chi2
tab gender if anlyz_sum==0
tab gender if anlyz_sum==1
tab anlyz_sum gender, chi2
tab hxbleed if anlyz_sum==0
tab hxbleed if anlyz_sum==1
tab anlyz_sum hxbleed, chi2
tab stroke if anlyz_sum==0
tab stroke if anlyz_sum==1
tab anlyz_sum stroke, chi2
tab dm if anlyz_sum==0
tab dm if anlyz_sum==1
tab anlyz_sum dm, chi2
tab ht if anlyz_sum==0
tab ht if anlyz_sum==1
tab anlyz_sum ht, chi2
tab chf if anlyz_sum==0
tab chf if anlyz_sum==1
tab anlyz_sum chf, chi2

*Analyze UNDER VS Rec
drop if anlyz_sum==1
replace anlyz_sum=1 if anlyz_sum==.
tab anlyz_sum
tab agegr if anlyz_sum==0
tab agegr if anlyz_sum==1
tab anlyz_sum agegrp, chi2
```

```
tab renalgr2 if anlyz_sum==0
tab renalgr2 if anlyz_sum==1
tab renalgr2 anlyz_sum, chi2
tab dx_ua if anlyz_sum==0
tab dx_ua if anlyz_sum==1
tab dx_ua anlyz_sum, chi2
tab dx_nstemi if anlyz_sum==0
tab dx_nstemi if anlyz_sum==1
tab dx_nstemi anlyz_sum, chi2
tab dx_stemi if anlyz_sum==0
tab dx_stemi if anlyz_sum==1
tab dx_stemi anlyz_sum, chi2
tab gender if anlyz_sum==0
tab gender if anlyz_sum==1
tab anlyz_sum gender, chi2
tab hxbleed if anlyz_sum==0
tab hxbleed if anlyz_sum==1
tab anlyz_sum hxbleed, chi2
tab stroke if anlyz_sum==0
tab stroke if anlyz_sum==1
tab anlyz_sum stroke, chi2
tab dm if anlyz_sum==0
tab dm if anlyz_sum==1
tab anlyz_sum dm, chi2
tab ht if anlyz_sum==0
tab ht if anlyz_sum==1
tab anlyz_sum ht, chi2
tab chf if anlyz_sum==0
tab chf if anlyz_sum==1
tab anlyz_sum chf, chi2
```

3. Bleeding complications and risk factors

3.1 Bleeding date and time

```
use "D:\Original\Bleeding.dta"
drop if bleeding==0
gen datebl=mdy( startm, startd, starty)
gen datestbl=mdy( stopm , stopd,  stopy)
drop startd startm starty stopd stopm stopy
gen tim=length(time)
gen timmm=substr(time,1,1) if tim==4
sort timmm
replace timmm=substr(time,1,2) if tim==5
sort timmm
gen ntime=real(timmm)
drop time tim timmm
drop if id==232|id==292 | id==392
```

```
sort id
save "D:\Bleeding_Date_Time.dta"
```

3.2 ID patients who experienced enoxaparin-associated bleeding

```
use "D:\Original\Dose.dta"
drop if order==1
sort id
tab order

*DATE
gen daterc=mdy( month , date,  year)
sort id
by id: egen mindaterc=min(daterc)
by id: egen maxdaterc=max(daterc)
gen afterstop= maxdaterc+1
drop maxdaterc date month year dose frequency order off cont selection

*TIME
gen tim=length(time)
gen timm=substr(time,1,1) if tim==4
replace timm=substr(time,1,2) if tim==5
sort timm
tab timm
gen ntime=real(timm)
sort id daterc ntime
drop time tim timm
by id: gen n=_n
by id: egen minn=min(n)
by id: egen maxn=max(n)
keep if n== minn| n== maxn
drop n minn maxn

sort id daterc
bysort id:gen n=_n
reshape wide daterc mindaterc ntime afterstop, i(id)j(n)
drop  daterc1 daterc2 afterstop2 mindaterc2
rename mindaterc1 dateeff_on
rename afterstop1 dateeff_off
rename ntime1 timeeff_on
rename ntime2 timeeff_off
replace timeeff_off= timeeff_on if timeeff_off== .
sort id
save "D:\Actual_rcv_Date_and_Time.dta"

*Merge ENOX EFFECT date&time with BLEEDING date&time
*to assess case "Enox associated Bleeding"
merge id using "D:\Bleeding_Date_Time.dta"
tab _merge
keep if _merge==3
```

```
drop _merge
rename ntime bltime
*Assess case enox associated bleeding
gen enoxbl=0 if datebl<dateeff_on | datebl>dateeff_off
replace enoxbl=1 if dateeff_on < datebl & datebl < dateeff_off
replace enoxbl=2 if datebl==dateeff_on
replace enoxbl=3 if datebl==dateeff_off

gen tenoxbl=1 if enoxbl==2 & bltime>= timeeff_on
replace tenoxbl=1 if enoxbl==3 & bltime<= timeeff_off
replace tenoxbl=0 if tenoxbl== .
sort id enoxbl tenoxbl

gen nenoxbl=1 if enoxbl==1
replace nenoxbl=1 if  enoxbl==2 & tenoxbl==1
replace nenoxbl=1 if  enoxbl==3 & tenoxbl==1
replace nenoxbl=0 if nenoxbl== .
tab nenoxbl
keep if nenoxbl==1
drop dateeff_on timeeff_on dateeff_off timeeff_off enoxbl tenoxbl
sort id
save "D:\IDnEnoxBleed.dta"
```

3.3 Incidence of Bleeding

```
use "D:\Original\Bleeding.dta"
drop startd startm starty time stopd stopm stopy
sort id
merge id using "D:\IDnEnoxBleed.dta"
keep if _merge==3
drop _merge

*BLEEDING code
*0=Not found ==> CHANGE CODE to 15!
*1=Hematoma 2=Ecchymosis 3= Hematuria 4=Secretion 5=GIB
*6=Bleeding Groin from CAG 7=Int Jugular
*8=Ecchymosis SC site 9=Bleeding per GUM 10=Mouth bleed
*11=Epistaxis(Nosebleed) 12=ICH 13=Pericardial effusion 14=Bruise
*15=bleed not found

*HEMODYNAMIC
*0=Stable ==> CHANGE CODE to 3! 1=Unstable from other cause
*2=Unstable from bleeding

*LOAD IV FLUID
*0=No ==> CHANGE CODE to 3! 1=Y, from other 2=Y, from
bleeding

*VASOPRESSOR
```

```
*0=No ==> CHANGE CODE to 3! 1=Y, from other 2=Y, from
bleeding

*OUTCOME
*0=Alive ==> CHANGE CODE to 3! 1=Death, other 2=Death,
bleeding
replace bleeding=15 if bleeding==0
replace hemodynamic=3 if hemodynamic==0
replace loadivfluid=3 if loadivfluid==0
replace vasopressor=3 if vasopressor==0
replace outcome=3 if outcome==0

sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop _merge
replace bleeding=15 if bleeding==.
drop if id==241
drop if id==232
drop if id==292
drop if id==392
tab bleeding
tab hemodynamic
tab loadivfluid
tab vasopressor
tab outcome
sort id
save "D:\Describe_Bleeding.dta"
```

3.4 Bleeding severity

3.4.1 GUSTO criteria

3.4.1.1 ID Blood Transfusion associated bleeding

```
use "D:\Original\Transfusion.dta"
keep if transfusion==2
gen datetrans=mdy(month, transfdate, year)
drop transfdate month year
gen tim=length(time)
gen timmm=substr(time,1,1) if tim==4
replace timmm=substr(time,1,2) if tim==5
sort timmm
gen ntime=real(timmm)
drop if id==232|id==292|id==392
drop time tim timmm
sort id ntime
bysort id:gen n=_n
```

```
reshape wide  transfusion bltype unit datetrans ntime, i(id)j(n)
keep id  transfusion1
save "D:\Transfusion_for_Merge.dta"
```

1.4.1.2 Merge data with ID bleeding and hemodynamic status

```
use "D:\IDnEnoxBleed.dta"
sort id
merge id using "D:\Transfusion_for_Merge.dta"
drop _merge
replace transfusion1=0 if  transfusion1== .
gen g_severity=1 if bleeding==12 | hemodynamic==2
replace g_severity=2 if transfusion==2 & bleeding !=12 &
hemodynamic !=2
replace g_severity=3 if transfusion !=2 & bleeding !=12 &
hemodynamic !=2
tab g_severity
sort id
save "D:\GUSTO_bleeding.dta"
keep id g_severity

sort id
merge id using "D:\ID_total_359.dta"
tab _merge
drop _merge
replace g_severity=4 if  g_severity==.
drop if id==22
drop if id==89
drop if id==191
drop if id==246
drop if id==291
drop if id==385
drop if id==392
drop if id==411
drop if id==420
drop if id==449
drop if id==479
drop if id==232
drop if id==292
drop if id==392
tab g_severity
sort id
save "D:\GUSTO_bleeding_346.dta"
```

3.4.2 TIMI bleeding criteria

3.4.2.1 Bleeding found

- Date start and stop bleed

```
use "D:\IDnEnoxBleed.dta"
drop hemodynamic loadivfluid vasopressor outcome nenoxbl
rename datebl startbl
rename  datestbl stopbl
save "D:\EnoxBleed_start_stop_for_TIMI.dta"
```

- Hb and Hct of bleeding patients

```
use "D:\Original\Lab.dta"
keep if lab==1 | lab==2
gen datelab=mdy( month, date, year)
drop date month year
sort id
merge id using "D:\EnoxBleed_start_stop_for_TIMI.dta"
tab _merge
replace bleeding=0 if bleeding== .
drop if startbl== .
drop _merge
save "D:\TIMI_Hb_Hct_before_Separate.dta"
```

3.4.2.1.1 Hemoglobin (Hb)

- Baseline Hb

```
use "D:\TIMI_Hb_Hct_before_Separate.dta"
keep if lab==1
gen difstart=datelab-startbl
sum difstart
sort id difstart
keep if difstart<=0
sort id difstart
gen redif=abs(difstart)
sort id redif
by id: gen n=_n
keep if n==1 | n==2
drop n
sum difstart

gen select=1 if difstart<0
replace select=2 if difstart<-1
replace select=3 if difstart<-2
replace select=4 if difstart<-3
replace select=5 if difstart<-4
replace select=6 if difstart<-5
replace select=7 if difstart<-6
replace select=8 if difstart<-7
replace select=9 if difstart<-8
replace select=10 if select== .
tab select
sort id select
by id: egen nselect=min(select)
```

```
keep if  select==nselect
sum difstart
drop startbl stopbl bltime select nselect redif
sort id
save "D:\Baseline_Hb_140_RENEW.dta"
```

- Hb after bleed

```
use"D:\TIMI_Hb_Hct_before_Separate.dta"
keep if lab==1
gen difdate=datelab-startbl
keep if difdate>=0
sum difdate
gen difstop=datelab-stopbl
sum difstop
drop if difstop<=0
sort id
by id: gen n=_n
by id: egen nmin=min(n)
keep if  n==nmin
sort id
save "D:\Hb_post_start_bleed_POST_stop_bleed.dta"
clear
use"D:\TIMI_Hb_Hct_before_Separate.dta"
keep if lab==1
gen difdate=datelab-startbl
keep if difdate>=0
sum difdate
gen difstop=datelab-stopbl
sum difstop
drop if difstop>0
drop bleeding startbl stopbl bltime datelab
sort id
bysort id:gen n=_n
reshape wide lab value difdate difstop, i(id)j(n)

sort id
save "D:\Hb_post_start_bleed_pre_stop_bleed.dta"

merge id using "D:\Hb_post_start_bleed_POST_stop_bleed.dta"
keep id value1 value2 value3 value4 value5 value6 value7 value
rename value value8
sort id
reshape long value, i(id) j(n)
drop if value==.
drop n
sort id
by id: egen posthb=min(value)
keep if value==posthb
drop posthb
```

```
sum
rename value hb_post
sort id
by id: gen n=_n
keep if n==1
drop n
sum
sort id
save "D:\Hb_Post_Bleed_Complete.dta"
```

- Hb <end>

```
use "D:\Baseline_Hb_140_RENEW.dta"
drop datelab difstart
rename value hb_pre
merge id using "D:\Hb_Post_Bleed_Complete.dta"
tab _merge
drop _merge
gen hbdif= hb_pre-hb_post
sum hbdif
gen t_sev_hb=1 if hbdif>=5
replace t_sev_hb=2 if 3<=hbdif & hbdif<5
replace t_sev_hb=3 if hbdif<3
replace t_sev_hb=5 if hbdif==.
replace t_sev_hb=4 if hbdif<=0
replace t_sev_hb=1 if bleeding==12
tab t_sev_hb
drop lab hb_pre hb_post
sort id
save "D:\TIMI_Severity_BlFound_Hb_RENEW.dta"
```

3.4.2.1.2 Hematocrit (Hct)

- baseline Hct

```
use "D:\TIMI_Hb_Hct_before_Separate.dta"

keep if lab==2
gen difstart= datelab-startbl
sort id difstart
keep if difstart<=0
sort id difstart
gen redif=abs(difstart)

sort id redif
by id: gen n=_n
keep if n==1 | n==2
drop n
sum difstart
```

```
gen select=1 if difstart<0
replace select=2 if difstart<-1
replace select=3 if difstart<-2
replace select=4 if difstart<-3
replace select=5 if difstart<-4
replace select=6 if difstart<-5
replace select=7 if difstart<-6
replace select=8 if difstart<-7
replace select=9 if difstart<-8
replace select=10 if select== .
sort id select
by id: egen nselect=min(select)
keep if  select==nselect
sum value difstart
drop startbl stopbl bltime select nselect redif
sort id
save "D:\Baseline_Hct_140_RENEW.dta"
```

- Hct after bleed

```
use"D:\TIMI_Hb_Hct_before_Separate.dta"
keep if lab==2
gen difdate=datelab-startbl

keep if difdate>=0
sum difdate
gen difstop=datelab-stopbl
sum difstop
drop if difstop<=0
sort id
by id: gen n=_n
by id: egen nmin=min(n)
keep if  n==nmin
sort id
save "D:\Hct_post_start_bleed_POST_stop_bleed.dta"
clear
use"D:\TIMI_Hb_Hct_before_Separate.dta"
keep if lab==2
gen difdate=datelab-startbl
keep if difdate>=0
sum difdate
gen difstop=datelab-stopbl
sum difstop
drop if difstop>0
drop bleeding startbl stopbl bltime datelab
sort id
bysort id:gen n=_n
reshape wide lab value difdate difstop, i(id)j(n)
 sort id
```

```
save "D:\Hct_post_start_bleed_pre_stop_bleed.dta"

merge id using "D:\Hct_post_start_bleed_POST_
stop_bleed.dta"
drop n nmin _merge difstop1 difstop2 difstop3 difstop4 difstop5
difstop6 difstop7 difstop8 difstop bltime startbl stopbl datelab bleeding
rename lab lab9
rename value value9
rename difdate difdate9
keep id value1 value2 value3 value4 value5 value6 value7 value8

sort id
reshape long value, i(id) j(n)
drop if value==.
drop n
sort id
by id: egen posthct=min(value)

keep if value==posthct
drop posthct
sum
rename value hct_post
sort id
by id: gen n=_n
keep if n==1
sum
sort id
save "D:\Hct_Post_Bleed_Complete.dta"
```

- Hct <end>

```
use "D:\Baseline_Hct_140_RENEW.dta"
drop datelab difstart
rename value hct_pre

sort id
merge id using "D:\Hct_Post_Bleed_Complete.dta"
tab _merge
drop n _merge
gen hctdif= hct_pre-hct_post
sum hctdif

gen t_sev_hct=1 if hctdif>=15
replace t_sev_hct=2 if 9<=hctdif & hctdif<15
replace t_sev_hct=3 if hctdif<9
replace t_sev_hct=4 if hctdif<=0
replace t_sev_hct=5 if hctdif== .
replace t_sev_hct=1 if bleeding==12
tab t_sev_hct
```

```
drop lab hct_pre hct_post
sort id
save "D:\TIMI_Severity_BlFound_Hct_RENEW.dta"
```

3.4.2.2 Bleeding NOT found

3.4.2.2.1 Hb and Hct for bleed not found

```
use "D:\Original\Lab.dta"
keep if lab==1 | lab==2
gen datelab=mdy( month, date, year)
drop date month year
sort id
save "D:\LAB_for_blNOTfound_merge.dta"
```

3.4.2.2.2 ID Bleeding NOT found & Hb/Hct before separate

```
use "D:\Original\Gen.dta"
keep id
sort id
merge id using "D:\IDnEnoxBleed.dta"
drop if _merge==3
keep id
sum
sort id
save "D:\ID_blNOTfound_220.dta"

merge id using "D:\Actual_rcv_Date_and_Time.dta"
tab _merge
keep if _merge==3
drop _merge

sort id
merge id using "D:\LAB_for_blNOTfound_merge.dta"
tab _merge
keep if _merge==3
drop _merge
sort id
save "D:\Hb_Hct_blNOTfound_before_Separate.dta"
```

3.4.2.2.3 Hemoglobin (Hb)

- Baseline Hb (bleeding not found)

```
use "D:\Hb_Hct_blNOTfound_before_Separate.dta"
drop timeeff_on timeeff_off
keep if lab==1
gen difstart=datelab-dateeff_on
sum difstart
keep if difstart<=0
```

```
sort id difstart

gen redif=abs(difstart)
sort id redif

by id: gen n=_n
keep if n==1 | n==2
drop n
sum difstart

gen select=1 if difstart<0
replace select=2 if difstart<-1
replace select=3 if difstart<-2
replace select=4 if difstart<-3
replace select=5 if difstart<-4
replace select=6 if difstart<-5
replace select=7 if difstart<-6
replace select=8 if difstart<-7
replace select=9 if difstart<-8
replace select=10 if select== .
tab select
sort id select
by id: egen nselect=min(select)
keep if select==nselect
sum value difstart
drop dateeff_on dateeff_off datelab redif select nselect
sort id
save "D:\Baseline_Hb_blNOTFOUND_RENEW.dta"
```

- Hb after bleed (bl not found)

```
use "D:\Hb_Hct_blNOTfound_before_Separate.dta"
keep if lab==1
gen difdate=datelab-dateeff_on
keep if difdate>=0
sum difdate
gen difstop=datelab-dateeff_off
sum difstop
drop if difstop<=0

sort id
by id: gen n=_n
by id: egen nmin=min(n)
keep if  n==nmin
sort id
save "D:\TIMI\Hb_POST_StartEff_POST_StopEff.dta"
clear
use "D:\TIMI\Hb_Hct_blNOTfound_before_Separate.dta"
keep if lab==1
```

```
gen difdate=datelab-dateeff_on
keep if difdate>=0
gen difstop=datelab-dateeff_off
sum difstop
drop if difstop>0
drop dateeff_on dateeff_off timeeff_on timeeff_off datelab

sort id
bysort id:gen n=_n
reshape wide lab value difdate difstop, i(id)j(n)
save "D:\TIMI\blNOTFOUND_Hb_PostStart_PreStop.dta"

merge id using "D:\Hb_POST_StartEff_POST_StopEff.dta"
keep id value1 value2 value3 value4 value5 value
rename value value6
sort id
reshape long value, i(id) j(n)
drop if value==.
drop n
sort id
by id: egen posthb=min(value)
keep if value==posthb
drop posthb
sum
rename value hb_post

sort id
by id: gen n=_n
keep if n==1
drop n
sum
sort id
save "D:\BlNOTFOUND_Hb_PostEffect_Complete.dta"
```

- Hb <end>

```
use "D:\Baseline_Hb_blNOTFOUND_RENEW.dta"
drop  difstart
rename value hb_pre
sort id

merge id using "D:\BlNOTFOUND_Hb_PostEffect_Complete.dta"
tab _merge
drop _merge
sum hb_pre hb_post
gen hbdif=hb_pre-hb_post
sum hbdif

gen t_sev_hb=2 if hbdif>=4
```

```
replace t_sev_hb=6 if hbdif<4
replace t_sev_hb=7 if hbdif==.
tab t_sev_hb
drop lab hb_pre hb_post
sort id
save "D:\TIMI_Sev_blNOTfound_Hb_RENEW.dta"
```

3.4.2.2.4 Hematocrit

- Baseline Hct (bl not found)

```
use "D:\Hb_Hct_blNOTfound_before_Separate.dta"
drop timeeff_on timeeff_off
keep if lab==2
gen difstart=datelab-dateeff_on
sum difstart
keep if difstart<=0
sort id difstart

gen redif=abs(difstart)
sort id redif
by id: gen n=_n
keep if n==1 | n==2
drop n
sum difstart
gen select=1 if difstart<0
replace select=2 if difstart<-1
replace select=3 if difstart<-2
replace select=4 if difstart<-3
replace select=5 if difstart<-4
replace select=6 if difstart<-5
replace select=7 if difstart<-6
replace select=8 if difstart<-7
replace select=9 if difstart<-8
replace select=10 if select== .
tab select

sort id select
by id: egen nselect=min(select)
keep if select==nselect
sum value difstart
drop dateeff_on dateeff_off datelab redif select nselect
sort id
save "D:\Baseline_Hct_blNOTFOUND_RENEW.dta"
```

- Hct after bleed (bl not found)

```
use "D:\Hb_Hct_blNOTfound_before_Separate.dta"
keep if lab==2
```

```
gen difdate=datelab-dateeff_on
keep if difdate>=0
sum difdate
gen difstop=datelab-dateeff_off
sum difstop
drop if difstop<=0
sort id
by id: gen n=_n
by id: egen nmin=min(n)
keep if  n==nmin
sort id
save "D:\Hct_POST_StartEff_POST_StopEff.dta"
clear
use "D:\Hb_Hct_blNOTfound_before_Separate.dta"
keep if lab==2
gen difdate=datelab-dateeff_on
keep if difdate>=0
gen difstop=datelab-dateeff_off
sum difstop
drop if difstop>0
drop dateeff_on dateeff_off timeeff_on timeeff_off datelab

sort id
bysort id:gen n=_n
reshape wide lab value difdate difstop, i(id)j(n)
save "D:\TIMI\blNOTFOUND_Hct_PostStart_PreStop.dta"

merge id using "D:\Hct_POST_StartEff_POST_StopEff.dta"
keep id value1 value2 value3 value4 value5 value6 value7 value
rename value value8

sort id
reshape long value, i(id) j(n)
drop if value==.

sort id
by id: egen posthct=min(value)
keep if value==posthct
drop posthct
sum
rename value hct_post

sort id
by id: gen n=_n
keep if n==1
sum
drop n
sort id
```

```
save "D:\BlNOTFOUND_Hct_PostEffect_Complete.dta"
```

- Hct <end>

```
use "D:\Baseline_Hct_blNOTFOUND_RENEW.dta"
drop difstart
rename value hct_pre

merge id using "D:\BlNOTFOUND_Hct_PostEffect_Complete.dta"
tab _merge
sum hct_pre hct_post
drop _merge
gen hctdif=hct_pre-hct_post
sum hctdif
gen t_sev_hct=2 if hctdif>=12
replace t_sev_hct=6 if hctdif<12
replace t_sev_hct=7 if hctdif==.
tab t_sev_hct
drop lab hct_pre hct_post
sort id
save "D:\TIMI_Sev_blNOTfound_Hct_RENEW.dta"
```

3.4.2.2.5 TIMI <end>

- Hb

```
use "D:\TIMI_Severity_BlFound_Hb_RENEW.dta"
merge id using "D:\TIMI_Sev_blNOTfound_Hb_RENEW.dta"
tab _merge
sum hbdif
drop bleeding hbdif _merge
tab t_sev_hb
sort id
save "D:\TIMI_Hb_Complete_352.dta"
```

- Hct

```
use "D:\TIMI_Severity_BlFound_Hct_RENEW.dta"
sort id
merge id using "D:\TIMI_Sev_blNOTfound_Hct_RENEW.dta"
tab _merge
sum hctdif
tab t_sev_hct
drop bleeding hctdif _merge
sort id
save "D:\TIMI_Hct_Complete_355.dta"
```

- TIMI Severity <end>

```
use "D:\TIMI_Hb_Complete_352.dta"
sort id
merge id using "D:\TIMI_Hct_Complete_355.dta"
```

```
replace t_sev_hb=0 if t_sev_hb==.
drop _merge
sum

gen nt_sev= t_sev_hb if  t_sev_hb<t_sev_hct
replace nt_sev= t_sev_hct if t_sev_hct<t_sev_hb
replace nt_sev=t_sev_hb if t_sev_hb==t_sev_hct
tab nt_sev
replace nt_sev=3 if nt_sev==4
replace nt_sev=3 if nt_sev==5
sort id
save "D:\TIMI_Bleeding.dta"

keep id nt_sev
merge id using "D:\ID_total_359.dta"
replace nt_sev=8 if nt_sev==.
drop _merge
replace nt_sev=4 if nt_sev>3
tab nt_sev

*drop patients who participated in drug trial
drop if id==22
drop if id==89
drop if id==191
drop if id==246
drop if id==291
drop if id==385
drop if id==392
drop if id==411
drop if id==420
drop if id==449
drop if id==479
drop if id==232
drop if id==292
drop if id==392
tab nt_sev
sort id
save "D:\TIMI_Bleeding_total346.dta"
```

3.4.3 TACSR Criteria

```
use "D:\GUSTO_bleeding_346.dta"
sort id
merge id using "D:\TIMI_Bleeding_total346.dta"
tab _merge
drop  _merge
tab g_severity
tab nt_sev
gen tacsr_mjb=1 if  nt_sev==1
```

```
replace tacsr_mjb=1 if g_severity==1 | g_severity==2
replace  tacsr_mjb=0 if  tacsr_mjb==.
tab tacsr_mjb
sort id
save "D:\TACRS_MajorBleeding.dta"
```

3.5 Risk factors of bleeding

3.5.1 Chi-2 (dosing status)

```
use "D:\AnalyzedDose_MDRDplusCG_359.dta"
keep id dosegr
sum
sort id
merge id using "D:\TACSR_MajorBleeding.dta"
tab _merge
drop if id==22
drop if id==89
drop if id==191
drop if id==246
drop if id==291
drop if id==385
drop if id==392
drop if id==411
drop if id==420
drop if id==449
drop if id==479
drop if id==232
drop if id==292
drop if id==392
drop if _merge!=3
drop _merge

*Excess vs Recommended Dose
gen ex_rec=1 if dosegr==2
replace ex_rec=0 if dosegr==0
sum ex_rec

*Excess vs Low Dose
gen ex_low=1 if dosegr==2
replace ex_low=0 if dosegr==1
sum ex_low

*Recommended vs Low Dose
gen rec_low=1 if dosegr==0
replace rec_low=0 if dosegr==1

*TACSR Major Bleeding
```

```
tab tacsr_mjb ex_rec, chi2
tab tacsr_mjb ex_low, chi2
tab tacsr_mjb rec_low, chi2

* GUSTO All Bleeding
gen gus_all=1 if g_severity!=4
replace gus_all=0 if gus_all==.
tab gus_all ex_rec, chi2
tab gus_all ex_low, chi2
tab gus_all rec_low, chi2

* GUSTO Severe Bleeding
gen gus_sev=1 if g_severity==1
replace gus_sev=0 if gus_sev==.
tab gus_sev ex_rec, chi2
tab gus_sev ex_low, chi2
tab gus_sev rec_low, chi2

* TIMI All Bleeding
gen timi_all=1 if nt_sev!=4
replace timi_all=0 if timi_all==.
tab timi_all ex_rec, chi2
tab timi_all ex_low, chi2
tab timi_all rec_low, chi2

* TIMI Major Bleeding
gen timi_mj=1 if nt_sev==1
replace timi_mj=0 if timi_mj==.
tab timi_mj ex_rec, chi2
tab timi_mj ex_low, chi2
tab timi_mj rec_low, chi2
```

3.5.2 Univariate logistic regression analysis

3.5.2.1 GUSTO Bleeding

```
use "D:\GUSTO_bleeding_346.dta"
tab g_severity
gen gsevere=1 if g_severity==1
replace gsevere=0 if gsevere==.
tab gsevere
gen gsevere2=1 if g_severity<3
replace gsevere2=0 if gsevere2==.
tab gsevere2
gen gsevere3=1 if g_severity<4
replace gsevere3=0 if gsevere3==.
tab gsevere3

sort id
```

```
merge id using "D:\Analyze_Dose_CGplusMDRD_359.dta"
tab _merge
drop if _merge!=3
drop _merge
tab anlyz_sum
gen overdose=1 if anlyz_sum==2
replace overdose=0 if overdose==.
tab overdose
logistic gsevere overdose
logistic gsevere2 overdose
logistic gsevere3 overdose

sort id
save "D:\CohortStudy_GUSTO_346.dta"
sort id
merge id using "D:\Age.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere age
logistic gsevere2 age
logistic gsevere3 age
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr
logistic gsevere agegr
logistic gsevere2 agegr
logistic gsevere3 agegr

sort id
merge id using "D:\Gender.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere gender
logistic gsevere2 gender
logistic gsevere3 gender

sort id
merge id using "D:\Weigth.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere wt
logistic gsevere2 wt
logistic gsevere3 wt

sort id
```

```
merge id using "D:\endCrCl_359.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere ncrcl
logistic gsevere2 ncrcl
logistic gsevere3 ncrcl
gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.
tab crclgr
Logistic gsevere crclgr
logistic gsevere2 crclgr
logistic gsevere3 crclgr
gen crclgr2=1 if ncrcl<=30
replace crclgr2=0 if crclgr2==.
tab crclgr2
logistic gsevere crclgr2
logistic gsevere2 crclgr2
logistic gsevere3 crclgr2

sort id
merge id using "D:\CHF.dta"
tab _merge
drop if _merge!=3
logistic gsevere chf
logistic gsevere2 chf
logistic gsevere3 chf

sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere ppi
logistic gsevere2 ppi
logistic gsevere3 ppi

sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere dual
logistic gsevere2 dual
logistic gsevere3 dual

sort id
merge id using "D:\Concomed_War.dta"
```

```
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere war
logistic gsevere2 war
logistic gsevere3 war

sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere gpi
logistic gsevere2 gpi
logistic gsevere3 gpi

sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere thr
logistic gsevere2 thr
logistic gsevere3 thr

sort id
merge id using "D:\Concomed_NSAID.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere nsaid
logistic gsevere2 nsaid
logistic gsevere3 nsaid

sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic gsevere difdate
logistic gsevere2 difdate
logistic gsevere3 difdate

sort id
merge id using "D:\Accumulative_enox_mg.dta"
tab _merge
drop if _merge!=3
drop _merge
```

```
logistic gsevere acenox
logistic gsevere2 acenox
logistic gsevere3 acenox
```

3.5.2.2 TIMI Bleeding

```
use "D:\TIMI_Bleeding_total346.dta"
tab nt_sev
gen tsevere=1 if nt_sev==1
replace tsevere=0 if tsevere==.
tab tsevere
gen tsevere2=1 if nt_sev<3
replace tsevere2=0 if tsevere2==.
tab tsevere2
gen tsevere3=1 if nt_sev<4
replace tsevere3=0 if tsevere3==.
tab tsevere3

sort id
merge id using "D:\Analyze_Dose_CGplusMDRD_359.dta"
tab _merge
drop if _merge!=3
drop _merge
tab anlyz_sum
gen overdose=1 if anlyz_sum==2
replace overdose=0 if overdose==.
tab overdose
logistic tsevere overdose
logistic tsevere2 overdose
logistic tsevere3 overdose
sort id
save "D:\CohortStudy_TIMI_346.dta"

sort id
merge id using "D:\Age.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere age
logistic tsevere2 age
logistic tsevere3 age
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr
logistic tsevere agegr
logistic tsevere2 agegr
logistic tsevere3 agegr

sort id
```

```
merge id using "D:\Gender.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere gender
logistic tsevere2 gender
logistic tsevere3 gender
sort id
merge id using "D:\Weigth.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere wt
logistic tsevere2 wt
logistic tsevere3 wt

sort id
merge id using "D:\endCrCl_359.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere ncrcl
logistic tsevere2 ncrcl
logistic tsevere3 ncrcl
gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.
tab crclgr
logistic tsevere crclgr
logistic tsevere2 crclgr
logistic tsevere3 crclgr
gen crclgr2=1 if ncrcl<30
replace crclgr2=0 if crclgr2==.
logistic tsevere crclgr2
logistic tsevere2 crclgr2
logistic tsevere3 crclgr2

sort id
merge id using "D:\CHF.dta"
tab _merge
drop if _merge!=3
logistic tsevere chf
logistic tsevere2 chf
logistic tsevere3 chf

sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
```

```
drop _merge
logistic tsevere ppi
logistic tsevere2 ppi
logistic tsevere3 ppi

sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere dual
logistic tsevere2 dual
logistic tsevere3 dual

sort id
merge id using "D:\Concomed_War.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere war
logistic tsevere2 war
logistic tsevere3 war

sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere gpi
logistic tsevere2 gpi
logistic tsevere3 gpi

sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere thr
logistic tsevere2 thr
logistic tsevere3 thr

sort id
merge id using "D:\Concomed_NSAID.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere nsaid
logistic tsevere2 nsaid
```

```
logistic tsevere3 nsaid

sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere difdate
logistic tsevere2 difdate
logistic tsevere3 difdate

sort id
merge id using "D:\Accumulative_enox_mg.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tsevere acenox
logistic tsevere2 acenox
logistic tsevere3 acenox
```

3.5.2.3 TACSR major bleeding

```
use "D:\TACSR_MajorBleeding.dta"
tab tacsr_mjb
sort id
merge id using "D:\Analyze_Dose_CGplusMDRD_359.dta"
tab _merge
drop if _merge!=3
drop _merge
tab anlyz_sum
gen overdose=1 if anlyz_sum==2
replace overdose=0 if overdose==.
tab overdose
logistic tacsr_mjb overdose

sort id
merge id using "D:\Age.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb age
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr
logistic tacsr_mjb agegr

sort id
merge id using "D:\Gender.dta"
tab _merge
```

```
drop if _merge!=3
drop _merge
logistic tacsr_mjb gender

sort id
merge id using "D:\Weigth.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb wt

sort id
merge id using "D:\endCrCl_359.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb ncrcl
gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.
logistic tacsr_mjb crclgr
gen crclgr2=1 if ncrcl<30
replace crclgr2=0 if crclgr2==.
logistic tacsr_mjb crclgr2

sort id
merge id using "D:\CHF.dta"
tab _merge
drop if _merge!=3
logistic tacsr_mjb chf

sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb ppi

sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb dual

sort id
merge id using "D:\Concomed_War.dta"
tab _merge
drop if _merge!=3
```

```
drop _merge
logistic tacsr_mjb war

sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb gpi

sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb thr

sort id
merge id using "D:\Concomed_NSAID.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb nsaid

sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb difdate

sort id
merge id using "D:\Accumulative_enox_mg.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic tacsr_mjb acenox
```

3.5.3 Multivariate logistic regression analysis

3.5.3.1 GUSTO overall bleeding

```
use "D:\CohortStudy_GUSTO_346.dta"
sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
drop if _merge!=3
drop dateact1 dateact2 _merge
logit gsevere3 overdose
```

```
logistic gsevere3 overdose
estimates store A
logit gsevere3 overdose difdate
logistic gsevere3 overdose difdate
estimates store B
lrtest A B
logistic gsevere3 overdose difdate
estimates store C

sort id
merge id using "D:\Accumulative_Dose_Enox.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate acenox
logistic gsevere3 overdose difdate acenox
estimates store B
lrtest C B

sort id
merge id using "D:\Age.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate age
logistic gsevere3 overdose difdate age
estimates store B
lrtest C B
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr
tab agegr
logit gsevere3 overdose difdate agegr
logistic gsevere3 overdose difdate agegr
estimates store B
lrtest C B

sort id
merge id using “D:\Gender.dta”
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate gender
logistic gsevere3 overdose difdate gender
estimates store B
lrtest C B

sort id
```

```
merge id using “D:\1stday_pres_Cr.dta”
tab _merge
drop if _merge!=3
drop _merge fdaydose datepres datefactor
logit gsevere3 overdose difdate cr
logistic gsevere3 overdose difdate cr
estimates store B
lrtest C B

sort id
merge id using “D:\endCrCl_359.dta”
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate ncrcl
logistic gsevere3 overdose difdate ncrcl
estimates store B
lrtest C B
gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.
tab crclgr
logit gsevere3 overdose difdate crclgr
logistic gsevere3 overdose difdate crclgr
estimates store B
lrtest C B
gen crclgr2=1 if ncrcl<30
replace crclgr2=0 if crclgr2==.
tab crclgr2
logit gsevere3 overdose difdate crclgr2
logistic gsevere3 overdose difdate crclgr2
estimates store B
lrtest C B

sort id
merge id using "D:\Original\FBleed.dta"
tab _merge
drop if _merge!=3
drop _merge ht dm stroke
logit gsevere3 overdose difdate chf
logistic gsevere3 overdose difdate chf
estimates store B
lrtest C B

sort id
merge id using "D:\Concomed_War.dta"
tab _merge
drop if _merge!=3
drop _merge
```

```
logit gsevere3 overdose difdate warfarin
logistic gsevere3 overdose difdate warfarin
estimates store B
lrtest C B
logistic gsevere3 overdose difdate warfarin
estimates store D

sort id
merge id using "D:\Concomed_ASA.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin asa
logistic gsevere3 overdose difdate warfarin asa
estimates store B
lrtest D B

sort id
merge id using "D:\Concomed_Clopi.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin clo
logistic gsevere3 overdose difdate warfarin clo
estimates store B
lrtest D B

sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin dual
logistic gsevere3 overdose difdate warfarin dual
estimates store B
lrtest D B

sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin ppi
logistic gsevere3 overdose difdate warfarin ppi
estimates store B
lrtest D B

sort id
```

```
merge id using "D:\Concomed_H2RA.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin h2ra

logistic gsevere3 overdose difdate warfarin h2ra
estimates store B
lrtest D B

sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin gpi
logistic gsevere3 overdose difdate warfarin gpi
estimates store B
lrtest D B
logistic gsevere3 overdose difdate warfarin gpi
estimates store E

sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin gpi thr
logistic gsevere3 overdose difdate warfarin gpi thr
estimates store B
lrtest E B

sort id
merge id using "D:\Concomed_NSAID.dta"
tab _merge
drop if _merge!=3
drop _merge
logit gsevere3 overdose difdate warfarin gpi nsaid
logistic gsevere3 overdose difdate warfarin gpi nsaid
estimates store B
lrtest E B
logistic gsevere3 overdose difdate warfarin gpi
```

3.5.3.2 TIMI overall bleeding

```
use "D:\CohortStudy_TIMI_346.dta"
sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
```

```
drop if _merge!=3
drop dateact1 dateact2 _merge
logit tsevere3 overdose
logistic tsevere3 overdose
estimates store A
logit tsevere3 overdose difdate
logistic tsevere3 overdose difdate
estimates store B
lrtest A B
logistic tsevere3 overdose difdate
estimates store C

sort id
merge id using "D:\Accumulative_Dose_Enox.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate acenox
logistic tsevere3 overdose difdate acenox
estimates store B
lrtest C B

sort id
merge id using "D:\Age.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate age
logistic tsevere3 overdose difdate age
estimates store B
lrtest C B
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr
logit tsevere3 overdose difdate agegr
logistic tsevere3 overdose difdate agegr
estimates store B
lrtest C B

sort id
merge id using "D:\Gender.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate gender
logistic tsevere3 overdose difdate gender
estimates store B
lrtest C B
```

```
sort id
merge id using "D:\1stday_pres_Cr.dta"
tab _merge
drop if _merge!=3
drop _merge fdaydose datepres datefactor
logit tsevere3 overdose difdate cr
logistic tsevere3 overdose difdate cr
estimates store B
lrtest C B

sort id
merge id using "D:\endCrCl_59.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate ncrcl
logistic tsevere3 overdose difdate ncrcl
estimates store B
lrtest C B
gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.
tab crclgr2
logit tsevere3 overdose difdate crclgr
logistic tsevere3 overdose difdate crclgr
estimates store B
lrtest C B
gen crclgr2=1 if ncrcl<=30
replace crclgr2=0 if crclgr2==.
tab crclgr2
logit tsevere3 overdose difdate crclgr2
logistic tsevere3 overdose difdate crclgr2
estimates store B
lrtest C B

sort id
merge id using "D:\CHF.dta"
tab _merge
drop if _merge!=3
logit tsevere3 overdose difdate chf
logistic tsevere3 overdose difdate chf
estimates store B
lrtest C B

sort id
merge id using "D:\Concomed_War.dta"
tab _merge
drop if _merge!=3
drop _merge
```

```
logit tsevere3 overdose difdate warfarin
logistic tsevere3 overdose difdate warfarin
estimates store B
lrtest C B
logistic tsevere3 overdose difdate warfarin
estimates store D

sort id
merge id using "D:\Concomed_ASA.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin asa
logistic tsevere3 overdose difdate warfarin asa
estimates store B
lrtest D B

sort id
merge id using "D:\Concomed_Clopi.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin clo
logistic tsevere3 overdose difdate warfarin clo
estimates store B
lrtest D B

sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin dual
logistic tsevere3 overdose difdate warfarin dual
estimates store B
lrtest D B

sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin ppi
logistic tsevere3 overdose difdate warfarin ppi
estimates store B
lrtest D B
logistic tsevere3 overdose difdate warfarin ppi
estimates store E
```

```
sort id
merge id using "D:\Concomed_H2RA.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin ppi h2ra
logistic tsevere3 overdose difdate warfarin ppi h2ra
estimates store B
lrtest D B

sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin ppi gpi
logistic tsevere3 overdose difdate warfarin ppi gpi
estimates store B
lrtest E B
logistic tsevere3 overdose difdate warfarin ppi gpi
estimates store F

sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin ppi gpi thr
logistic tsevere3 overdose difdate warfarin ppi gpi thr
estimates store B
lrtest F B

sort id
merge id using "D:\Concomed_NSAID.dta"
tab _merge
drop if _merge!=3
drop _merge
logit tsevere3 overdose difdate warfarin ppi gpi nsaid
logistic tsevere3 overdose difdate warfarin ppi gpi nsaid
estimates store B
lrtest F B
logistic tsevere3 overdose difdate warfarin ppi gpi
```

3.5.3.3 Unadjusted and adjusted risks of bleeding between patients with severe renal impairment receiving renally adjusted once daily dosing versus patients with normal renal function receiving twice daily dosing

```
use "D:\AnalyzedDose_MDRDplusCG_359.dta"

keep id recfq dosegr
keep if dosegr==0
sum

rename recfq actfq
tab actfq

gen oddose=1 if actfq==1
replace oddose=0 if oddose==.
tab oddose

sort id
merge id using "D:\TACSR_MajorBleeding.dta"
tab _merge

****************************************
*Drop 1 id exclude cz cr
drop if id==241

*Drop 11 id drug trial
drop if id==22
drop if id==89
drop if id==191
drop if id==246
drop if id==291
drop if id==385
drop if id==392
drop if id==411
drop if id==420
drop if id==449
drop if id==479

*Drop 3 id can't evaluate bleeding
drop if id==232
drop if id==292
drop if id==392

drop if _merge!=3
drop _merge

*************************
* TACSR Major Bleeding
tab tacsr_mjb
tab oddose tacsr_mjb, chi2

*************************
```

```
*  GUSTO Bleeding
tab g_severity
*g_severity=1=severe, g_severity=2= moderate, g_severity=3= mild,
g_severity=4= no bleeding

*SELECT ONLY SEVERE BLEEDING

gen gsevere=1 if g_severity==1
replace gsevere=0 if gsevere==.
tab gsevere

tab oddose gsevere, chi2

*****************************************
*gsevere=1= GUSTO severe, gsevere=0 =etc.

*SELECT SEVERE+MODERATE = gsevere2

gen gsevere2=1 if g_severity<3
replace gsevere2=0 if gsevere2==.
tab gsevere2

tab oddose gsevere2, chi2


*SELECT GUSTO ALL BLEEDING = gsevere3
gen gsevere3=1 if g_severity<4
replace gsevere3=0 if gsevere3==.
tab gsevere3

tab oddose gsevere3, chi2

*SELECT GUSTO moderate bleeding
gen gmoderate=1 if g_severity==2
replace gmoderate=0 if gmoderate==.
tab gmoderate

tab oddose gmoderate, chi2

*SELECT GUSTO mild bleeding
gen gmild=1 if g_severity==3
replace gmild=0 if gmild==.
tab gmild

tab oddose gmild, chi2

************************
*     TIMI Bleeding
```

```
tab nt_sev
*nt_sev=1 =major, nt_sev=2 =minor, nt_sev=3 =minimal


*SELECT ONLY SEVERE BLEEDING
                    gen tsevere=1 if nt_sev==1
replace tsevere=0 if tsevere==.
tab tsevere

tab oddose tsevere, chi2
*tsevere=1= TIMI major, tsevere=0 =etc.

*SELECT Major+Minor = tsevere2
gen tsevere2=1 if nt_sev<3
replace tsevere2=0 if tsevere2==.
tab tsevere2

tab oddose tsevere2, chi2

*SELECT TIMI ALL BLEEDING = tsevere3
gen tsevere3=1 if nt_sev<4
replace tsevere3=0 if tsevere3==.
tab tsevere3

tab oddose tsevere3, chi2

*SELECT TIMI MINOR
gen tminor=1 if nt_sev==2
replace tminor=0 if tminor==.
tab tminor

tab oddose tminor, chi2

*SELECT TIMI MINIMAL
gen tminimal=1 if nt_sev==3
replace tminimal=0 if tminimal==.
tab tminimal

tab oddose tminimal, chi2

*EFFICACY
sort id
merge id using "D:\Dead_all_cause.dta"
tab _merge
drop if _merge!=3
drop _merge

tab oddose dead, chi2
```

```
sort id
merge id using "D:\Gift_MU\EC RAMA\Post A
Nathon\AnalyzeStata\Dead_from_ACS.dta"
tab _merge
drop if _merge!=3
drop _merge

tab oddose dead_acs, chi2

sort id
merge id using "D:\Readmit_ACS_within_30d.dta"
tab _merge
drop if _merge!=3
drop _merge
tab oddose read_acs_1mo, chi2

sort id
merge id using "D:\ReIschemia_ReVasc.dta"
tab _merge
drop if _merge!=3
drop _merge

tab oddose reischemia, chi2
tab oddose revasc, chi2

*****************************************
*Multivariate Logistic Regression (n=145)
* OD vs Q12, among rec dose
*Merge Confounders

*****************************************************
*    Duration of enox therapy (actual receiving)
*merge duration(days)
sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
drop if _merge!=3
drop dateact1 dateact2 _merge
sum difdate

*****************************************************
*    Acumulative dose of enox (actual receiving)
*merge accum dose
sort id
merge id using "D:\Accum_EnoxDose_general.dta"
tab _merge
drop if _merge!=3
drop _merge
```

```
**********
*       AGE
*merge age
sort id
merge id using "D:\Age_360.dta"
tab _merge
drop if _merge!=3
drop _merge
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr

**********
*   Female GENDER
*merge gender
sort id
merge id using "D:\Gender.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*   Cr
*merge cr
sort id
merge id using "D:\1stday_pres_Cr.dta"
tab _merge
drop if _merge!=3
drop _merge fdaydose datepres datefactor
gen crgr=1 if cr>2
replace crgr=0 if crgr==.
tab crgr

**********
*   CrCl
*merge CrCl(CGplusMDRD)
sort id
merge id using "D:\nCrCl_CGplusMDRG_359.dta"
tab _merge
drop if _merge!=3
drop _merge

gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.

**********
*       CHF
*merge CHF
```

```
sort id
merge id using "D:\FBleed.dta"
tab _merge
drop if _merge!=3
drop _merge ht dm stroke

**********
*         Warfarin
*merge warfarin
sort id
merge id using "D:\Concomed_War.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*         ASA
*merge ASA
sort id
merge id using "D:\Concomed_ASA.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*   Clopidogrel
*merge clo
sort id
merge id using "D:\Concomed_Clopi.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*  Dual Antiplatelet
sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*    PPI&H2RA
*merge PPI&H2RA
sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
```

```
drop _merge

**********
*      GPI
*merge GPI
sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*   Thrombolysis
*merge thrombolysis
sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge

**********
*       NSAIDs
sort id
merge id using "D:\Concomed_NSAID.dta"
tab _merge
drop if _merge!=3
drop _merge

* confounders= difdate acenox age agegr gender cr ncrcl crclgr hxbleed chf
warfarin asa clo dual ppi gpi thr nsaid

**************************************
* Analyze only Univariate=SIGnificant
* 1) TACSR Major Bleeding
* 2) GUSTO severe+mod
* 3) GUSTO mod
* 4) Dead, all cause
**************************************

*1) TACSR Mj Bleed

logit tacsr_mjb oddose
logistic isth_mjb oddose
estimates store A

logit tacsr_mjb oddose difdate
logistic tacsr_mjb oddose difdate
```

estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose acenox
logistic tacsr_mjb oddose acenox

estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose age
logistic tacsr_mjb oddose age

estimates store B
lrtest A B

logit tacsr_mjb oddose agegr
logistic tacsr_mjb oddose agegr

estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose gender
logistic tacsr_mjb oddose gender

estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose cr
logistic tacsr_mjb oddose cr

estimates store B
lrtest A B

logit tacsr_mjb oddose crgr
logistic tacsr_mjb oddose crgr

estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose ncrcl
logistic tacsr_mjb oddose ncrcl
estimates store B
lrtest A B

*not significant

logit tacsr_mjb oddose crclgr
logistic tacsr_mjb oddose crclgr
estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose hxbleed
logistic tacsr_mjb oddose hxbleed

estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose chf
logistic tacsr_mjb oddose chf
estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose warfarin
logistic tacsr_mjb oddose warfarin
estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose asa
logistic tacsr_mjb oddose asa
estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose clo
logistic tacsr_mjb oddose clo
estimates store B
lrtest A B
*not significant

logit tacsr_mjb oddose dual
logistic tacsr_mjb oddose dual
estimates store B
lrtest A B

****
*NOW MODEL is
*logit tacsr_mjb oddose dual
*logistic tacsr_mjb oddose dual

```
*estimates store B
************************************

logit tacsr_mjb oddose dual ppi
logistic tacsr_mjb oddose dual ppi

estimates store C
lrtest B C
*not significant

logit tacsr_mjb oddose dual gpi
logistic tacsr_mjb oddose dual gpi
estimates store C
lrtest B C
*not significant

logit tacsr_mjb oddose dual thr
logistic tacsr_mjb oddose dual thr
estimates store C
lrtest B C

*thr != 0 predicts failure perfectly
*thr dropped and 7 obs not used

logit tacsr_mjb oddose dual nsaid
logistic tacsr_mjb oddose dual nsaid
estimates store C
lrtest B C

*nsaid != 0 predicts failure perfectly
*nsaid dropped and 1 obs not used

*****************************************
*SUMMARY TACSR Mj Bl Model is
logit isth_mjb oddose dual
logistic isth_mjb oddose dual
*****************************************

* 2) GUSTO severe+moderate = gsevere2

logit gsevere2 oddose
logistic gsevere2 oddose
estimates store A

logit gsevere2 oddose difdate
logistic gsevere2 oddose difdate
estimates store B
lrtest A B
```

*not significant

logit gsevere2 oddose acenox
logistic gsevere2 oddose acenox
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose age
logistic gsevere2 oddose age
estimates store B
lrtest A B

logit gsevere2 oddose agegr
logistic gsevere2 oddose agegr
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose gender
logistic gsevere2 oddose gender
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose cr
logistic gsevere2 oddose cr

estimates store B
lrtest A B
*not significant

logit gsevere2 oddose crgr
logistic gsevere2 oddose crgr
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose ncrcl
logistic gsevere2 oddose ncrcl
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose crclgr
logistic gsevere2 oddose crclgr
estimates store B
lrtest A B

*not significant

logit gsevere2 oddose hxbleed
logistic gsevere2 oddose hxbleed
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose chf
logistic gsevere2 oddose chf
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose warfarin
logistic gsevere2 oddose warfarin
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose asa
logistic gsevere2 oddose asa
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose clo
logistic gsevere2 oddose clo
estimates store B
lrtest A B
*not significant

logit gsevere2 oddose dual
logistic gsevere2 oddose dual
estimates store B
lrtest A B
*SIGNIFICANT

****
*NOW MODEL is
*logit gsevere2 oddose dual
*logistic gsevere2 oddose dual
*estimates store B
****

logit gsevere2 oddose dual ppi
logistic gsevere2 oddose dual ppi

```
estimates store C
lrtest B C

*ppi != 1 predicts failure perfectly
*ppi dropped and 26 obs not used

logit gsevere2 oddose dual gpi
logistic gsevere2 oddose dual gpi

estimates store C
lrtest B C
*not significant

logit gsevere2 oddose dual thr
logistic gsevere2 oddose dual thr

estimates store C
lrtest B C

*thr != 0 predicts failure perfectly
*thr dropped and 7 obs not used

logit gsevere2 oddose dual nsaid
logistic gsevere2 oddose dual nsaid

estimates store C
lrtest B C

*nsaid != 0 predicts failure perfectly
*nsaid dropped and 1 obs not used

*****************************************
*SUMMARY GUSTO severe+mod Model is
logit gsevere2 oddose dual
logistic gsevere2 oddose dual
*****************************************

* 3) GUSTO moderate = gmoderate

logit gmoderate oddose
logistic gmoderate oddose
estimates store A

logit gmoderate oddose difdate
logistic gmoderate oddose difdate
estimates store B
lrtest A B
```

*not significant

logit gmoderate oddose acenox
logistic gmoderate oddose acenox
estimates store B
lrtest A B
*not significant

logit gmoderate oddose age
logistic gmoderate oddose age
estimates store B
lrtest A B

logit gmoderate oddose agegr
logistic gmoderate oddose agegr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose gender
logistic gmoderate oddose gender
estimates store B
lrtest A B
*not significant

logit gmoderate oddose cr
logistic gmoderate oddose cr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose crgr
logistic gmoderate oddose crgr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose ncrcl
logistic gmoderate oddose ncrcl
estimates store B
lrtest A B
*not significant

logit gmoderate oddose crclgr
logistic gmoderate oddose crclgr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose hxbleed
logistic gmoderate oddose hxbleed
estimates store B
lrtest A B
*not significant

logit gmoderate oddose chf
logistic gmoderate oddose chf
estimates store B
lrtest A B
*not significant

logit gmoderate oddose warfarin
logistic gmoderate oddose warfarin
estimates store B
lrtest A B
*not significant

logit gmoderate oddose asa
logistic gmoderate oddose asa
estimates store B
lrtest A B
*not significant

logit gmoderate oddose clo
logistic gmoderate oddose clo
estimates store B
lrtest A B
*not significant

logit gmoderate oddose dual
logistic gmoderate oddose dual
estimates store B
lrtest A B
*SIGNIFICANT

****
*NOW MODEL is
*logit gmoderate oddose dual
*logistic gmoderate oddose dual
*estimates store B
****

logit moderate oddose dual ppi
logistic gmoderate oddose dual ppi
estimates store C
lrtest B C

```
*ppi != 1 predicts failure perfectly
*ppi dropped and 26 obs not used

logit gmoderate oddose dual gpi
logistic gmoderate oddose dual gpi

estimates store C
lrtest B C
*not significant

logit gmoderate oddose dual thr
logistic gmoderate oddose dual thr
estimates store C
lrtest B C

*thr != 0 predicts failure perfectly
*thr dropped and 7 obs not used

logit gmoderate oddose dual nsaid
logistic gmoderate oddose dual nsaid
estimates store C
lrtest B C

*nsaid != 0 predicts failure perfectly
*nsaid dropped and 1 obs not used

*******************************************
*SUMMARY GUSTO moderate Bl Model is
logit gmoderate oddose dual
logistic gmoderate oddose dual
*******************************************

* 4) DEAD, all cause =

logit dead oddose
logistic dead oddose
estimates store A

logit gmoderate oddose difdate
logistic gmoderate oddose difdate
estimates store B
lrtest A B
*not significant

logit gmoderate oddose acenox
logistic gmoderate oddose acenox

estimates store B
```

lrtest A B
*not significant

logit gmoderate oddose age
logistic gmoderate oddose age
estimates store B
lrtest A B

logit gmoderate oddose agegr
logistic gmoderate oddose agegr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose gender
logistic gmoderate oddose gender
estimates store B
lrtest A B
*not significant

logit gmoderate oddose cr
logistic gmoderate oddose cr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose crgr
logistic gmoderate oddose crgr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose ncrcl
logistic gmoderate oddose ncrcl
estimates store B
lrtest A B
*not significant

logit gmoderate oddose crclgr
logistic gmoderate oddose crclgr
estimates store B
lrtest A B
*not significant

logit gmoderate oddose hxbleed
logistic gmoderate oddose hxbleed
estimates store B
lrtest A B

*not significant

logit gmoderate oddose chf
logistic gmoderate oddose chf

estimates store B
lrtest A B
*not significant

logit gmoderate oddose warfarin
logistic gmoderate oddose warfarin
estimates store B
lrtest A B
*not significant

logit gmoderate oddose asa
logistic gmoderate oddose asa
estimates store B
lrtest A B
*not significant

logit gmoderate oddose clo
logistic gmoderate oddose clo
estimates store B
lrtest A B

*not significant

logit gmoderate oddose dual
logistic gmoderate oddose dual
estimates store B
lrtest A B
*SIGNIFICANT

****
*NOW MODEL is
*logit gmoderate oddose dual
*logistic gmoderate oddose dual
*estimates store B
****

logit moderate oddose dual ppi
logistic gmoderate oddose dual ppi
estimates store C
lrtest B C

*ppi != 1 predicts failure perfectly
*ppi dropped and 26 obs not used

```
logit gmoderate oddose dual gpi
logistic gmoderate oddose dual gpi
stimates store C
lrtest B C
*not significant

logit gmoderate oddose dual thr
logistic gmoderate oddose dual thr
estimates store C
lrtest B C

*thr != 0 predicts failure perfectly
*thr dropped and 7 obs not used

logit gmoderate oddose dual nsaid
logistic gmoderate oddose dual nsaid
estimates store C
lrtest B C

*nsaid != 0 predicts failure perfectly
*nsaid dropped and 1 obs not used

*****************************************
*SUMMARY GUSTO moderate Bl Model is
logit gmoderate oddose dual
logistic gmoderate oddose dual
*****************************************
```

3.6 Risks of in-hospital death

```
use "D:\ Bleeding.dta"
tab outcome
keep id outcome
sort id
merge id using "D:\Analyze_Dose_CGplusMDRD_359.dta"
tab _merge
*drop id not actual receiving
drop if id==232
drop if id==292
drop if id==392

keep id outcome anlyz_sum

gen death=0 if outcome==0
replace death=1 if death==.
tab death

***********************************
*Overdose
```

```
tab anlyz_sum
gen overdose=1 if  anlyz_sum==2
replace overdose=0 if overdose==.
tab overdose

logistic death overdose

*************************************
*Low Dose
gen lowdose=1 if anlyz_sum==1
replace lowdose=0 if lowdose==.
tab lowdose

logistic death lowdose

****************
*         AGE
*merge age
sort id
merge id using "D:\Age_359.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death age
gen agegr=1 if age>65
replace agegr=0 if agegr==.
tab agegr
logistic death agegr

****************
*    GENDER
*merge gender
sort id
merge id using "D:\Gender.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death gender

****************
*    Cr
*merge cr
sort id
merge id using "D:\1stday_pres_Cr.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death cr
```

```
gen crgr=1 if cr>2
replace crgr=0 if crgr==.
tab crgr
logistic death crgr

**********
*    CrCl
*merge CrCl(CGplusMDRD)
sort id
merge id using "D:\nCrCl_CGplusMDRG_359.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death ncrcl

gen crclgr=1 if ncrcl<60
replace crclgr=0 if crclgr==.
logistic death crclgr

gen crclgr2=1 if ncrcl<=30
replace crclgr2=0 if crclgr2==.
logistic death crclgr2

**************************************************
*    Duration of enox therapy (actual receiving)
*merge duration(days)
sort id
merge id using "D:\DurationEnoxTher_actual_day.dta"
tab _merge
drop if _merge!=3
drop _merge
drop dateact1 dateact2
logistic death difdate

**************************************************
*    Acumulative dose of enox (actual receiving)
*merge accum dose
sort id
merge id using "D:\Accum_EnoxDose_general.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death acenox

**********
*         CHF
*merge CHF
sort id
```

```
merge id using "D:\FBleed.dta"
tab _merge
drop if _merge!=3
drop _merge ht dm stroke
logistic death chf

**********
*         Warfarin
*merge warfarin
sort id
merge id using "D:\Concomed_War.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death warfarin

**********
*         ASA
*merge ASA
sort id
merge id using "D:\Concomed_ASA.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death asa

**********
*   Clopidogrel
*merge clopidogrel usage
sort id
merge id using "D:\Concomed_Clopi.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death clo

**********
*  Dual Antiplatelet
*merge dual
sort id
merge id using "D:\Dual_Antiplt.dta"
tab _merge
drop if _merge!=3
drop _merge

logistic death dual

**********
```

```
*        PPI
*merge ppi
sort id
merge id using "D:\Concomed_PPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death ppi

**************************
*        H2RA
*merge ppi
sort id
merge id using "D:\Concomed_H2RA.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death h2ra

*********************
*      GPI
*merge GPI
sort id
merge id using "D:\Concomed_GPI.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death gpi

*********************
*   Thrombolysis
*merge Thrombolysis
sort id
merge id using "D:\Concomed_THR.dta"
tab _merge
drop if _merge!=3
drop _merge
logistic death thr

***********************
*  GUSTO Bleeding
sort id
merge id using "D:\CohortStudy_GUSTO_346.dta"
tab _merge
drop if _merge!=3
drop _merge

keep id death wt g_severity gsevere3
```

```
gen gsevere=1 if g_severity==1
replace gsevere=0 if gsevere==.
gen gmoderate=1 if  g_severity==2
replace gmoderate=0 if gmoderate==.
gen gmild=1 if  g_severity==3
replace  gmild=0 if gmild==.
logistic death gsevere3
logistic death gsevere
logistic death gmoderate
logistic death gmild

*************************
*         TIMI Bleeding
sort id
merge id using "D:\CohortStudy_TIMI_346.dta"
tab _merge
drop if _merge!=3
drop _merge
keep id death nt_sev tsevere3 wt
tab nt_sev
gen tmajor=1 if  nt_sev==1
replace tmajor=0 if  tmajor==.
gen tminor=1 if  nt_sev==2
replace tminor=0 if  tminor==.
gen tminimal=1 if  nt_sev==3
replace tminimal=0 if  tminimal==.
logistic death tsevere3
logistic death tmajor
logistic death tminor
logistic death tminimal
logistic death wt

*************************
*  TACSR Major Bleeding
sort id
merge id using "D:\TACSR_MajorBleeding.dta"
tab _merge
drop if _merge!=3
drop _merge
keep id death tacsr_mjb
tab tacsr_mjb
logistic death tacsr_mjb
```

3.7 Length of stay and bleeding severity

```
use "D:\TACSR_MajorBleeding.dta"
sort id
merge id using "D:\LOS.dta"
tab _merge
```

```
*drop case dead & no actual rcv
drop if _merge!=3
drop _merge
*SELECT only each bleeding severity
* Wilcoxon-Mann-Whitney test

*************************
* TACSR Major Bleeding
tab tacsr_mjb
sum los if tacsr_mjb==1
sum los if tacsr_mjb==0
ranksum los, by(tacsr_mjb)

*************************
*  GUSTO Bleeding
tab g_severity
*g_severity=1=severe, g_severity=2= moderate, g_severity=3= mild,
*g_severity=4= no bleeding

*SELECT ONLY SEVERE BLEEDING
gen gsevere=1 if g_severity==1
replace gsevere=0 if gsevere==.
tab gsevere
sum los if gsevere==1
sum los if gsevere==0
ranksum los, by(gsevere)

*****************************************
*gsevere=1= GUSTO severe, gsevere=0 =etc.
*****************************************

*SELECT MODERATE = gsevere2
gen gsevere2=1 if g_severity==2
replace gsevere2=0 if gsevere2==.
tab gsevere2
sum los if gsevere2==1
sum los if gsevere2==0
ranksum los, by(gsevere2)

  *SELECT GUSTO overALL BLEEDING = gsevere3
gen gsevere3=1 if g_severity<4
replace gsevere3=0 if gsevere3==.
tab gsevere3
sum los if gsevere3==1
sum los if gsevere3==0
ranksum los, by(gsevere3)

*SELECT GUSTO mild bleeding
```

```
gen gmild=1 if g_severity==3
replace gmild=0 if gmild==.
tab gmild
sum los if gmild==1
sum los if gmild==0
ranksum los, by(gmild)

*************************
*     TIMI Bleeding
tab nt_sev
*********************************************************
*nt_sev=1 =major, nt_sev=2 =minor, nt_sev=3 =minimal
*********************************************************

*SELECT ONLY SEVERE BLEEDING
gen tsevere=1 if nt_sev==1
replace tsevere=0 if tsevere==.
tab tsevere
sum los if tsevere==1
sum los if tsevere==0
ranksum los, by(tsevere)

*SELECT TIMI overALL BLEEDING = tsevere3
gen tsevere3=1 if nt_sev<4
replace tsevere3=0 if tsevere3==.
tab tsevere3
sum los if tsevere3==1
sum los if tsevere3==0
ranksum los, by(tsevere)

*SELECT TIMI MINOR
gen tminor=1 if nt_sev==2
replace tminor=0 if tminor==.
tab tminor
sum los if tminor==1
sum los if tminor==0
ranksum los, by(tminor)

*SELECT TIMI MINIMAL
gen tminimal=1 if nt_sev==3
replace tminimal=0 if tminimal==.
tab tminimal
sum los if tminimal==1
sum los if tminimal==0
ranksum los, by(tminimal)
```

3.8 Exploratory analysis: Effect of lower-than-recommended enoxaparin dose

```
use "D:\ReIschemia_ReVasc.dta"
sort id
merge id using "D:\Dead_all_cause.dta"
tab _merge
drop _merge

sort id
merge id using "D:\Dead_from_ACS.dta"
tab _merge
drop _merge

sort id
merge id using "D:\Readmit_ACS_within_30d.dta"
tab _merge
drop _merge

**********************************************
*Drop 4 id that not actual receving enox!!!
drop if id==241
drop if id==232
drop if id==292
drop if id==392
**********************************************
*Drop 11 id drug trial
drop if id==22
drop if id==89
drop if id==191
drop if id==246
drop if id==291
drop if id==385
drop if id==392
drop if id==411
drop if id==420
drop if id==449
drop if id==479
**********************************************

sort id
merge id using "D:\Analyze_Dose_CGplusMDRD_359.dta"
tab _merge
drop if _merge!=3

drop ncrcl fdaydose wt recfq rec_ddose subgr outcome _merge

******************************************************
gen lsubgr=-4 if difdose <-90
replace lsubgr=-3 if difdose >=-90 & difdose <-60
replace lsubgr=-2 if difdose >=-60 & difdose <-30
```

```
replace lsubgr=-1 if difdose >=-30 & difdose <-10

tab lsubgr
*********************************************************
*Recoding 0/1

gen low1=1 if lsubgr==-1
replace low1=0 if anlyz_sum==0
tab low1

gen low2=1 if lsubgr==-2
replace low2=0 if anlyz_sum==0
tab low2

gen low3=1 if lsubgr==-3
replace low3=0 if anlyz_sum==0
tab low3

gen low4=1 if lsubgr==-4
replace low4=0 if anlyz_sum==0
tab low4

*************************************************
*                    Chi2 Test
*************************************************

tab low1 reischemia, chi2
tab low1 revasc, chi2
tab low1 dead, chi2
tab low1 dead_acs, chi2
tab low1 read_acs_1mo, chi2

tab low2 reischemia, chi2
tab low2 revasc, chi2
tab low2 dead, chi2
tab low2 dead_acs, chi2
tab low2 read_acs_1mo, chi2

tab low3 reischemia, chi2
tab low3 revasc, chi2
tab low3 dead, chi2
tab low3 dead_acs, chi2
tab low3 read_acs_1mo, chi2

tab low4 reischemia, chi2
tab low4 revasc, chi2
tab low4 dead, chi2
tab low4 dead_acs, chi2
```

```
tab low4 read_acs_1mo, chi2

*********************************************************
*               Composite Endpoint
*********************************************************
* c1=1+2, c2=1+2+3, c3=1+2+4, c4=1+2+3+5, c5=1+2+4+5
*********************************************************

gen c1=1 if  reischemia==1 |  revasc==1
replace c1=0 if c1==.
tab c1

tab low1 c1, chi2
tab low2 c1, chi2
tab low3 c1, chi2
tab low4 c1, chi2

gen c2=1 if reischemia==1 | revasc==1 | dead==1
replace c2=0 if c2==.
tab c2

tab low1 c2, chi2
tab low2 c2, chi2
tab low3 c2, chi2
tab low4 c2, chi2

gen c3=1 if reischemia==1 | revasc==1 | dead_acs==1
replace c3=0 if c3==.
tab c3

tab low1 c3, chi2
tab low2 c3, chi2
tab low3 c3, chi2
tab low4 c3, chi2

gen c4=1 if reischemia==1 | revasc==1 | dead==1 | read_acs_1mo==1
replace c4=0 if c4==.
tab c4

tab low1 c4, chi2
tab low2 c4, chi2
tab low3 c4, chi2
tab low4 c4, chi2

gen c5=1 if reischemia==1 | revasc==1 | dead_acs==1 | read_acs_1mo==1
replace c5=0 if c5==.
tab c5
```

```
tab low1 c5, chi2
tab low2 c5, chi2
tab low3 c5, chi2
tab low4 c5, chi2

**********************
* Length of Stay
**********************

sort id
merge id using "D:\LOS_renew.dta"

tab _merge
drop if _merge!=3
drop _merge

sdtest los, by(low1)
*Equal variances
ttest los, by(low1)

sdtest los, by(low2)
*unEqual variances
ttest los, by(low2) unequal

sdtest los, by(low3)
*unEqual variances
ttest los, by(low3) unequal

sdtest los, by(low4)
*unEqual variances
ttest los, by(low4) unequal
```

_

APPENDIX E
STATISTICAL RESULTS

1. Enoxaparin dosing

1.1 Characteristics of patients with excess and recommended doses

- t-test

```
.
. sdtest age, by(overdose)

Variance ratio test
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	**151**	**68.03311**	**.9913274**	**12.18163**	**66.07434**	**69.99188**
1	**56**	**72.42857**	**1.464484**	**10.95919**	**69.49368**	**75.36346**
combined	**207**	**69.22222**	**.8339139**	**11.99793**	**67.57812**	**70.86632**

```
    ratio = sd(0) / sd(1)                                     f =   1.2355
Ho: ratio = 1                         degrees of freedom =  150, 55

    Ha: ratio < 1               Ha: ratio != 1                 Ha: ratio > 1
  Pr(F < f) = 0.8148         2*Pr(F > f) = 0.3703           Pr(F > f) = 0.1852

.
. ttest age, by(overdose)

Two-sample t test with equal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	**151**	**68.03311**	**.9913274**	**12.18163**	**66.07434**	**69.99188**
1	**56**	**72.42857**	**1.464484**	**10.95919**	**69.49368**	**75.36346**
combined	**207**	**69.22222**	**.8339139**	**11.99793**	**67.57812**	**70.86632**
diff		**-4.395459**	**1.856556**		**-8.055852**	**-.7350658**

```
    diff = mean(0) - mean(1)                                  t =  -2.3675
Ho: diff = 0                          degrees of freedom =      205

    Ha: diff < 0                Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0094         Pr(|T| > |t|) = 0.0188          Pr(T > t) = 0.9906
```

```
. ttest wt, by(overdose) unequal

Two-sample t test with unequal variances

   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |     151    60.21722    .5562423    6.83522    59.11814    61.3163
       1 |      56    55.75357    1.475576    11.0422    52.79645    58.71069
---------+--------------------------------------------------------------------
combined |     207    59.00966    .5836945    8.397902   57.85888    60.16044
---------+--------------------------------------------------------------------
    diff |            4.463647    1.576937               1.319489    7.607806
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   2.8306
Ho: diff = 0                     Satterthwaite's degrees of freedom =  71.2147

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9970         Pr(|T| > |t|) = 0.0060          Pr(T > t) = 0.0030

.
.
.
. sdtest bmi, by(overdose)

Variance ratio test

   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |      82    23.56517    .2685176    2.43153    23.0309    24.09943
       1 |      15    20.38295    .4428261    1.715058   19.43318   21.33271
---------+--------------------------------------------------------------------
combined |      97    23.07307    .2638939    2.599054   22.54924   23.59689
------------------------------------------------------------------------------
    ratio = sd(0) / sd(1)                                         f =   2.0100
Ho: ratio = 1                              degrees of freedom =  81, 14

    Ha: ratio < 1                Ha: ratio != 1                Ha: ratio > 1
  Pr(F < f) = 0.9281         2*Pr(F > f) = 0.1437          Pr(F > f) = 0.0719

.
. ttest bmi, by(overdose)

Two-sample t test with equal variances

   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |      82    23.56517    .2685176    2.43153    23.0309    24.09943
       1 |      15    20.38295    .4428261    1.715058   19.43318   21.33271
---------+--------------------------------------------------------------------
combined |      97    23.07307    .2638939    2.599054   22.54924   23.59689
---------+--------------------------------------------------------------------
    diff |            3.182218     .657062               1.877785    4.486651
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   4.8431
Ho: diff = 0                               degrees of freedom =       95

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

.
.
.
. sdtest ncrcl, by(overdose)

Variance ratio test

   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |     151    35.67431    1.893816    23.2716    31.93231    39.41631
       1 |      56    33.19464    2.585732    19.34984   28.01272    38.37656
---------+--------------------------------------------------------------------
combined |     207    35.00348    1.547212    22.2605    31.95308    38.05388
------------------------------------------------------------------------------
    ratio = sd(0) / sd(1)                                         f =   1.4464
Ho: ratio = 1                              degrees of freedom =  150, 55

    Ha: ratio < 1                Ha: ratio != 1                Ha: ratio > 1
  Pr(F < f) = 0.9415         2*Pr(F > f) = 0.1170          Pr(F > f) = 0.0585

.
. ttest ncrcl, by(overdose)

Two-sample t test with equal variances

   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |     151    35.67431    1.893816    23.2716    31.93231    39.41631
       1 |      56    33.19464    2.585732    19.34984   28.01272    38.37656
---------+--------------------------------------------------------------------
combined |     207    35.00348    1.547212    22.2605    31.95308    38.05388
---------+--------------------------------------------------------------------
    diff |            2.479664     3.48706              -4.395435    9.354763
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   0.7111
Ho: diff = 0                               degrees of freedom =      205

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.7611         Pr(|T| > |t|) = 0.4778          Pr(T > t) = 0.2389
```

- Chi-2

```
. tab renalgr2 anlyz_sum, chi2
```

renalgr2	anlyz_sum 0	1	Total
0	**79**	**17**	**96**
1	**72**	**39**	**111**
Total	**151**	**56**	**207**

Pearson chi2(**1**) = **7.9220** Pr = **0.005**

```
. tab anlyz_sum gender, chi2
```

anlyz_sum	gender 0	1	Total
0	**103**	**48**	**151**
1	**26**	**30**	**56**
Total	**129**	**78**	**207**

Pearson chi2(**1**) = **8.2547** Pr = **0.004**

```
.
. tab anlyz_sum chf, chi2
```

anlyz_sum	CHF 0	1	Total
0	**75**	**76**	**151**
1	**32**	**24**	**56**
Total	**107**	**100**	**207**

Pearson chi2(**1**) = **0.9138** Pr = **0.339**

```
. tab anlyz_sum hxbleed, chi2
```

anlyz_sum	HxBleed 0	1	Total
0	**132**	**19**	**151**
1	**45**	**11**	**56**
Total	**177**	**30**	**207**

Pearson chi2(**1**) = **1.6431** Pr = **0.200**

```
. tab anlyz_sum stroke, chi2
```

anlyz_sum	Stroke 0	1	Total
0	**128**	**23**	**151**
1	**48**	**8**	**56**
Total	**176**	**31**	**207**

Pearson chi2(**1**) = **0.0287** Pr = **0.865**

```
. tab anlyz_sum dm, chi2
```

anlyz_sum	DM 0	1	Total
0	**75**	**76**	**151**
1	**30**	**26**	**56**
Total	**105**	**102**	**207**

Pearson chi2(**1**) = **0.2489** Pr = **0.618**

```
. tab anlyz_sum ht, chi2
```

anlyz_sum	HT 0	1	Total
0	**44**	**107**	**151**
1	**12**	**44**	**56**
Total	**56**	**151**	**207**

Pearson chi2(**1**) = **1.2307** Pr = **0.267**

UA

```
. tab ndx anlyz_sum, chi2
```

ndx	anlyz_sum 0	1	Total
0	**124**	**44**	**168**
1	**27**	**12**	**39**
Total	**151**	**56**	**207**

Pearson chi2(**1**) = **0.3363** Pr = **0.562**

NSTEMI

```
. tab ndx anlyz_sum, chi2
```

ndx	anlyz_sum 0	1	Total
0	**60**	**25**	**85**
1	**91**	**31**	**122**
Total	**151**	**56**	**207**

Pearson chi2(**1**) = **0.4066** Pr = **0.524**

STEMI

```
. tab ndx anlyz_sum, chi2
```

ndx	anlyz_sum 0	1	Total
0	**118**	**43**	**161**
1	**33**	**13**	**46**
Total	**151**	**56**	**207**

Pearson chi2(**1**) = **0.0437** Pr = **0.834**

1.2 Characteristics of patients with excess and lower-than-recommended doses

- t-test

```
.
. sdtest age, by(underdose)

Variance ratio test
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	**151**	**68.03311**	**.9913274**	**12.18163**	**66.07434**	**69.99188**
1	**152**	**63.42105**	**.8966032**	**11.05407**	**61.64954**	**65.19256**
combined	**303**	**65.71947**	**.6800706**	**11.83792**	**64.38119**	**67.05775**

ratio = sd(**0**) / sd(**1**) f = **1.2144**
Ho: ratio = 1 degrees of freedom = **150, 151**

Ha: ratio < 1 Ha: ratio != 1 Ha: ratio > 1
Pr(F < f) = **0.8828** 2*Pr(F > f) = **0.2344** Pr(F > f) = **0.1172**

```
.
. ttest age, by(underdose)

Two-sample t test with equal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	**151**	**68.03311**	**.9913274**	**12.18163**	**66.07434**	**69.99188**
1	**152**	**63.42105**	**.8966032**	**11.05407**	**61.64954**	**65.19256**
combined	**303**	**65.71947**	**.6800706**	**11.83792**	**64.38119**	**67.05775**
diff		**4.61206**	**1.336219**		**1.982545**	**7.241575**

diff = mean(**0**) - mean(**1**) t = **3.4516**
Ho: diff = 0 degrees of freedom = **301**

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = **0.9997** Pr(|T| > |t|) = **0.0006** Pr(T > t) = **0.0003**

```
. sdtest wt, by(underdose)

Variance ratio test
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	151	60.21722	.5562423	6.83522	59.11814	61.3163
1	152	70.64408	.9971499	12.29369	68.67391	72.61425
combined	303	65.44785	.6449662	11.22686	64.17866	66.71705

```
    ratio = sd(0) / sd(1)                                     f =   0.3091
Ho: ratio = 1                             degrees of freedom = 150, 151

    Ha: ratio < 1               Ha: ratio != 1                 Ha: ratio > 1
  Pr(F < f) = 0.0000         2*Pr(F < f) = 0.0000           Pr(F > f) = 1.0000

. ttest wt, by(underdose) unequal

Two-sample t test with unequal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	151	60.21722	.5562423	6.83522	59.11814	61.3163
1	152	70.64408	.9971499	12.29369	68.67391	72.61425
combined	303	65.44785	.6449662	11.22686	64.17866	66.71705
diff		-10.42686	1.141803		-12.67626	-8.177459

```
    diff = mean(0) - mean(1)                                  t =  -9.1319
Ho: diff = 0                     Satterthwaite's degrees of freedom =  236.54

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
. sdtest bmi, by(underdose)

Variance ratio test
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	82	23.56517	.2685176	2.43153	23.0309	24.09943
1	100	26.308	.3620055	3.620055	25.5897	27.02629
combined	182	25.07222	.2533983	3.418529	24.57222	25.57221

```
    ratio = sd(0) / sd(1)                                     f =   0.4512
Ho: ratio = 1                             degrees of freedom =  81, 99

    Ha: ratio < 1               Ha: ratio != 1                 Ha: ratio > 1
  Pr(F < f) = 0.0001         2*Pr(F < f) = 0.0003           Pr(F > f) = 0.9999


. ttest bmi, by(underdose) unequal

Two-sample t test with unequal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	82	23.56517	.2685176	2.43153	23.0309	24.09943
1	100	26.308	.3620055	3.620055	25.5897	27.02629
combined	182	25.07222	.2533983	3.418529	24.57222	25.57221
diff		-2.742831	.4507213		-3.632428	-1.853235

```
    diff = mean(0) - mean(1)                                  t =  -6.0854
Ho: diff = 0                     Satterthwaite's degrees of freedom =  173.657

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000


. sdtest ncrcl, by(underdose)

Variance ratio test
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	151	35.67431	1.893816	23.2716	31.93231	39.41631
1	152	47.84483	2.073294	25.56128	43.74842	51.94124
combined	303	41.77965	1.445184	25.15616	38.93575	44.62356

```
    ratio = sd(0) / sd(1)                                     f =   0.8289
Ho: ratio = 1                             degrees of freedom = 150, 151

    Ha: ratio < 1               Ha: ratio != 1                 Ha: ratio > 1
  Pr(F < f) = 0.1254         2*Pr(F < f) = 0.2509           Pr(F > f) = 0.8746
```

```
.
. ttest ncrcl, by(underdose)

Two-sample t test with equal variances

   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |     151    35.67431    1.893816    23.2716    31.93231    39.41631
       1 |     152    47.84483    2.073294   25.56128    43.74842    51.94124
---------+--------------------------------------------------------------------
combined |     303    41.77965    1.445184   25.15616    38.93575    44.62356
---------+--------------------------------------------------------------------
    diff |           -12.17053     2.80891               -17.69811   -6.642939
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =  -4.3328
Ho: diff = 0                                     degrees of freedom =      301

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000


. tab renalgr2 anlyz_sum, chi2

           |  anlyz_sum
renalgr2   |         0          1 |     Total
-----------+----------------------+----------
         0 |        79        122 |       201
         1 |        72         30 |       102
-----------+----------------------+----------
     Total |       151        152 |       303

          Pearson chi2(1) =  26.4901   Pr = 0.000


. tab anlyz_sum gender, chi2

           |    gender
anlyz_sum  |         0          1 |     Total
-----------+----------------------+----------
         0 |       103         48 |       151
         1 |       110         42 |       152
-----------+----------------------+----------
     Total |       213         90 |       303

          Pearson chi2(1) =   0.6268   Pr = 0.429
. tab anlyz_sum chf, chi2

           |       CHF
anlyz_sum  |         0          1 |     Total
-----------+----------------------+----------
         0 |        75         76 |       151
         1 |        90         62 |       152
-----------+----------------------+----------
     Total |       165        138 |       303

          Pearson chi2(1) =   2.7807   Pr = 0.095
. tab anlyz_sum hxbleed, chi2

           |    HxBleed
anlyz_sum  |         0          1 |     Total
-----------+----------------------+----------
         0 |       132         19 |       151
         1 |       129         23 |       152
-----------+----------------------+----------
     Total |       261         42 |       303

          Pearson chi2(1) =   0.4121   Pr = 0.521
. tab anlyz_sum stroke, chi2

           |    Stroke
anlyz_sum  |         0          1 |     Total
-----------+----------------------+----------
         0 |       128         23 |       151
         1 |       129         23 |       152
-----------+----------------------+----------
     Total |       257         46 |       303

          Pearson chi2(1) =   0.0006   Pr = 0.981
```

```
. tab anlyz_sum dm, chi2
```

anlyz_sum	DM 0	1	Total
0	**75**	**76**	**151**
1	**75**	**77**	**152**
Total	**150**	**153**	**303**

Pearson chi2(**1**) = **0.0032** Pr = **0.955**

```
. tab anlyz_sum ht, chi2
```

anlyz_sum	HT 0	1	Total
0	**44**	**107**	**151**
1	**33**	**119**	**152**
Total	**77**	**226**	**303**

Pearson chi2(**1**) = **2.2053** Pr = **0.138**

UA

```
. tab ndx anlyz_sum, chi2
```

ndx	anlyz_sum 0	1	Total
0	**124**	**127**	**251**
1	**27**	**25**	**52**
Total	**151**	**152**	**303**

Pearson chi2(**1**) = **0.1095** Pr = **0.741**

NSTEMI

```
. tab ndx anlyz_sum, chi2
```

ndx	anlyz_sum 0	1	Total
0	**60**	**71**	**131**
1	**91**	**81**	**172**
Total	**151**	**152**	**303**

Pearson chi2(**1**) = **1.5018** Pr = **0.220**

STEMI

```
. tab ndx anlyz_sum, chi2
```

ndx	anlyz_sum 0	1	Total
0	**118**	**106**	**224**
1	**33**	**46**	**79**
Total	**151**	**152**	**303**

Pearson chi2(**1**) = **2.7788** Pr = **0.096**

2. Risk factors of bleeding

2.1 Univariate logistic regression analysis

2.1.1 GUSTO criteria

- GUSTO severe bleeding

```
. logistic gsevere overdose

Logistic regression                                     Number of obs   =        346
                                                        LR chi2(1)      =       0.24
                                                        Prob > chi2     =     0.6260
Log likelihood = -21.698628                             Pseudo R2       =     0.0054

------------------------------------------------------------------------------
     gsevere | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |    1.81761   2.116273     0.51   0.608      .185538    17.80609
------------------------------------------------------------------------------
```

- GUSTO overall bleeding

```
. logistic gsevere3 overdose

Logistic regression                                     Number of obs   =        346
                                                        LR chi2(1)      =       4.54
                                                        Prob > chi2     =     0.0331
Log likelihood = -228.69159                             Pseudo R2       =     0.0098

------------------------------------------------------------------------------
    gsevere3 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |   1.889695   .5637063     2.13   0.033      1.05311    3.390859
------------------------------------------------------------------------------
```

2.1.2 TIMI criteria

- TIMI major bleeding

```
Logistic regression                                     Number of obs   =        346
                                                        LR chi2(1)      =       0.24
                                                        Prob > chi2     =     0.6260
Log likelihood = -21.698628                             Pseudo R2       =     0.0054

------------------------------------------------------------------------------
     tsevere | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |    1.81761   2.116273     0.51   0.608      .185538    17.80609
------------------------------------------------------------------------------
```

- TIMI overall bleeding

```
. logistic tsevere3 overdose

Logistic regression                                     Number of obs   =        346
                                                        LR chi2(1)      =       4.14
                                                        Prob > chi2     =     0.0420
Log likelihood = -229.78666                             Pseudo R2       =     0.0089

------------------------------------------------------------------------------
    tsevere3 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |   1.834758   .5469605     2.04   0.042      1.022885    3.291022
------------------------------------------------------------------------------
```

2.1.3 TACSR criteria

- TACSR major bleeding

```
Logistic regression                                     Number of obs   =        346
                                                        LR chi2(1)      =       0.72
                                                        Prob > chi2     =     0.3951
Log likelihood = -96.872181                             Pseudo R2       =     0.0037

------------------------------------------------------------------------------
    isth_mjb | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |   1.534091   .7462973     0.88   0.379      .5912384    3.980518
------------------------------------------------------------------------------
```

2.2 Multivariate logistic regression analysis

2.2.1 GUSTO overall bleeding

```
. logistic gsevere3 overdose difdate warfarin gpi

Logistic regression                               Number of obs   =        346
                                                  LR chi2(4)      =      37.75
                                                  Prob > chi2     =     0.0000
Log likelihood = -212.08409                       Pseudo R2       =     0.0817

------------------------------------------------------------------------------
    gsevere3 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |   2.177718   .6766144     2.50   0.012     1.184498    4.003769
     difdate |   1.129471   .0421416     3.26   0.001     1.049823    1.215162
    warfarin |   .2136746   .1315216    -2.51   0.012     .0639468    .7139813
         gpi |   5.078562   1.946125     4.24   0.000     2.396388    10.76278
------------------------------------------------------------------------------
```

2.2.2 TIMI overall bleeding

```
. logistic tsevere3 overdose difdate warfarin ppi gpi

Logistic regression                               Number of obs   =        346
                                                  LR chi2(5)      =      43.90
                                                  Prob > chi2     =     0.0000
Log likelihood = -209.90351                       Pseudo R2       =     0.0947

------------------------------------------------------------------------------
    tsevere3 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |   2.082357   .6515166     2.34   0.019      1.12781    3.844807
     difdate |   1.132173   .0432709     3.25   0.001     1.050463     1.22024
    warfarin |   .2035771   .1257066    -2.58   0.010     .0606906    .6828672
         ppi |   1.693052   .5146427     1.73   0.083     .9330991    3.071941
         gpi |   5.627189   2.216113     4.39   0.000     2.600574    12.17626
------------------------------------------------------------------------------
```

BIOGRAPHY

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