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PROFILE:

- Pharmacoepidemiologist with extensive epidemiology training and research experience in critical care.
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EDUCATION:

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(Pharmaceutical Health Services Research)
School of Pharmacy, University of Maryland 2014
Dissertation Title: Stress Ulcer Prophylaxis in Intensive care units: Use, Benefit and Risk
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Doctor of Pharmacy

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Bachelor Degree of Pharmaceutical Sciences

College of Pharmacy, University of Maryland 2001

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Stress Ulcer Prophylaxis in Intensive care units: Use, Benefit and Risks

Principle Investigator: Mohammad Aljawadi 2013-2014
Sponsor: eICU Research Institute

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Beta Blockers Utilization in Intensive Care Units and Adherence to Best Practice Guidelines

Principle Investigator: Craig Lilly 2012-2013
Sponsor: eICU Research Institute

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Adherence to ICU Best Practice Guidelines in Older Adults

Principle Investigator: Nicholas Capogna 2011-2012
Sponsor: eICU Research Institute

Descriptive and hypothesis-testing analyses, tables preparation and manuscript writing.

Elevated economic burden in obstructive lung disease patients with concomitant sleep apnea syndrome.

Principle Investigator: Shaya FT 2008-2009
Sponsor: self-funded
Literature Review and manuscript writing.

Diabetic Retinopathy

Principle Investigator: Shaya FT 2006-2007
Sponsor: self-funded
Literature Review and manuscript writing

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International Society of Pharmacoepidemiology (ISPE)

Student Chapter Secretary 2009-2010
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Fall 2004, 2005, 2006, 2007 Spring, 2005, 2006, 2007, 2008
School of Pharmacy, University of Maryland

Rho Chi Pharmacy Honor Society

2005-Present

I was chosen in both the Pharm.D. and Ph.D. programs to join the Rho Chi Pharmacy honor society.

First Class Honor

January 2002

College of pharmacy, King Saud University

PROFESSIONAL MEMBERSHIPS

Society of Critical Care Medicine

International Society of Pharmacoeconomics and Outcomes Research

International Society of Pharmacoepidemiology

PUBLICATIONS:

Mohammad Aljawadi, Omar Badawi, Ebere Onukwugha, Laurence S Magder, Sarah Tom, Ilene Zuckerman "The Risk of Clostridium Difficile Infection between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in Intensive Care Units " (In progress)

Mohammad Aljawadi, Omar Badawi, Ebere Onukwugha, Laurence S Magder, Sarah Tom, Ilene Zuckerman "The Risk of Clinically Important Gastrointestinal Bleeding and Nosocomial Pneumonia between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in Intensive Care Units" (In progress)

Mohammad Aljawadi, Omar Badawi, Ebere Onukwugha, Laurence S Magder, Sarah Tom, Ilene Zuckerman "Stress Ulcer Prophylaxis in Intensive Care Units Between 2008 and 2012" (In Progress)

Xian Shen, Sarah Dutcher, Xinggang Liu, Zippora Kiptanui, Bilal Khokhar, Jacqueline Palmer, **Mohammad Aljawadi**, Yue Zhu, Ilene Zuckerman. "A Systematic Review of the Benefits and Risks of Anticoagulation Following Traumatic Brain Injury"

Shaya FT, **Aljawadi** MH, Mullins CD, Pandya N, Seal B, Hanna N. "Determinants of TACE treatment assignment in HCC patients in SEER-Medicare" (Accepted poster at the American Association for the Study of Liver Diseases meeting, Nov 4-8, 2011 San Francisco, California)

Shaya FT, Lin PJ, **Aljawadi** MH, Scharf SM. Elevated economic burden in obstructive lung disease patients with concomitant sleep apnea syndrome. Sleep Breath. 2009 Nov;13(4):317-23. Epub 2009 May 30.

Shaya FT, **AlJawadi** M. Diabetic Retinopathy. Clinical Ophthalmology, 2007, 1(3):1-7.

EXPERIENTIAL ROTATIONS

Patient Care I (Sep 2005 – May 2006) and Patient Care II (Sep 2006 – May 2007):

- Interviewed, evaluated, and made recommendations on the drug and non-drug therapy for two patients.
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Carroll Hospital Center, Feb-Apr 2008

In this anticoagulation clinic I had the opportunity to interview, evaluate, and made recommendations regarding anticoagulant therapy.

The Medicine Shoppe Pharmacy; Oct 2004

- Processed and filled prescriptions
- Counseled patients about prescription and OTC medications
- Prepared for inventory

The Medicine Shoppe Pharmacy; June-July 2007

Processed and filled prescriptions

Counseled patients about prescription and OTC medications

Participate in a small project aimed to reduce medications errors inside a community pharmacy.

Raise public awareness regarding smoking cessation and the available resources such as 1-800 quit-now.

University of Maryland Medical Center Pharmacy, Jan – 2007

Filled Prescriptions.

Prepared Intravenous medications.

Participated in journal club meetings.

Shadowed clinical pharmacist during medical rounds.

Participated in a project aimed to assess the adherence of pharmacists, nurses, and pharmacy technicians to handling procedures of Narcotics as well as modifying the existing IV narcotic form to more user-friendly form.

Mercy Medical Center; Mar 2005

Filled Prescriptions., Prepared Intravenous medications, Participated in journal club meetings, Shadowed clinical pharmacist during medical rounds, Participated in a project aimed to distinguish look alike medications.

Kaiser Permanente, Aug- Sep 2007

In this diabetes and cholesterol clinic. I followed up, counseled patient regarding their drug use.

I made drug and non-drug recommendations. I also educated patients on the proper use of glucose meters.

I participated in Medicare's medication therapy management program.

Howard County General Hospital; Oct- Nov 2007

Attended medical rounds

Interviewed patients to obtain their medical history and evaluated the appropriateness of their drug therapy

Made recommendations for alternative drug therapy when appropriate

VA Medical Center, Jan- Feb 2008

This rotation was in the cardiac intensive care unit where I participated in medical rounds and made drug therapy changes.

NeighborCare Pharmacy, Inc. Dec-Jan 2007/2008

Interviewed, evaluated, and made recommendations on the drug and non-drug therapy for patients.

Counseled patients about prescription and OTC medications

Participated in medication therapy management (MTM) program where I did many comprehensive reviews for patient's medications.

Howard County Substance Abuse Services; Jan 2005

One-day rotation that exposed me to pharmacist's role in drug abuse prevention and treatment.

Drug Information, MedImmune, Inc. July – August 2007

In this specialized drug information center, I was able to perform many literature review to and prepare response letters to public inquires as well as health care professionals.

University of Maryland Drug Treatment Center; Sep – Oct 2007

This rotation focused on drug addiction and the available modalities for treatment. I rounded with the substance abuse team at the hospital for two weeks. I also worked on my paper that was about prenatal alcohol exposure and its effect on cognitive functions in children.

Abstract

Title of Dissertation: Stress Ulcer Prophylaxis in Intensive Care Units: Use, Benefit and Risk

Mohammad Aljawadi, Doctor of Philosophy, 2014

Dissertation Directed by: Ilene Zuckerman, Professor, Pharmaceutical Health Services Research

Stress ulcer prophylaxis (SUP) is a standard of care for intensive care unit (ICU) patients with stress ulcer risk factors (SURFs). Proton pump inhibitors (PPIs) and histamine-2 receptor blockers (H2Bs) are commonly used as SUP. The higher potency of PPIs suggests more reduction in clinically important gastrointestinal bleeding (CIGIB) compared to H2Bs but higher risk of nosocomial pneumonia (NP) and clostridium-difficile associated diseases (CDAD). The goals of this study are to describe factors associated with SUP use and determine whether PPIs are associated with lower risk of CIGIB and higher risk of NP and CDAD compared to H2Bs in the ICU.

Using Philips eICU Research Institute ICU database, a cohort of 572,519 adults admitted to 293 ICUs between 1/1/2008 and 6/30/2012 was created to study SUP use, overuse and outcomes. SUP use was defined as the administration PPIs, H2Bs, sucralfate or antacids during the ICU stay while overuse was defined as the use of the aforementioned classes without an indication. Multivariable logistic regression was used to identify factors associated with use and with overuse. Discrete-time Cox proportional

hazard multivariable regression models were used to compare PPIs to H2Bs with regard to CIGIB, NP and CDAD.

The cohort comprised 76% Caucasians and 54% males. SUP use was high (86.4%). While most of SURFs predicted SUP receipt, mechanical ventilation for more than 24 hours (odds ratio (OR) =10.6, 99% CI: 9.8-11.5) and organ transplantation (OR=13.3, 99% CI: 6.9-25.7) were the strongest predictors. Overuse of SUP medications was observed in 80% of patients with no indications. Hazard of CIGIB was two times greater for PPI users compared to H2B users (adjusted hazard ratio (HR) 1.97 (95% CI: 1.48-2.63). Hazard of CDAD was not significantly different between the PPIs and H2B users (HR: 1.12, 95% CI: 0.89-1.41), while the risk of NP was lower among PPI compared to H2B users (HR: 0.87, 95% CI: 0.77-0.97). Knowledge generated from this study on factors associated with SUP use in the ICU, and comparative risks and benefits, can be used to identify and design interventions to improve guideline adherence and improve appropriateness of use and outcomes.

Stress Ulcer Prophylaxis in Intensive Care Units: Use, Benefit and Risk

by
Mohammad Hasan Aljawadi

Dissertation submitted to the faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2014

Acknowledgments

I begin with praising and thanking Allah who showered me with his bounties and blessings. Prophet Mohammad, peace be upon him, said: “Whoever does not thank people does not thank Allah.” Therefore, these are few words that barely represent my deep appreciation and gratitude to those amazing people whom Allah blessed me with.

To my advisor Dr. Ilene Zuckerman, thank you very much for sharing your knowledge and wisdom with me throughout this dissertation. Your high standards that were mixed with joyfulness inspired me to become a better researcher and mentor every day.

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To my colleagues, Abdulla Aly and Candice Young, I will always be grateful for the numerous hours we spent discussing this dissertation and for the beautiful times we spent together in the PHSR department.

To the PHSR faculty, staff and students, it is rare to find a place where everyone works in homogeneity and synchrony like the PHSR department. I will be always appreciative for the very productive yet friendly environment you all created.

To the dearest people in my life, my beautiful family, I would have not reached this level without your unconditional love and support. To my father, may Allah reward you the best of this life and the hereafter for pushing me forward when I was tangled in my own fears and self-doubts. To my mother, I will always remember that you sacrificed having me near to your death bed so I can fulfill my dream. I will always pray to Allah that one day we will be united again in his paradise.

To Mustafa, thank you for being my big brother who supported me with his advice and constant enthusiasm throughout my life. To Wasseem, my younger brother, thank you for being my problem solver while I am away from home. To my sisters, Hanady and Hayathem, you are the apple of my eyes. Thank you for all your kind words that continuously encouraged me.

Last but definitely not least, to my beloved wife Manal, you are the one who deserve this degree with me. I will never forget the numerous nights you waited for me after midnight to fix me a meal or, simply, to know if I need anything. I will never forget that you have sacrificed pursuing your higher education so our daughter, Mawadda, gets the best care possible. Thank you for your patience, for being there for me, for everything and anything. Thank you from the bottom of my heart.

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List of Abbreviation:

Abbreviation	Full Term
aPTT	Partial Thromboplastin Time
ASHP	American Society Of Health System Pharmacists
BSA	Body Surface Area
C.difficile	Clostridium Difficile
CDAD	Clostridium difficile-Associated Disease
CIGIB	Clinically Important Gastrointestinal Bleeding
EN	Enteral Nutrition
GI	Gastrointestinal
GIB	Gastrointestinal Bleeding
H. pylori	Helicobacter Pylori
H⁺/K⁺ pump	Hydrogen-Potassium ATPase Pump
H2Bs	Histamine-2 receptor Blockers
HF	Hepatic Failure
ICUs	Intensive Care Units
INR	International Normalized Ratio
LOS	Length of Stay
MV	Mechanical Ventilation
NG	Nasogastric
NP	Nosocomial Pneumonia
NNH	Number Needed to Harm
PPIs	Proton Pump Inhibitors
PT	Prothrombin Time
RBA	Risk-Benefit Assessment
RBAT	Risk–Benefit Acceptability Threshold
RBP	Risk–Benefit Plane
RF	Respiratory Failure
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error
SRMD	Stress-Related Mucosal Damage
SUP	Stress Ulcer Prophylaxis
APACHE-IV score	Acute Physiology and Chronic Health Evaluation Score Version IV
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
HIV	Human Immunodeficiency Virus
RCT	Randomized Clinical Trials
Hgb	Hemoglobin
SBP	Systolic Blood Pressure
OR	Odds Ratio
EAST	Eastern Association for the Surgery of Trauma
FDA	Food and Drug Administration

List of Abbreviation

Abbreviation	Full Term
CI	Confidence Interval
RD	Risk Difference
CAP	Community-acquired Pneumonia
GAMAS	Gastric Acid Modifying Drugs or Sucralfate
eRI	eICU Research Institute
ICD-9	International Classification of Diseases 9 th <i>ed</i>
2SRI	Two Stage Residual Inclusion
2SLS	Two Stage Least Squares
IV	Instrumental Variable
PSM	Propensity Score Matching
HR	Hazard Ratio
COPD	Chronic Obstructive Pulmonary Disease
ARDS	Acute Respiratory Distress Syndrome

Chapter I. Introduction

A. Study Motivation

The process of weighing the risk and benefit of therapies is a pivotal component of health care decision making. It is integrated in different levels of health care delivery from formulary decisions to clinicians' decisions. In Intensive Care Units (ICU_(s)), numerous interventions have been part of routine care after proving that their benefits outweigh their risks in clinical trials. However, in daily routine practice outside of the clinical trial environment, many factors influence the effectiveness and safety of these interventions. Consequently, the real world effectiveness and safety of such interventions are not well-known. Stress Ulcer Prophylaxis (SUP) is an example of these interventions. Many clinical trials have demonstrated that SUP leads to a reduction in the risk of gastrointestinal bleeding (GIB) and, hence, a reduction in ICU mortality and length of stay (LOS). However, the drugs used for SUP, mainly acid suppressants, have been implicated in increasing the incidence of nosocomial pneumonia (NP). Furthermore, recent studies have linked the use of proton pump inhibitors (PPIs), which are used as for SUP, with *Clostridium difficile*-associated disease (CDAD) in community settings. While multiple meta-analyses concluded that the benefit of SUP (i.e., a lower risk of GIB) outweigh the risk of NP, no clinical trial has explored the benefit of SUP while taking into account the risk of CDAD in the ICU.

Another piece of the puzzle is SUP utilization and overutilization in ICU practice. Since the introduction of the American Society of Health System Pharmacists guidelines, many aspects in ICU practice have changed such as the introduction of proton pump inhibitors (PPIs) as one of the main SUP modalities in many ICUs nowadays. In addition, ICU care itself has changed with the introduction of more sophisticated equipment and better staff training which may reduce the need for these medications. Furthermore, the nature of ICU care that requires close monitoring and the advances in information technology created large ICU-based databases that can be used in conducting observational studies on large number of patients. Despite all these changes, the majority of the SUP-related studies focused more on exploring the benefits and risks of SUP rather than exploring who is using these medications in real world and the degree of incongruence between the guidelines and real world. The latter is important in identifying SUP overutilization and the topics that require more investigations. Many studies have documented overuse of SUP both in ICUs and even in hospital wards where SUP is not indicated. Moreover, this overuse has been associated with significant financial burden not only due to unnecessary use in ICUs but also due to continuation of use after hospital discharge.

These knowledge gaps obscure clinicians, formulary decision makers and guidelines developers from arriving to a clear informed decision regarding the safety and effectiveness of SUP. In addition, understanding SUP utilization and overutilization is important to determine areas where more implementation of the guidelines is needed and the areas where more research is necessary.

B. Research Questions and Aims:

Research Question 1: How is SUP used in real world ICU settings and what are the characteristics of patients receiving these drugs?

Aim1a: To describe SUP utilization by exploring the use of different SUP strategies, determining its adherence to the guidelines and determining factors associated with SUP utilization.

Aim1b: To quantify SUP overutilization and determine factors associated with it.

Research Question 2: Compared to histamine type-2 receptors blockers (H2B), are proton pump inhibitors associated with lower risk of clinically important gastrointestinal bleeding (CIGIB)?

Aim2a. To determine whether or not PPIs are associated with a lower risk of CIGIB compared to H2Bs.

2a. I hypothesize that the receipt of PPIs leads to a lower risk of CIGIB compared to H2Bs.

Research Question 3: Between proton pump inhibitors and Histamine-2 receptors blockers, which therapeutic class is associated with higher risk of *Clostridium difficile*-associated disease (CDAD) and which is associated with higher risk of NP?

Aim3a. To determine whether or not PPIs are associated with a higher risk of CDAD compared to H2Bs in real world ICU settings.

3a. I hypothesize that the receipt of PPIs is associated with a higher risk of CDAD compared to H2Bs.

Aim3b. To determine whether or not PPIs are associated with a greater risk of NP compared to H2Bs in real world ICU settings.

3b. I hypothesize that the receipt of PPIs is associated with to a higher risk of NP compared to H2Bs.

C. Importance and Significance:

The proposed study is important for a number of reasons. First, while the results of clinical trials provide information regarding risks and benefits of SUP drugs, how clinicians actually use these drugs in daily practice is less clear. This is the first population-based study that describes the utilization of SUP drugs in the U.S. ICU setting. It will shed light on the characteristics of patients who are being prescribed these medications as well as the patterns of SUP utilization and overutilization in real world settings. Stress ulcer prophylaxis overutilization is defined as any use of SUP medications without indication for stress ulcer. Many studies have documented overuse of SUP both in ICUs and even in hospital wards where SUP is not indicated. Percentages of overutilization varied from 19% to 92%¹⁻⁴. Studies have reported in-hospital annual cost of inappropriate use between \$11,000 and \$23,000^{3,4}. Moreover, this overuse has been associated with significant financial burden not only due to unnecessary use in ICUs but also due to continuation of use after hospital discharge. For instance, in 2010 Thomas and colleagues used a managed care organization database of 29,348 beneficiaries who

were prescribed proton pump inhibitors (PPIs) in the ICU. They reported that 68.7% of the patients were inappropriately discharged on a PPI. In this study, between 2003 and 2006, the total cost of PPIs use after one month of being discharged from the hospital was \$3,013,069⁵. Such descriptive pharmacoepidemiological information identifies the degree of adherence to clinical guidelines and the gaps between real world practice and guidelines of best practice. Thus, it reveals the areas where more research is needed as well as the areas where more implementation of guidelines is warranted.

Second, despite the fact that studying the effectiveness of acid suppressants using real world data is important in its own, ignoring the risks that may be associated with their use provides incomplete information to clinicians, guidelines developers and formulary decision makers regarding the role of these drugs in improving care in ICU settings. Thus, studying the safety of these medications in real world settings where larger number of patients receives them provides this missing piece of research.

Third, CDAD is a condition that has been documented to increase ICU mortality and length of stay. However, few studies have looked at the association between CDAD and SUP in ICU settings. Therefore, ascertaining the association between acid suppressants and CDAD unveils crucial information about the safety of these drugs and the characteristics of patients who are vulnerable to this side effect if it truly exists. On the other hand, demonstrating a lack of association between acid suppressants and CDAD would be important to reinforce clinicians' knowledge and increase their confidence in using these drugs.

Fourth, the Philips eICU database that was used in this study comprises almost 300 ICUs from 40 health systems across 34 states. The novelty and the importance of this database come from the fact that it is the first large ICU database that is available for multiple years (2008-2012) and a large number of patients. Thus, the database allows detecting even small effect sizes and exploring the effect of PPIs and H2Bs among patients subgroups who are at varying risks of stress-ulcer; two advantages that could otherwise only be achieved by a very expensive clinical trial that has a very large number of patients. In addition, the database provides an advantage of controlling for clinical confounders that are not available in administrative claims data.

The remaining of the dissertation is divided as follows: Chapter 2 includes a comprehensive review of SUP literature. Chapter 3 delineates a detailed description of the data used in these studies. Chapters 4-6 provide three manuscripts corresponding to the three aforementioned research questions. Lastly, Chapter 7 is a discussion of the findings from the three manuscripts, implications for current practice and future research directions.

Chapter II. Background and Literature Review

Stress-related mucosal damage (SRMD) was first described in 1842 by T.B. Curling who presented a case series of patients who developed duodenal ulceration following extensive burns ⁶. Since that time, several observational studies and randomized controlled trials (RCTs) have shed light on the mechanisms by which stress leads to GIB as well the prophylactic modalities used in preventing GIB due to stress. Despite the rich literature, many controversies still exist regarding which therapeutic class provides the most benefit with the least risks in different patient subgroups.

A. Epidemiology:

1. Definitions of Stress Ulcer Bleeding:

Gastrointestinal stress ulcer bleeding has three main definitions in the literature; occult bleeding, overt bleeding and clinically important gastrointestinal bleeding (CIGIB). Occult bleeding is identified through a fecal sample that shows a positive guaiac test with no indication of overt bleeding ⁷. Overt bleeding is generally defined as vomiting of fresh blood (hematemesis) or digested blood, commonly described as coffee ground emesis, dark stools (melena) or the existence of blood in the aspirate of the nasogastric tube ^{8,9}. However, not all overt bleeding episodes are clinically important. Therefore, the definition of CIGIB includes bleeding episodes that may have an effect on morbidity or mortality. Clinically important bleeding is defined as gastrointestinal bleeding that is accompanied by hemodynamic changes. Cook et al ¹⁰ produced one of the widely accepted definitions of hemodynamic changes, including any of the following outcomes within 24 hours of bleeding:

- 1) At least 20 mmHg spontaneous reduction in systolic blood pressure (SBP)
- 2) At least 20 beats/minute increase in heart rate.
- 3) At least 10 mmHg reduction in SBP measured on sitting up.
- 4) At least 2 g/dl reduction in hemoglobin (Hgb) accompanied by the receipt of transfusion after which Hgb did not rise by the number of units received -2 g/dl.

a. The Incidence of Stress Ulcer and Related Bleeding:

In general, almost 60% to 100% of ICU patients develop SRMD with the majority occurring during the first 24 to 72 hours¹¹⁻¹³. Not all SRMD episodes progress to occult bleeding; the incidence of occult bleeding ranges between 13% and 50%^{14,15}. With regard to overt bleeding, old studies that had a placebo arm, which represented the natural progression of the disease, reported an incidence of overt bleeding that reached up to 30% in the placebo group¹⁵.

In 1999, the American Society of Health-System Pharmacists (ASHP) published guidelines for SUP in critical care settings. At that time, the guidelines reported the incidence of CIGIB to range between 2% to 6%¹⁶. Interestingly, the implementation of the ASHP guidelines have led to a reduction in the incidence of CIGIB in studies published after the guidelines implementation to range between 0.3% and 4%.¹⁷⁻²²

b. Clinically Important Bleeding and Mortality:

Clinically important bleeding has been linked to both an increase in mortality as well as LOS among patients in the ICU. In a prospective multi-center cohort study that included 2252 patients admitted to the ICU, Cook et al found that mortality among

patients with CIGIB was 48.5% compared to 9.1% among non-bleeders²³. Seven years later, in 2001, Cook and colleagues used three analytical methods to determine mortality and ICU LOS attributable to CIGIB among the aforementioned patients. Regardless of the method used, CIGIB was associated with higher mortality (Relative Risk (RR) = 2.9, 95 % Confidence Interval (95%CI) 1.6 to 5.5) and ICU LOS (Range: 4 and 8 days) compared to patients who did not develop CIGIB²⁴.

B. Pathophysiology of stress ulcer:

1. Natural Defense Mechanisms:

The gastric mucosa is protected via multiple mechanisms. A thick layer of mucus and bicarbonate protects gastric mucosa against hydrochloric acid and pepsin which are the main digestive compounds in the stomach. Just below the aforementioned layer, cells also are covered by a glycoprotein matrix that serves as a physical barrier against the gastric juice. Equally important, splanchnic blood supply insures adequate microcirculation to maintain constant gastric cell regeneration and prevent visceral ischemia. Furthermore, the continuous movements of the stomach reduce the contact between gastric juice and the stomach linings keeping gastric mucosa intact²⁵.

2. Mechanism of Stress Ulcer Development:

The exposure to stressful events such as respiratory failure, extensive burns, sepsis and other risk factors of stress ulcer leads to splanchnic hypo-perfusion and ischemia of gastric microcirculation^{25,26}. In addition, in most cases gastric motility is reduced due to lack of enteral feeding, lack of mobility and the use of medications such as muscle

relaxants, anticholinergics, narcotic analgesics or antacids. These factors lead to a reduction in nutrient absorption, accompanied by impairment in oxygen delivery. In addition, mucus and bicarbonate production becomes diminished. Consequently, the mucosal acid-buffering capacity deteriorates making the inner layer of the stomach exposed to the main destructive factors, i.e., gastric acid and pepsin^{26,27}. Despite the important role that visceral ischemia plays, it is noteworthy that gastric acid is an essential requirement for the pathogenesis of stress ulcers. For instance, in animal models, under ischemic conditions alone, SRMD involved 4% of the stomach's body and 3% of the antrum. In contrast, lesions involved 53% of the body and 45% of the antrum upon intra-gastric instillation of gastric acid^{28,29}.

3. Risk Factors for Stress Ulcer-Related Gastrointestinal Bleeding:

Cook et al's seminal paper in 1994 identified the main two risk factors for developing GIB²³. Around 2000 patients above 16 years old were included in this multicenter prospective cohort study. . Patients with an overt bleeding that occurred 48 hours before or 24 hours after admission to the ICU were excluded. To minimize the influence of acid suppressants on GIB rates, clinicians were advised to give them only to patients with a definite reason which included head injuries, burns that cover more than 30% of body surface area (BSA), peptic ulcer or gastritis diagnosed by radiography during the six weeks prior to enrollment and upper GIB three to six days prior to admission. The receipt of at least two doses of H2B, antacids, sucralfate, prostaglandins analogues or omeprazole defined the receipt of SUP. The primary outcome was CIGIB. The investigators examined the following risk factors of GIB: respiratory failure (RF)

that required mechanical ventilation (MV) for at least 48 hours, coagulopathy was defined as platelet count $< 50,000$ per/ml³; an international normalized ratio (INR) > 1.5 , prothrombin time (PT) > 1.5 of the control value or partial thromboplastin time (aPTT) > 2 of the control value; hypotension, sepsis, hepatic failure, renal failure, enteral nutrition, the use of glucocorticoids, organ transplantation and the use of anticoagulant therapy. Out of the 2252 patients, only one hundred (4.4%) patients developed overt bleeding among which 33 (1.5%) patients developed CIGIB. Among patients who had neither respiratory failure nor coagulopathy (n=1405), the incidence of CIGIB was 0.1% compared to 3.8% among patients who had at least one of the two conditions (n=845). The multivariable logistic regression results showed that out of all potential risk factors only respiratory failure and coagulopathy were associated with CIGIB with ORs of 15.6 (P= <0.001) and 4.3 (P= <0.001), respectively. The authors estimated that for other potential risk factors, it would be necessary to administer SUP to 900 patients to prevent one case of GIB. On the other hand, it is enough to administer SUP to 30 patients who have respiratory failure or coagulopathy to prevent one case of GIB.

Aside from the aforementioned risk factors, the ASHP guidelines recommended the administration of SUP to the following specific patients populations in the ICU settings: Patients with head injuries who have a Glasgow Coma Score (GCS) less than 10, thermal injuries that covers more than 35% of BSA, hepatic failure, partial hepatectomy, transplantation or multiple trauma. Because of pathophysiological differences in GIB, these special populations have been studied separately from the general ICU patients¹⁶. The majority of studies conducted on these patients populations were done in the 70s

12,30-34 and the 80s³⁵⁻⁴¹ with few that were done in the 90s⁴²⁻⁴⁵. Many of these studies compared cimetidine or ranitidine to no SUP^{33-40,42,44} and very few were RCTs^{43,45}. Thus, while most of these studies proved that H2Bs are beneficial in reducing overt bleeding and CIGIB in these specific patients populations, **the gaps in current literature concentrate the comparative effectiveness and safety of current SUP, i.e., PPIs and H2Bs, in these patients populations.** Table 2.1 summarizes patient subgroups that are at risk of GIB due to stress ulcer based on the 1999 ASHP guidelines¹⁶ and the 2008 guidelines⁴⁶ of the Eastern Association for the Surgery of Trauma (EAST).

Table 2.1: Risk Factors for Stress Ulcer Related Gastrointestinal Bleeding in Intensive Care Units

Risk factors of gastrointestinal bleeding due to stress ulcer	Source
Major	
Mechanical Ventilation > 48 hrs.	ASHP & EAST
Coagulopathy	ASHP & EAST
Major Head Injuries	ASHP & EAST
Major Burns (>35% of BSA)	ASHP & EAST
Minor	
Sepsis	ASHP & EAST
Multiple Trauma Injury	ASHP & EAST
Corticosteroid Therapy > 250 mg of hydrocortisone or equivalent daily	ASHP & EAST
Spinal cord injuries or Head injuries	ASHP
Renal Failure	ASHP
Hepatic Failure	ASHP
Partial Hepatectomy	ASHP
Transplantation	ASHP
History of Gastric Ulcer or bleeding a year prior to admission	ASHP
ICU stay of > 1 week	ASHP
Occult or overt bleeding for \geq 6 days	ASHP

ASHP: American Society of Health System Pharmacists; EAST: Eastern Association for the Surgery of Trauma; BSA: Body Surface Area, ICU: Intensive Care Unit

B. Mechanism of action and Efficacy of Stress-Ulcer Prophylactic Modalities

Over the past four decades, four main pharmacological classes have been used as SUP. These include PPIs, H2Bs, antacids and sucralfate. Cimetidine, a H2B, and antacids were the first used during the mid-seventies and early 80s. In 1981, sucralfate was

approved by the FDA. It was not until 1989 when the first PPI, omeprazole, was introduced to the US market. Interestingly, cimetidine and, more recently, omeprazole, are the only FDA approved drugs as drugs for SUP^{47,48}. Nevertheless, many H2Bs, other PPIs as well as sucralfate are used off-label for SUP. The following sections discuss the pharmacological properties and efficacy of these medications which are important in understanding the theory behind the expected difference in the effectiveness between PPIs and H2Bs in real world settings

1. Pharmacological Properties:

a. Mechanism of action of PPIs and H2Bs:

Secretion of gastric acid is mainly stimulated by histamine, acetylcholine and gastrin. These three compounds bind to their receptors on parietal cells. Parietal cells are responsible for producing Hydrogen ions and maintaining gastric pH around 1.4⁴⁹. The binding starts a series of intracellular cascade that ends up with the activation of a Hydrogen-Potassium ATPase pump (H^+/K^+ pump) that releases the hydrogen ions into the gastric lumen. Histamine receptor type-2 blockers inhibit acid production by blocking histamine receptors on parietal cells. On the other hand, PPIs suppress acid production by irreversibly inhibiting the H^+/K^+ pump itself⁵⁰. This distinction in mechanism of action illustrate why tolerance develops with H2Bs but not with PPIs. When histamine receptors are blocked, acetylcholine and gastrin secretions increase as a compensatory mechanism leading to activation of H^+/K^+ pump and hydrogen ion release from parietal cells despite the blockade. To the contrary, once the H^+/K^+ pumps are inactivated by PPIs the parietal cell itself does not produce hydrogen ions until new pump are formed. Thus, the PPIs

blockade is not influenced by the compensatory release of histamine, acetylcholine and gastrin⁵¹. Both the development of tolerance to H2Bs and the irreversible action of PPIs explain the higher potency of PPIs, as acid suppressors, compared to H2Bs. This higher potency of PPIs shifted the use from H2Bs to PPIs over the past two decades. In addition, it created the belief that PPIs are associated with higher incidence of NP and CDAD⁵²⁻⁵⁵.

b. Mechanism of action of sucralfate and antacids:

Unlike PPIs and H2Bs, sucralfate is minimally absorbed from the GI tract. Thus, its actions are based on local interactions with positively charged proteins and ions in the exudates of an ulcer. The interaction leads to the formation of viscous paste-like layer that adheres to the ulcer. Therefore, this layer protects the gastric mucosa from the action of hydrochloric acid, pepsin and bile acids⁵⁰. In contrast, antacids act by neutralizing the released hydrochloric acid inside the gastric lumen. Both sucralfate and antacids have a short duration of actions compared to PPIs and H2Bs. Therefore, based on their potency, PPIs are the most potent followed by H2Bs while sucralfate and antacids are considered the weakest due to their local and short duration of action. These differences in potency have reduced the use of antacids and sucralfate. In addition, both antacids and sucralfate required time-consuming administration techniques. For instance, antacids have to be administered every one to two hours accompanied by pH monitoring and sucralfate needs to be administered through a nasogastric tube and suspension of enteral feeding^{56, 48, 50}.

A large number of RCTs over the last 40 years have examined these four drug groups used in SUP. Many of the early studies included placebo arm to prove the concept of SUP. In the mid-80s, H2Bs became the standard of care upon the approval of cimetidine

as a drug that can be used in SUP. Upon the introduction of sucralfate, placebo and antacids studies started to fade out and studies comparing sucralfate to H2Bs became more prevalent in the literature^{8,57}. Later, after PPIs made it to the market, most of RCTs focused on comparing PPIs to H2Bs.

2. Efficacy of PPIs compared to H2Bs:

Because in the late 1980s cimetidine was the only FDA approved drug as SUP in the ICU, it was unethical to compare PPIs to any other class without H2Bs as a separate study arm. Alongside the FDA approval, the ease of administration of H2Bs abated the use of sucralfate as a SUP. Therefore, since 1993, thirteen RCTs were published comparing PPIs to H2Bs. Nine of these studies were published after 2000, i.e., after the publication of the ASHP guidelines that recommended the use of H2Bs⁵⁸⁻⁶⁶. While the exposure to a PPI or a H2B was fully defined, many had unclear definition for significant GIB and upper GIB. The most frequent definition used was CIGIB which was defined in six studies^{61,62,64-67}. Only four out of these six studies were powered to detect a significant difference between treatments arms^{61,62,64,66}. However, only two of the six studies looked at CIGIB as the primary outcome of interest^{62,67}. The remaining seven studies focused on gastric pH and Upper GIB^{58-60,63,68-70}.

Five meta-analyses summarized the results of these RCTs⁷¹⁻⁷⁵. In 2009, Pongprasobchai et al conducted the first meta-analysis that included any study that had critically ill patients who were mechanically ventilated for at least 48 hrs. or patients who had coagulopathy. The outcome of interest was CIGIB. Only three studies with a total of

569 patients were included^{61,62,67}. The pooled incidence of CIGIB among the PPIs was significantly lower than that among the H2Bs group (3.5% vs. 8%). Proton pump inhibitors were associated with lower incidence of CIGIB compared to H2Bs (OR=0.42, 95%CI: 0.20 to 0.91, I²=0).

In April 2010, Zhou et al and Lin et al^{72,73} published two meta-analyses. Unlike the previous study that focused only on patients on MV or with coagulopathy, Zhou and colleagues included any study that looked at adult patients who were in the ICU for at least 72 hours and who used PPIs or H2Bs during their ICU stay. Consequently, they included one additional study⁶⁴ over Pongprasobchai's meta-analysis which raised the number of patients to 771. Compared to H2Bs, Zhou et al found a lower risk of CIGIB among the PPIs group (Incidence: 2.2% vs. 6.8%, OR=0.45, 95%CI: 0.21 to 0.96. In addition, there was no difference in ICU mortality between PPIs (14.5%) and H2Bs (14.3%) (OR=1.17 95%CI: 0.76 to 1.8).

In contrast to the aforementioned two meta-analyses, Lin's meta-analysis did not use ICU LOS as an inclusion criterion for the meta-analysis. Instead, they included any RCT or quasi-experimental study for patients in a medical or surgical ICU who were given either PPIs or H2Bs as SUP. Thus, three additional studies were included^{60,68,70}. The main outcome of interest in Lin's meta-analysis was the pooled incidence of stress-related upper GIB of any definition. The study included 936 patients among which 540 patients received PPIs and 396 received H2Bs. A random effects model was used to account for variation between studies. The pooled incidence of upper GIB was 2.03%

among the PPIs group compared to 7.82% among the H2Bs group. Comparing PPIs to H2Bs, the pooled risk difference (RD) was -0.04 with 95%CI ranges from -0.09 to +0.01 (P=0.08, $I^2=66\%$). A high I^2 represent a high heterogeneity between the included studies. The influence analysis that is done by removing one study at a time and determining the influence of the excluded study on the pooled estimate showed a robust result of no statistically significant difference between PPIs and H2Bs. Moreover, the removal of Levy's study⁶⁷ reduced the I^2 to 26% with a corresponding pooled RD of -0.02 (95%CI: -0.05 to +0.01, P=0.19). Sensitivity analyses included assessing the effect of both treatments on the risk of upper GIB among RCTs that reported balanced covariates at baseline and studies that required being on mechanical ventilator for 48 hours. In both cases there was no statistically significant difference between the two treatments. In addition, irrespective of the quality of the study (high vs. low), upper GIB definition (poor vs. good), the number of risk factors (greater than one vs. one or more) or route of administration (enterally vs. intravenously), there was no difference in treatment effect between PPIs and H2Bs. However, PPIs showed an advantage over H2Bs only among studies published prior to 2000 (RD= -0.11, 95% CI: -0.21 to -0.01, p=0.03, $I^2=54\%$). This could be due to the fact that two of the three studies conducted prior to 2000 included high risk patients the fact that allowed the difference between PPIs and H2Bs to become significant. The funnel plot showed asymmetric distribution of studies estimates indicating a publication bias that could be due to language bias and small RCTs with inflated estimates. The mortality rate among the PPIs group was 16.7% compared to 15%

among the H2Bs group. This was translated to insignificant risk difference between the PPIs and H2Bs (RD=0.02, 95% CI: -0.04 to +0.08, p=0.73, I²=0).

In 2012, Barkun and colleagues included any RCTs or quasi-experimental studies that compared PPIs to H2Bs among patients at risk of GIB in the ICU settings⁷⁴. They excluded any study that did not have one of the two active comparators, studies on pediatric patients and studies that had only gastric pH readings as outcomes. Consequently, thirteen RCTs with a total of 1,587 patients were included in their meta-analysis. Any type of bleeding, NP, ICU mortality and ICU LOS were the main outcomes of interest. Fixed effects models were chosen after finding that the Q statistic, a measure that is used to determine the extent of heterogeneity between studies, was statistically insignificant.

Barkun et al. found that PPIs were superior to H2Bs in reducing the risk of GIB (OR=0.30, 95% CI: 0.17 to 0.54, RD= -0.026, 95% CI: -0.049 to -0.003, N=1,587). Furthermore, compared to H2Bs, PPIs were not associated with any additional risk ICU mortality (OR=1.19, 95%CI: 0.84 to 1.68, N=1,260) or increased ICU LOS (weighted mean difference=- 0.12, 95%CI: - 1.90 to +1.66, N=339). The results were robust when influence analysis was performed.

Lastly in 2013, similar to the Barkun's inclusion criteria, Al-Hazzani and colleagues included any RCTs that compared the risk of GIB between PPIs to H2Bs in adult patients admitted to a medical or surgical ICU. However, their systematic review yielded 14 RCTs with a total of 1614 patients. The outcomes of interest were CIGIB, overt bleeding,

NP, CDAD, ICU mortality and ICU LOS. Proton pump inhibitors were associated with a lower risk of CIGIB compared to H2Bs (Relative Risk [RR] =0.36, 95% CI=0.19 to 0.68, P=0.002, I2= 0%, N=1,614) and overt bleeding (RR=0.35, 95% CI=0.21 to 0.59, P=0.001, I2= 15%, N=1,720). On the other hand, no differences were found between the two treatments in terms of ICU mortality (RR=1.01, 95% CI 0.83 to 1.24, P=0.91, I2= 0%, N=1,196) or ICU LOS (mean difference=-0.54 days, 95% CI -2.20, +1.13, P=0.53, I2 = 39%, N=555). Regarding CDAD, there were no comparative efficacy studies that compared PPIs to H2Bs.⁷⁶

The main differences between the last two meta-analyses and Lin's meta-analysis are the number of studies included and the measure of association used. The additional four to five studies that were included in Al-Hazzani's and Barkun studies, respectively, almost doubled the sample size used in Lin's study. In addition, the use of risk difference in meta-analyses has been found to be less consistent than both OR and RR.⁷⁷ Nonetheless, when Barkun et al performed the analysis using a similar approach of Lin's study i.e., using a risk difference as measure of association and a random effect model, the result was still in favor of PPIs indicating that the issue was more a sample size issue than the measure of association itself. Figure 2.1 and Table 2.2 summarize the results of the RCTs used in these five meta-analyses and the results of the meta-analyses themselves, respectively. In February 2014, a large observational study of 35,312 patients, among which 21,873 (61.9%) received PPIs and 13,439 (38.1%) received H2Bs, found that PPIs were associated with higher risk of GIB compared to H2Bs (5.9% vs

2.1%). After propensity score and covariates adjustment, the investigators found that PPIs were associated with higher risk of GIB (OR=2.24, 95%CI: 1.81-2.76)⁷⁸.

In summary, one RCT and most of the aforementioned meta-analyses agreed on the superiority of PPIs over H2Bs in preventing stress ulcer-related GIB (Figure 2.1). However, other RCTs and Levy's meta-analysis showed no difference between the two therapeutic classes. In addition, more recently, MacLaren's study⁷⁸ showed completely the opposite suggesting that the risk of GIB was lower with H2Bs compared to PPIs. These inconsistencies in the results and the availability of large database of electronic medical records necessitate conducting a comparative effectiveness study to determine if there is a difference between the most widely used therapeutic classes in SUP and the direction of the difference if existed.

Figure 2. 1: Forrest Plot of Studies Comparing the Risk of Gastrointestinal Bleeding between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in the Intensive Care Units(Based on Al-Hazzani's meta-analysis)76

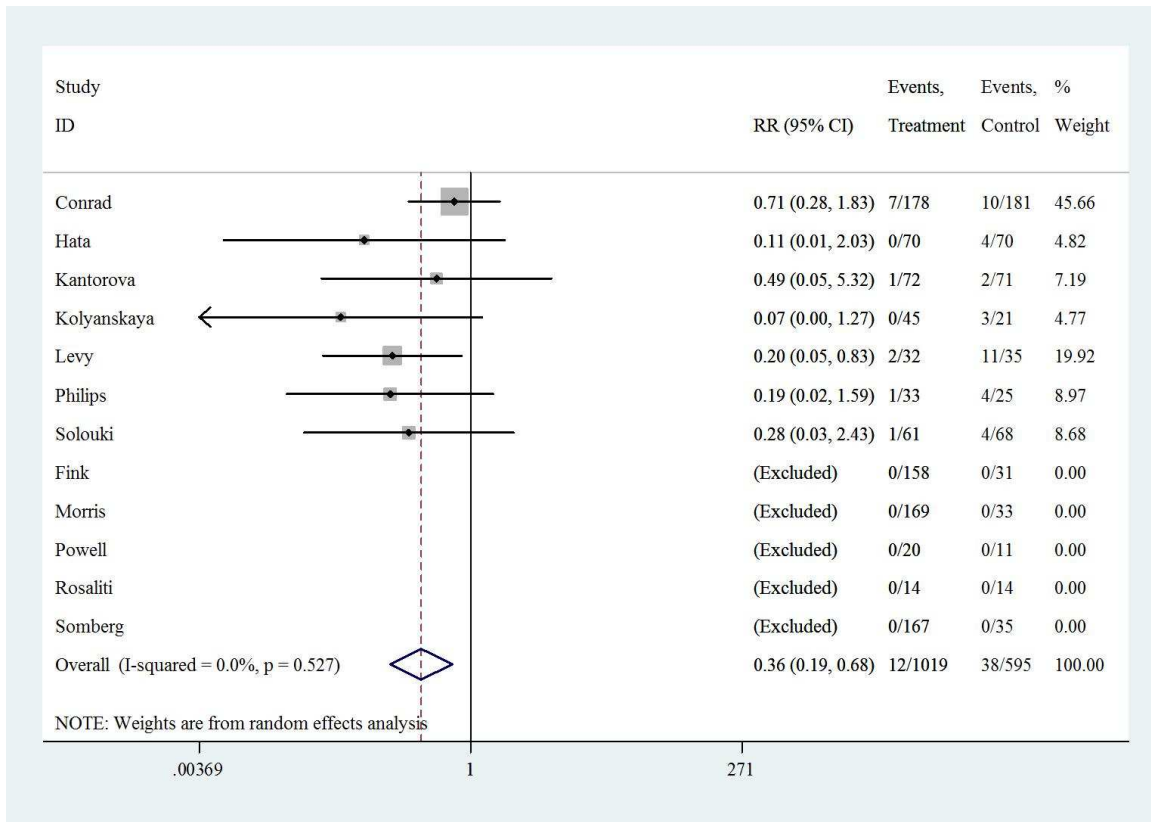


Table 2.2: Summary of the Meta-Analyses that Compared the Risk of Gastrointestinal Bleeding between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in the Intensive Care Units

Reference	Number of gastrointestinal bleeding episodes among the proton pump inhibitors group (%)	Number of gastrointestinal bleeding episodes among Histamine-2 receptor blockers group (%)	Point of estimate and 95% confidence interval of the risk gastrointestinal bleeding comparing PPIs to H2Bs
Pongprasobchai 2009 (n=569)	10/282 (3.5%)	23/287 (8.01%)	OR: 0.42 (95% CI: 0.20 to 0.91)
Zhou 2010 (n=771)	10/449 (2.2%)	22/322 (6.8%)	OR: 0.45 (95% CI: 0.21 to 0.96)
Lin PC 2010 (n=936)	11/540 (2.04%)	31/396 (7.8%)	RD: -0.04 (95% CI: -0.09 to +0.01)
Barkun AN 2012 (n=1,587)	13/967 (1.3%)	41/620 (6.6%)	OR: 0.30 (95% CI: 0.17 to 0.54)
Al-Hazzani 2013 (n=1,614)	12/1019 (1.2%)	38/595 (6.4%)	RR: 0.36 (95% CI: 0.19 to 0.68)

PPIs: Proton Pump Inhibitors; H2Bs: Histamine-2 receptor blockers; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk

3. Safety of Stress-Ulcer Prophylactic Modalities (Nosocomial Pneumonia):

a. Natural defense mechanism:

The oro-gastric tract is supported by multiple defense mechanisms that reduce bacterial colonization inside the GI system such as gastric acid secretion, salivary gland secretions, and the continuous peristaltic movements of the GI muscles. Focusing on gastric acid, its secretion maintains stomach pH around 1.4 to 2 which hinders bacterial growth and colonization^{49,79,80}.

b. Mechanisms by which acids suppressant may cause NP:

The use of acid suppressants as a prophylactic therapy in stress ulcer raised a concern that these drugs may lead to the development of pneumonia both in the community and the hospital. Acid suppressants, PPIs and H2Bs, have been shown to raise the pH above

four within the first 24 hrs.^{62,64,81}. This increase in pH allows bacterial colonization to take place in the stomach⁸². Proton pump inhibitors, in particular, have been shown to promote bacterial colonization through additional mechanisms. For instance, the H⁺/K⁺ pump, the main action site of PPIs, also was found in the laryngoesophageal tract as well as the lungs⁸³⁻⁸⁵. Therefore, at least in theory, the inhibition of these pumps also will augment bacterial colonization in these areas. Furthermore, in vitro studies demonstrated that PPIs reduce humoral immunity through reversible inhibition of Natural Killer (NK) cells^{86,87}.

In contrast to H₂Bs, PPIs also have been shown to reduce gastric emptying and gastric wall tension which increase stomach accommodation in humans^{79,88-92}. In addition, few studies suggested that PPIs relax the lower esophageal sphincter^{51,93,94}. Consequently, PPIs and, to a lower extent, H₂Bs enhance both tracheo-bronchial bacterial colonization and micro-aspiration of gastric contents into the respiratory tract which can lead to the development of NP. Based on the aforementioned studies, one should expect higher incidence of NP with PPIs when they are compared to H₂Bs.

c. Nosocomial Pneumonia in ICU settings:

Nosocomial pneumonia is associated with increased ICU LOS (2 to 15 days) and ICU mortality (20% to 50%)⁹⁵⁻⁹⁸. Recently, the research community started to differentiate between early-onset pneumonia that occurs in the first four days of ICU admission and late-onset pneumonia that happens after that time period. The distinction comes from the belief that micro-aspiration of gastric contents will be associated with late-onset pneumonia rather than early-onset pneumonia which is most likely caused by bacteria

that colonize the respiratory tract^{80,99}. Thus, one should expect acid suppressants to be associated with late-onset pneumonia more than early-onset pneumonia.

d. Evidence from the literature:

None of the RCTs that compared PPIs to H2Bs reported an increased risk of NP with any of the two groups (Figure 2.2). The five meta-analyses that were done using these RCTs also did not find any additional risk between the two groups. On average, the cumulative incidence of NP for each group was centered on 10% (Table 2.3). However, none of these RCTs were powered to detect a difference between PPIs and H2Bs. More importantly, because of small sample sizes, none of these RCTs and consequently the meta-analyses was able to differentiate between early-onset and late-onset pneumonia. Therefore, the observed lack of difference could be due to this lack of discrimination. Since gastric bacterial colonization and micro-aspiration may take time, it is more plausible to find acid suppressants associated with late-onset rather than early-onset pneumonia. Therefore, it could be that the true risk of pneumonia is the risk of late-onset pneumonia rather than the overall risk. Consequently, the risk of late-onset pneumonia may have been masked in the overall estimate due to lack of early-onset pneumonia risk.

Figure 2.2: Forrest Plot of Studies Comparing the Risk of Nosocomial Pneumonia between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in the Intensive Care Units (Based on Al-Hazzani's Meta-analysis)76

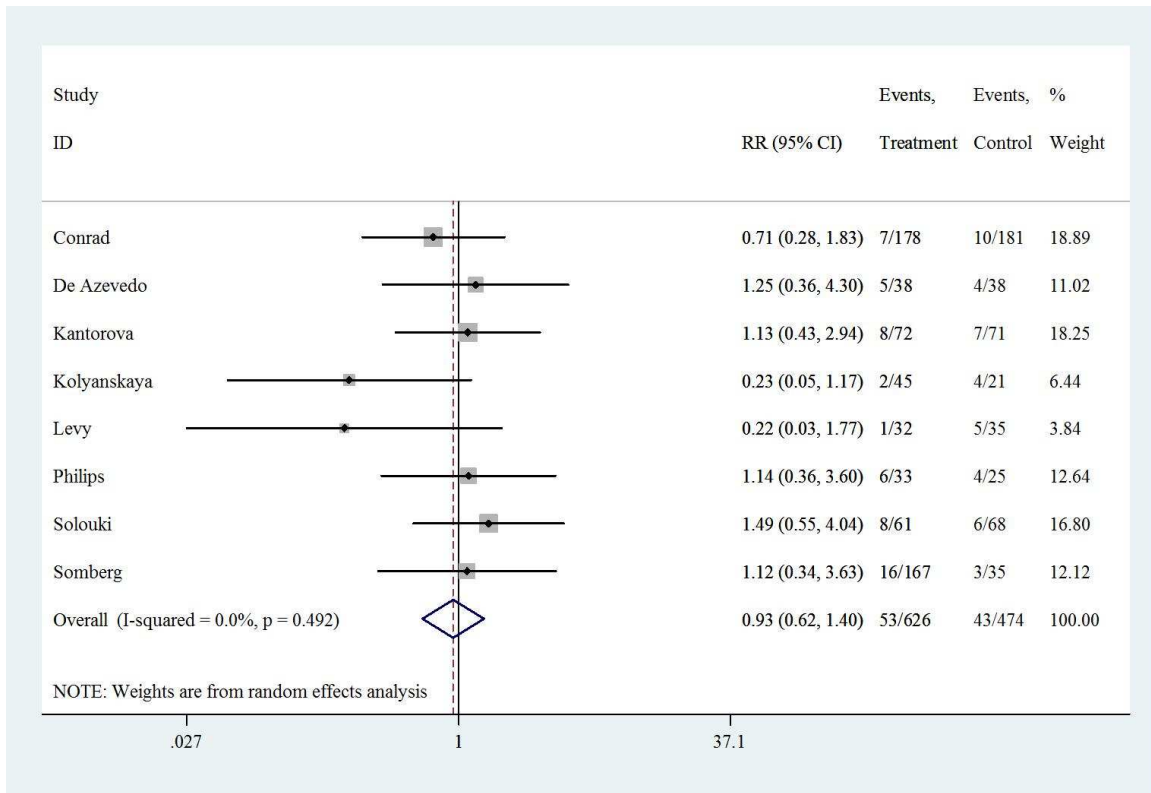


Table 2. 3: Summary of the Meta-Analyses that Compared the Risk of Nosocomial Pneumonia between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in the Intensive Care Units

Reference	Number of nosocomial pneumonia cases among the proton pump inhibitors group (%)	Number of nosocomial pneumonia cases among Histamine-2 receptor blockers group (%)	Point of estimate and 95% confidence interval of the risk of nosocomial pneumonia comparing PPIs to H2Bs
Pongprasobchai 2009 (n=569)	29/282 (10.3%)	29/287 (10.1%)	OR: 1.02 (95% CI: 0.59 to 1.75)
Zhou 2010 (n=771)	45/449 (10.0%)	32/322 (9.9%)	OR: 1.03 (95% CI: 0.63 to 1.70)
Lin PC 2010 (n=905)	56/520 (10.8%)	40/385 (10.4%)	RD: 0 (95% CI: -0.04 to +0.05)
Barkun AN 2012 (n=1,017)	63/610 (10.3%)	42/407 (10.3%)	OR: 1.05 (95% CI: 0.69 to 1.62)
Al-Hazzani 2013 (n=1,100)	66/626 (10.5%)	50/474 (10.6%)	RR: 1.06 (95% CI 0.73 to 1.52)

PPIs: Proton Pump Inhibitors; H2Bs: Histamine-2 receptor blockers; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk

Three population-based observational studies examined the relationship between PPIs and the risk of community-acquired pneumonia (CAP). Although beyond the scope of this project, it is relevant to know that the risk of CAP was the highest among current users compared to past users and during the first 30 days of initiation¹⁰⁰⁻¹⁰². More interestingly, the risk of CAP was the highest during the 7 to 14 days of initiation indicating that longer duration of acid suppressant therapy is not a requirement for the development of pneumonia.

In a study that focused on patients not admitted to the ICU but to any hospital wards for at least three days, Herzig et al examined whether acid suppressants were associated with higher incidence of NP when they are compared to patients who received neither PPIs nor H2Bs. After performing one to one propensity score matching, PPIs were associated with 30% increase in the odds of NP (95% CI: 1.1 to 1.4). On the other hand, H2Bs showed a trend toward higher odds of NP that did not reach statistical significance (OR: 1.2, 95% CI: 0.98 to 1.4)¹⁰³.

Miano et al, in a retrospective cohort study, examined the risk of NP among patients who underwent cardio-thoracic surgery and were prescribed either ranitidine or pantoprazole. Medication switching was not allowed during the entire study. The unadjusted cumulative incidence of NP among the pantoprazole was 9.3% (35/377) compared to 1.5% (7/457) among the ranitidine group. After adjusting for the imbalance between the two groups using propensity score analysis, the odds of NP were 2.7 times greater in the pantoprazole group compared to the ranitidine group (OR=2.7, 95% CI, 1.1 to 6.7)¹⁰⁴. Similarly, more recent studies that were done in ICU settings, the risk of NP was slightly greater among patients on PPIs compared to H2Bs with a significant HR of 1.2 and narrow confidence intervals^{78,105}.

In summary, it is unknown whether or not the lack of difference between PPIs and H2Bs in terms of NP in the five meta-analyses is a real equivalence, a power issue or a methodological flaw due to failure to tease out late-onset pneumonia. In addition, the few observational studies that showed higher NP with PPIs compared to H2Bs necessitate

exploring this question in a different cohort of patients to determine how robust is the result and who are the most vulnerable subgroups. Therefore, this retrospective observational study with a large sample size and different patient population is ideally suited for answering such question.

4. Safety of Stress-Ulcer Prophylactic Modalities (Clostridium difficile infections):

a. Epidemiology:

Clostridium difficile causes nosocomial diarrhea, colitis and pseudomembranous colitis a.k.a. Clostridium difficile-associated diseases (CDAD). The incidence rate of CDAD in acute hospital settings is approximately 8 cases per 1000 patient-days¹⁰⁶. In 2006, the prevalence of CDAD among hospitalized patients ranged from 0.7 % to 1%¹⁰⁷. However, in ICU settings, Lawrence et al reported 76 cases of CDAD (4%) among 1,872 ICU patients with 40 cases (2%) developed the infection during the ICU stay¹⁰⁸. Similarly, Zilberberg et al reported higher prevalence (5.34%) in ICU settings among patients on mechanical ventilator for more than 4 days¹⁰⁹. In addition to frequent use of antibiotic therapy, the higher incidence and prevalence in the ICU settings, compared to community settings, is believed to be partially due the emergence of a more virulent strain of CDAD, BI/NAP1/027, that is resistant to some of the antibiotics used in the hospital¹¹⁰.

b. Mode of transmission:

Clostridium difficile exists in two forms: vegetative cells that are acid-sensitive and acid-resistant spores¹¹¹. As previously discussed, the elevation of gastric pH promotes

bacterial overgrowth and colonization inside the stomach. Both forms are implicated in the pathogenesis of CDAD. For instance, above the pH of five, *C.difficile* spores germinate and produce vegetative cells that can live under this elevated pH. In addition, inside hospital settings, the vegetative cells themselves can live up to 6 hours on moist surfaces at room temperature ¹¹². Therefore, exposure to either form plays a role in the pathogenesis of CDAD among patients on acid suppressants. *Clostridium difficile* bacteria produce toxin A and toxin B that cause watery diarrhea and other CDAD ¹¹¹. These two toxins are discriminating markers for *C.difficile* infection that are used for diagnosis.

c. CDAD in the ICU settings:

Clostridium difficile-associated diseases have been implicated in increasing ICU mortality and ICU LOS. It has been estimated that the mortality rate attributable to CDAD is between 5.5% and 6.9% ¹¹³⁻¹¹⁶. In addition, several studies have reported a longer hospital LOS with CDAD that ranges from 3 to 16 days and twice longer stays in the ICU settings ^{108,116-119}. Patients are more prone to CDAD infection due to frequent use of medications that have been associated with CDAD such as cephalosporins, fluoroquinolones, glucocorticoids and clindamycin. In addition, the risk of CDAD increases proportionally with *C.difficile* colonization pressure which is generally defined as the number of ICU patients infected with *C.difficile* divided by the number of patients in the ICU. Furthermore, *C.difficile* transmission via health care professional has also been linked to the risk of CDAD in ICU settings. In addition to the virulence of the strain,

all these factors come together to increase the incidence and prevalence of CDAD within the ICU environment.

d. The association between acid suppressants and CDAD:

The majority of studies that explored the association between acid suppressants and the risk of CDAD focused on the use of PPIs and, to a lesser extent, on H2Bs^{106,120-135}. In addition, hospital-based studies^{106,120-128,130-132,135} consisted the majority of the literature followed by community-based studies^{129,133,134}. Case-control^{120-123,125,127-130,133-135} and cohort studies^{106,124,126,128,131,132} were the only study designs seen in the literature. There is one ongoing RCT that is comparing EN to EN plus pantoprazole as SUP where the outcomes of interest are GIB and CDAD¹³⁶.

In 2012, Tleyjah and colleagues conducted a meta-analysis that included any empirical study that explored the association between PPIs and CDAD. The majority of the studies included community-dwelling patients and hospitalized patients. The authors reported a 65% increase in the odds of developing CDAD with the use of PPIs compared to not receiving PPIs (OR: 1.65, 95% CI: 1.47 to 1.85), $P < 0.0001$, $I^2 = 89.9\%$.). They estimated that in the hospital, the number needed to harm (NNH) among patients who are on antibiotics is 50 with a 95% CI (31 to 97) and 367 patients (95%CI: 226 to 718) among those who are not on antibiotics. Thus, one should expect, at least, similar if not lower NNH among patients in ICU settings who are most likely to be on an antibiotic regimen as a prophylaxis or treatment¹³⁷. Similarly, Deshpande and colleagues conducted another meta-analysis that included 30 observational studies (n=202,965) and

found that the use of PPIs was associated with higher odds of CDAD (OR: 2.15, 95% CI: 1.81 to 2.55), $P < 0.0001$, $I^2 = 87\%$.)¹³⁸.

The significant heterogeneity seen in these meta-analyses necessitates a keen look at the association between CDAD and PPIs to validate the results in ICU settings, where patients are at a higher risk of developing CDAD, and to determine which group of patients is at greater risk of developing CDAD inside ICU settings.

Very few observational studies were conducted in ICU settings to explore the association between acid suppressants and CDAD. In 2007, Beaulieu and colleagues examined the association between acid suppressants and the risk of CDAD as a consequence to an outbreak of CDAD that led to shutting down a medial ICU for a period of time. The study included any patient who was admitted to the ICU for more than 24 hours during the study period (March 2002-May 2004). Ascertainment of CDAD started from the second day of ICU admission until the end of the second month after discharge. Any case of diarrhea for more than 24 hours that is accompanied by a positive immunoassay for *C. difficile* toxins A and B was considered a CDAD case. A detailed description of acid suppressants use was not defined. The final cohort included 827 patients among which 335 (40.5%) were on PPIs, 470 (56.8%) on H2Bs and 182 (22%) on neither PPIs nor H2Bs. No information was provided regarding the incidence of CDAD among these groups. A Cox-proportional hazard model was used to adjust for antibiotic use, gender, age, pre-ICU length of stay and comorbidities. The time used in survival analysis was the start of ICU admission. The adjusted hazard ratio (HR) did not

show a significant association between acid suppressants and the risk of CDAD (**PPIs: HR: 0.90 (95%CI: 0.59 to 1.38), H2Bs: HR: 0.78 (95%CI: 0.50 to 1.23)**)¹⁰⁶. However, the study was not powered to detect less than 50% difference between patients who received one of the two classes and patients who received neither one. In addition, the generalizability of the results of this one ICU is limited given the differences in practice between different ICU, the differences in patient populations and the unclear definition of exposure in this study. On the other hand, in 2014, MacLaren and colleagues reported a slight increase in the risk of CDAD among patients on PPIs compared to H2Bs (HR=1.29; 95%CI: 1.04-1.64) in a retrospective study of 35,312 ICU patients.

In summary, CDAD are considered rare in the general population. That fact that the prevalence of CDAD in ICU settings is two to five times greater than general population and that SUP is prescribed in the ICU make ICU settings a good setting to examine the relationship between CDAD and SUP. The paucity of studies in ICU settings and the methodological problems associated with previous studies give this study its importance in exploring the association between acid suppressants and CDAD

Chapter III. Research Design and Methodology

Each paper in the series shares several methodological considerations, including the data source used and the study sample inclusion and exclusion criteria. Therefore, all these commonalities will be described in detail prior to the manuscripts. Following these sections, the definition of exposure, outcomes and covariates; and the proposed statistical analysis plan are discussed. Please keep in mind that because of the three-paper nature of the dissertation and the similarities between aim 2 and aim 3, as the reader moves forward through the dissertation sections, he or she will be cordially referred to sections that have been previously discussed.

1. Data source:

The data that was used in these manuscripts came from the eICU Research Institute (eRI) data repository. The eICU Research Institute is a product of the Philips Healthcare eICU Program. The eICU program provides technology solutions to enable health systems to transform critical care with an integrated, system-wide approach that allows efficient utilization of scarce critical care resources with integration of therapeutic decision support and standardization of evidence-based care throughout the enterprise¹³⁹.

The eICU Research Institute gathers information from more than 40 health systems encompassing approximately 300 ICUs across 34 states from 2008 to June of 2012. In each participating ICU, information pertaining to patients' admission and discharge, disease diagnoses, therapeutic management, laboratory results, and demographics are electronically documented with time of occurrence in minutes since ICU admission. In

addition, through an automated interface that gathers information at five minute intervals, patients' vital signs are collected and incorporated into the eRI database repository. Selection of disease diagnosis was done through a menu of discrete diagnoses strings. The aforementioned data and diagnoses strings were then collected and sent to the eRI repository where the diagnosis strings were linked to the International Classification of Diseases 9th ed. (ICD-9) codes. In addition, patient's health status was measured using the acute physiology and chronic health evaluation score version IV (APACHE-IV score). The APACHE-IV score methodology uses 27 variables that cover patient's age, vital signs, laboratory results and diagnoses during the first 24 to 36 hours of ICU admission to assign a severity score to the patient and predict both hospital and ICU mortality and LOS¹⁴⁰. The score is widely acceptable as a measure of severity within the ICU environment. Furthermore, clinicians' remarks and nursing charts are transferred from the health system and linked to corresponding terms in the eRI repository. All patient information that is deemed to be protected health information was not included in the database. The data has been certified as completely de-identified by Privacert, Inc. (Pittsburgh, PA). Therefore, each patient stay is represented by a unique unit stay number, and time is indexed from admission time in minutes rather than calendar time. Finally, the study was exempted from Institutional Review Board review (HP-00055985) at University of Maryland.

2. Inclusion and Exclusion Criteria:

The main cohort that was used in the first descriptive aim (and from which the Aims 2 and 3 cohorts were selected) included any patient who was admitted to ICUs between

2008 and June 2012. Patients who were not admitted to the ICU, not discharged from the hospital during study period (dead or alive) or under 18 years old or with missing age were excluded. In addition, patients who had negative ICU length of stay, invalid admission and discharge dates (e.g. admission date is after discharge date), discordant ICU and hospital discharge status (e.g. patients died in the ICU but were alive at hospital discharge), missing APACHE-IV score or earlier versions, had multiple ICU admissions within one health system stay, or missing SUP flags or diagnoses were also excluded from the study cohort. Lastly, to ensure complete ascertainment of medication information the cohort was restricted to ICUs that fully implemented the medication interface in their systems. Figure 3.1 showed the exclusion criteria for the study's main cohort.

Figure 3.1: Selection Criteria for the Main Cohort of the Study

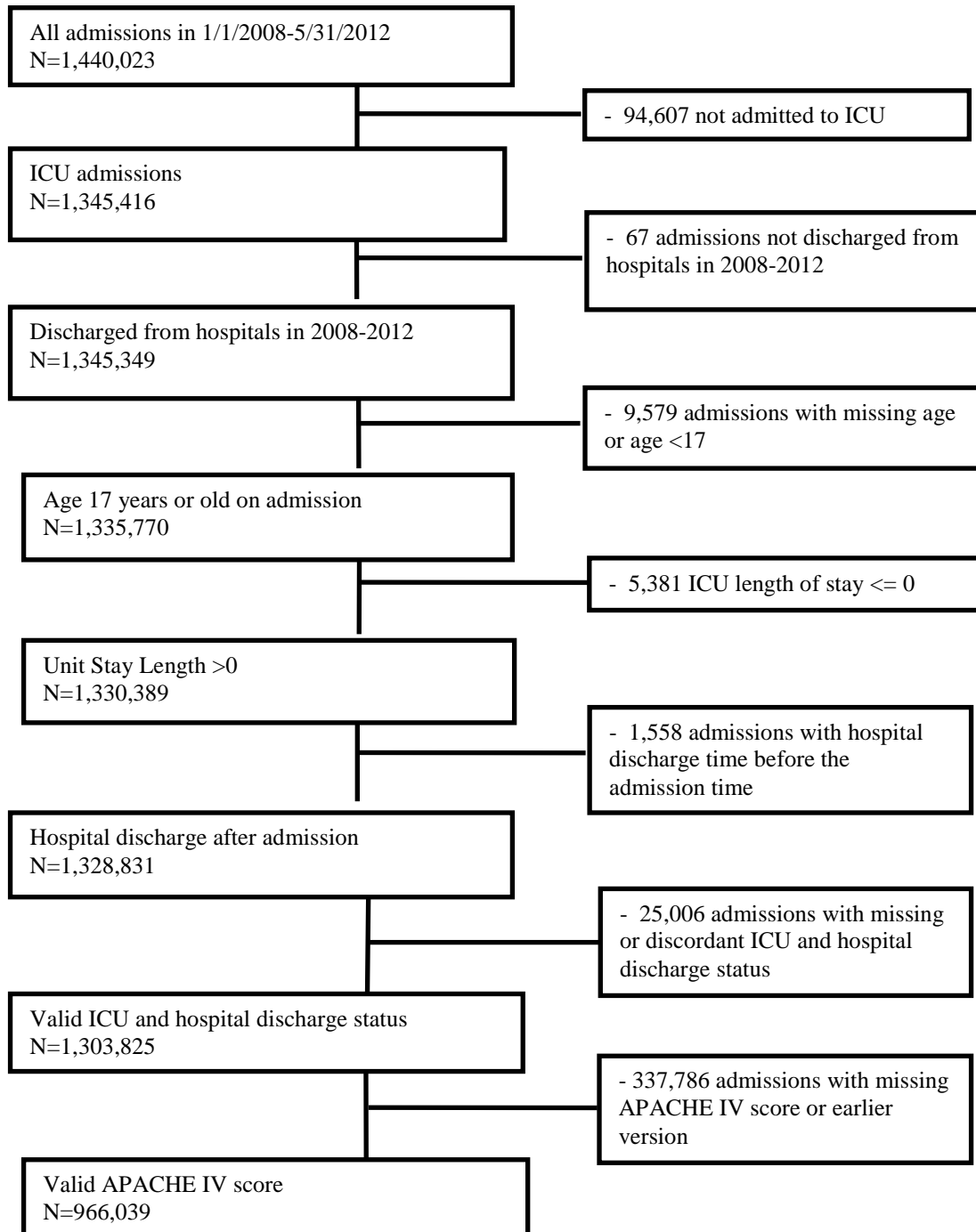
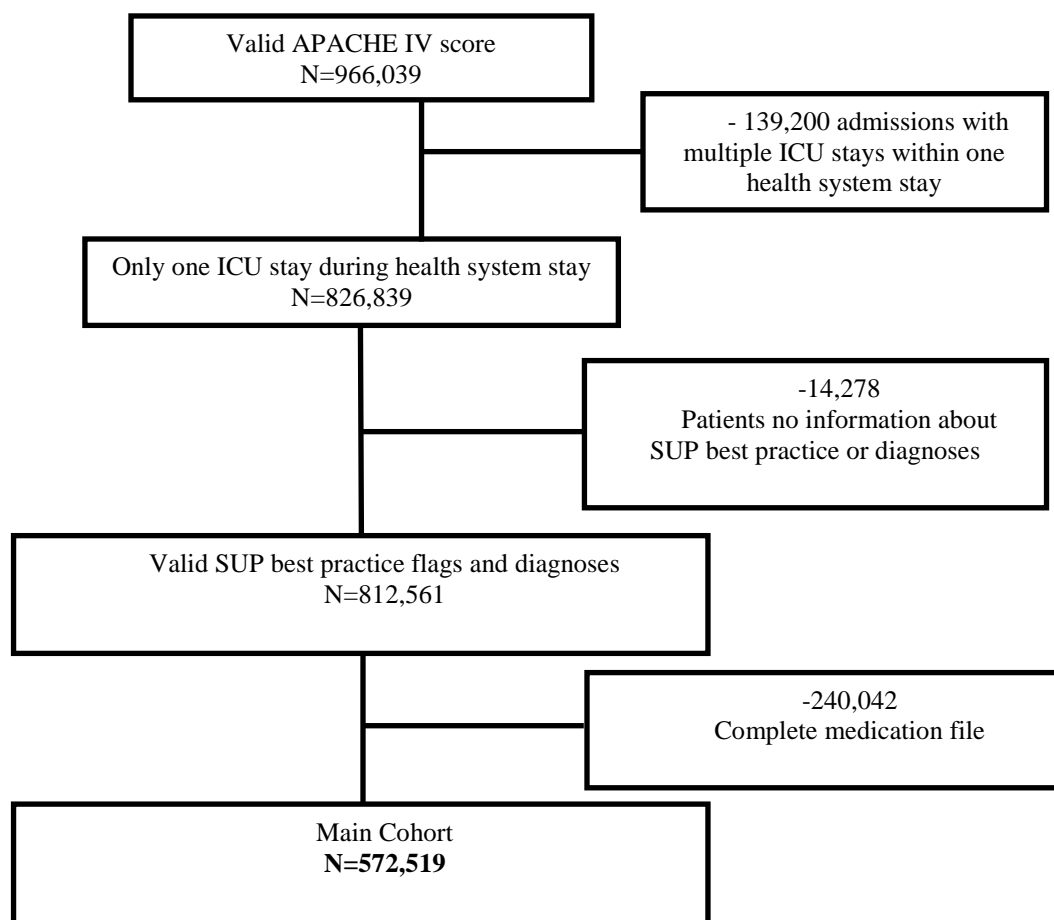


Figure 3.1: Continued



ICU: Intensive Care Unit; SUP Stress Ulcer Prophylaxis; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV

To create the cohorts used in Aim2 and Aim3 additional exclusion criteria were implemented as follow:

a. For studying the association between acid suppressants and CIGIB:

Patients with at least one risk factor of CIGIB due to stress ulcer are included in the study. These include patients with at least one of the following conditions: MV > 24 hrs. , coagulopathy, major head injuries, major burns, sepsis, corticosteroids therapy > 250 mg

of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week. Table 3.1 contains the criteria by which these risk factors were identified. Patients were excluded if any of the followings existed: ICU length of stay less than 48 hours, gastrointestinal bleeding within the first 48 hours of admission, no risk factors for CIGIB, receipt of PPIs and H2Bs concomitantly or consecutively, the receipt of PPIs or H2Bs for less than three days, and missing platelet counts, source of admission or teaching hospital status. Figure 3.2 contains the selection criteria for each of the aforementioned conditions.

Unlike administrative claims data where using one claim with a specific ICD-9 code may not be very specific and does not always imply that the patient has the diagnosis, the diagnosis strings are chosen directly by the clinicians and mapped to the ICD-9 codes. Therefore, the choice of only one ICD-9 code entry in a patient's diagnosis file during the ICU stay is a reasonable approach to identify a disease.

Figure 3. 2: Selection Criteria for the Cohort Used in Studying CIGIB

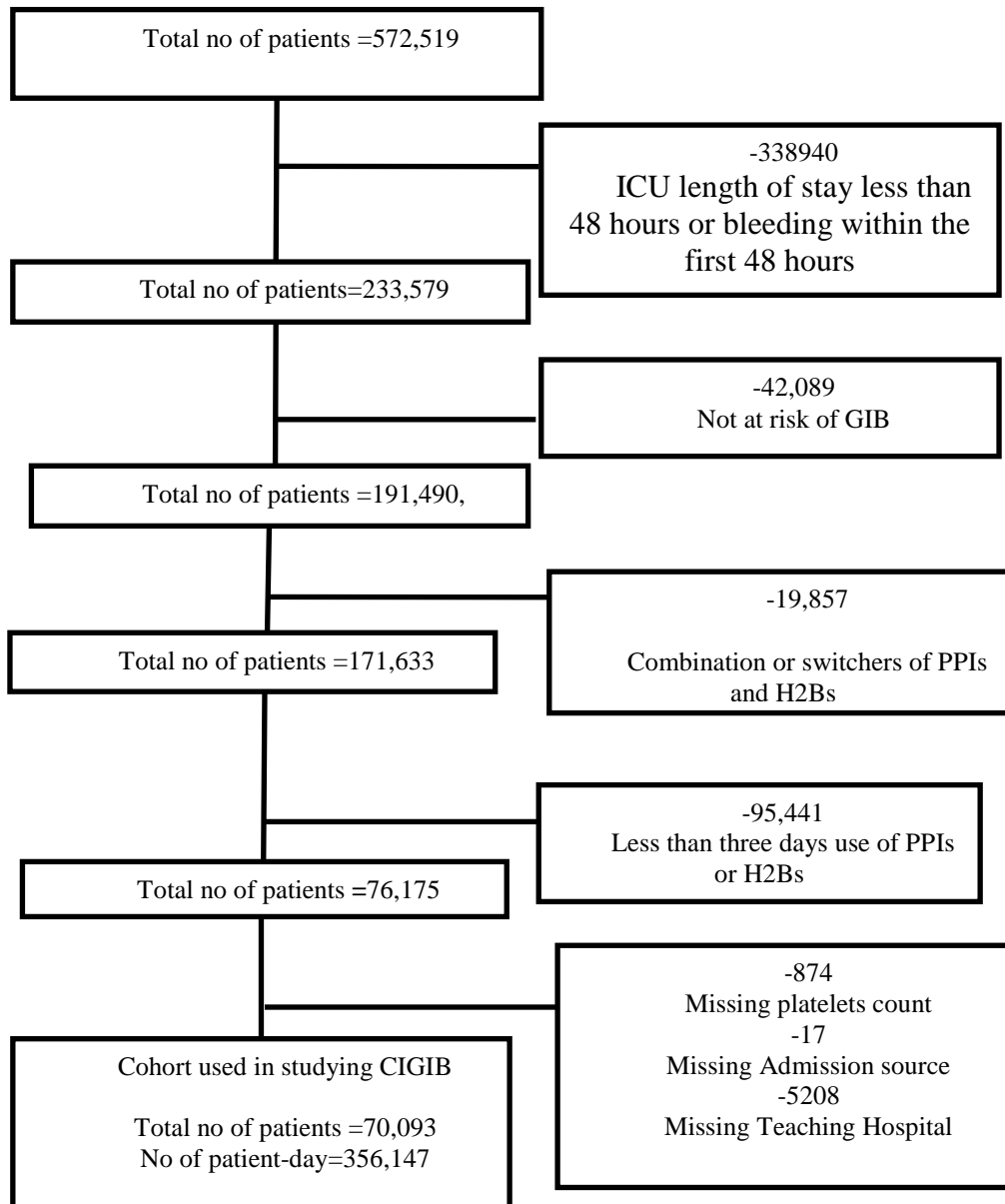


Table 3. 1: Proposed criteria for identifying patients at risk of stress ulcer gastrointestinal bleeding

Risk factors of gastrointestinal bleeding due to stress ulcer	Selection method	Comments
Mechanical Ventilation > 24 hrs.	Using a continuous variable: continuous invasive ventilation duration	From the ventilation data file
Coagulopathy	Any of the followings during an ICU stay: Platelets 50,000 per/ml ³ ; an INR > 1.5, a PT > 50 sec	From the hematology or laboratory results data file
Traumatic Brain Injuries	Any ICD-9 code: 800.0-801.9 803.0-804.9 850.0-854.1 950.1-950.3 959.01	From active diagnosis file
Major Burns	Any ICD-9 code: 940.*-949.*	From active diagnosis file
Sepsis	Any ICD-9 code: 038, 040.82, 599.0, 996.64, 998.5, 999.3	From active diagnosis file
Corticosteroid Therapy > 250 mg of hydrocortisone or equivalent daily		Medications file
Acute Renal Failure	Any ICD-9 code: 584.*	From active diagnosis file
Hepatic Failure	Any ICD-9 code: 570.*	From active diagnosis file
Transplantation	Using admission diagnosis string “operative transplant”	From the APACHE admission diagnosis file
ICU stay of > 1 week	From ICU length of stay variable that is available in the raw data files	From APACHE Patient Results file
Neurological Injuries/Spinal Injuries	Using admission diagnosis string “spinal trauma”, “spinal cord decompression”, “Spinal cord only trauma”, “Spinal cord surgery, other”, “Spinal/extremity trauma”, “Spinal/face trauma”, “Abdomen/spinal trauma” Or any ICD-9Code: Coma:780.01, 780.03, 850.3, 850.4, Embolic stroke:433, 434; Encephalitis: 348.1, 348.4, 348.5 Hemorrhage: 430, 431, 432, 997.02, 997.09 Spinal cord injury:806, 952	From the APACHE admission diagnosis file and active diagnosis file
Shock/Hypotension	Any ICD-9 Code: 427.5, 441.1, 441.3, 441.5, 441.6, 785, 958.4, 977.9,995.0, 995.4, 995.92, 998.0, 999.8	
Surgery/Trauma	Using admission diagnosis string “multiple trauma” or Any ICD-9 Code:	From the APACHE

Table 3.1, Continued

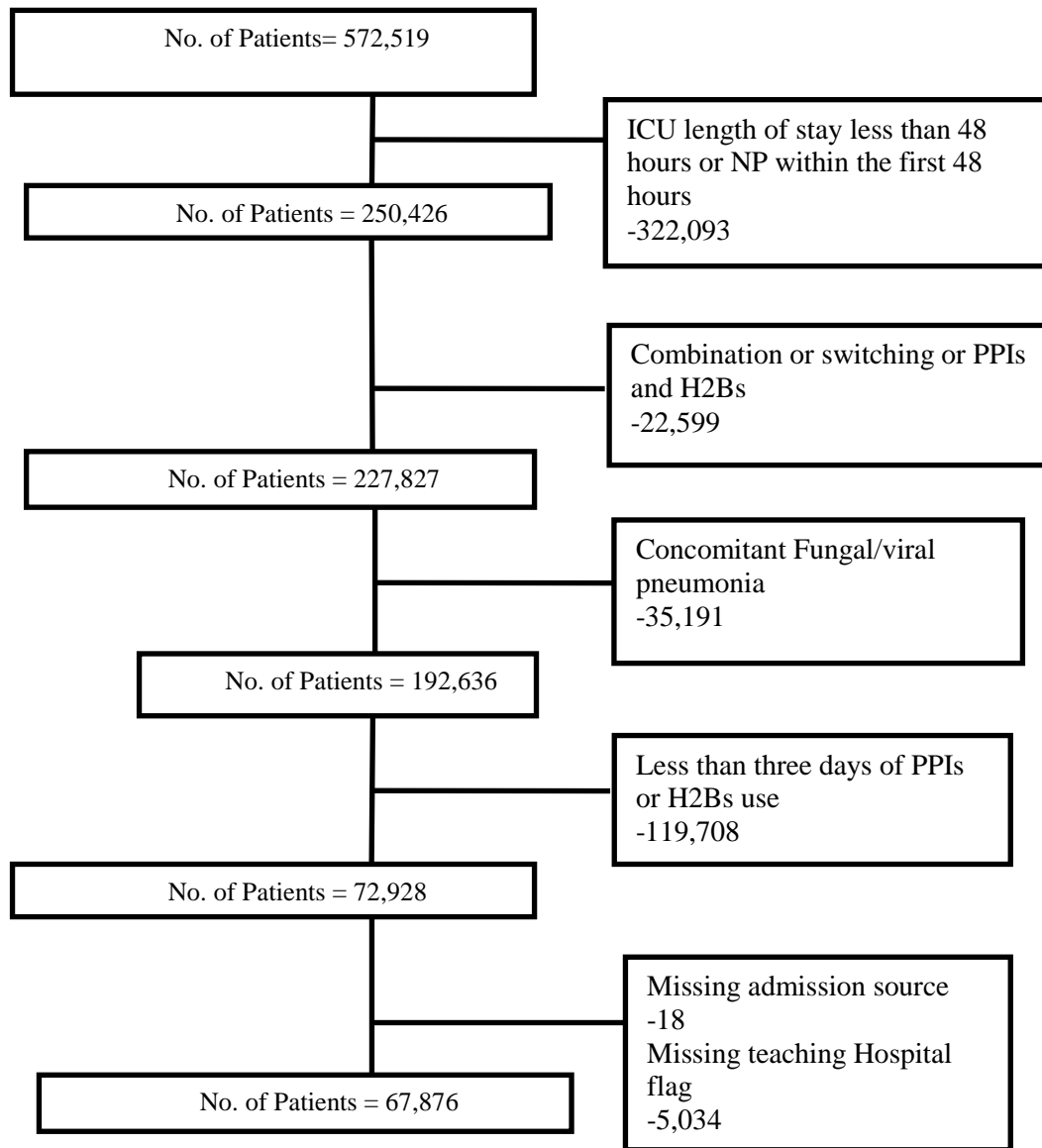
Risk factors of gastrointestinal bleeding due to stress ulcer	Selection method	Comments
	802, 805, 807.2, 807.3, 807.4, 807.5, 807.6, 808, 809, 810, 811, 812, 819, 820, 821, 827, 828, 839, 860, 861,862, 863, 864, 865, 866, 867, 868, 869, 874, 875, 876, 877, 878, 879.2, 879.3, 879.4, 879.5, 879.6, 879.7,879.8, 879.9, 887, 890, 896, 897, 900, 901, 902, 903,904, 922, 924.0, 924.4, 924.8,925, 926, 927, 928,929	admission diagnosis file and active diagnosis file

INR: International normalized ratio;PT: prothrombin time; aPTT partial thromboplastin time;ICD-9 International Classification of Diseases 9th ed. ; ICU Intensive Care Unit; APACHE Acute Physiology and Chronic Health Evaluation

b. For studying the association between acid suppressants and NP:

Patients were excluded if any of the followings existed: ICU length of stay less than 48 hours, nosocomial pneumonia within the first 48 hours of admission, receipt of PPIs and H2Bs concomitantly or consecutively, concomitant viral or fungal infection, the receipt of PPIs or H2Bs for less than three days, and missing source of admission or teaching hospital status. Figure 3.3 illustrate the selection criteria for this cohort.

Figure 3. 3: Selection Criteria for the Cohort that was used in Studying the Association between Acid Suppressants and Nosocomial Pneumonia.

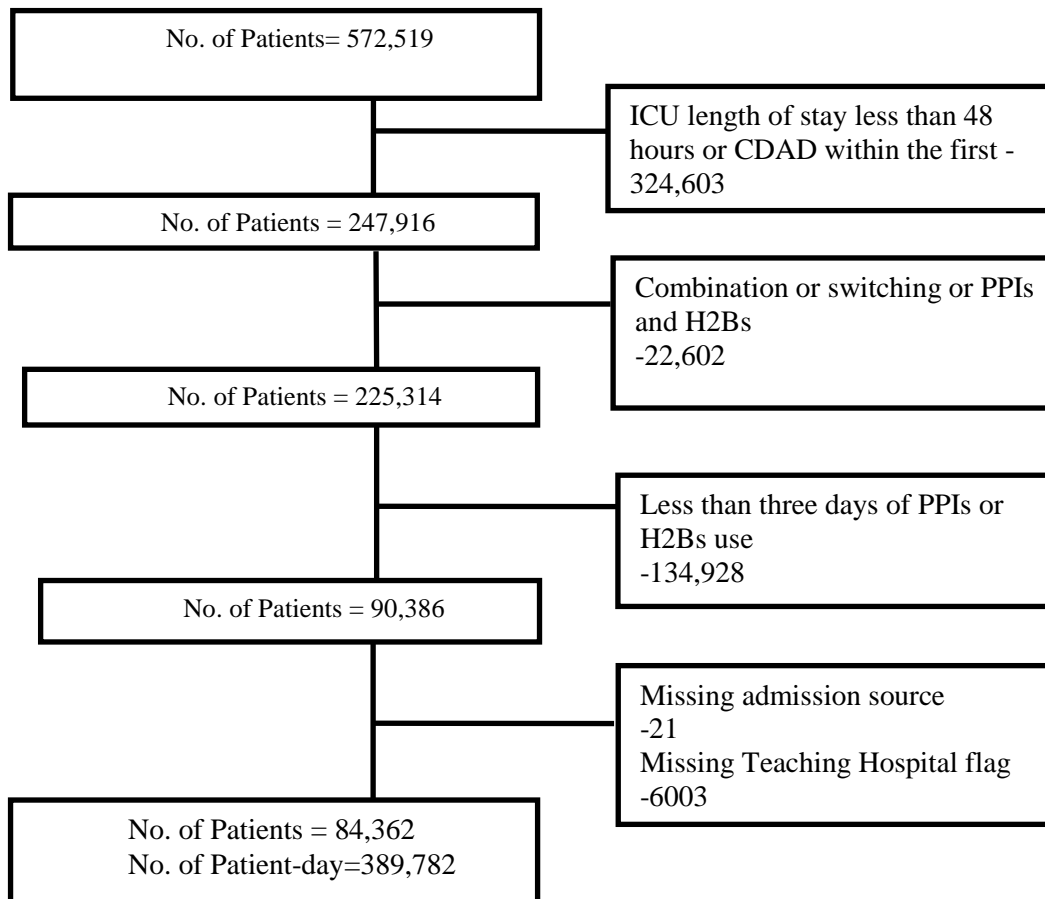


c. For studying the association between acid suppressants and CDAD:

Patients were excluded if any of the followings existed: ICU length of stay less than 48 hours, clostridium-difficile associated disease infection within the first 48 hours of admission, receipt of PPIs and H2Bs concomitantly or consecutively, the receipt of PPIs

or H2Bs for less than three days, and missing source of admission or teaching hospital status. Figure 3.4 illustrate the selection criteria for this cohort.

Figure 3.4: Selection Criteria for the Cohort Used to Study the Association between Acid Suppressants and CDAD



3. Study objectives and Designs:

The objectives of this study were to provide a detailed description of the use and overuse of SUP in ICUs and the efficacy and safety of PPIs and H2Bs as the main and the most common modalities of SUP. Two study designs were used to analyze the data: first, cross-sectional study design was used to determine factors associated with SUP utilization and overutilization (first, manuscript); Second, retrospective cohort study

designs to explore the association between PPIs, H2Bs and clinically important gastrointestinal bleeding, nosocomial pneumonia and Clostridium difficile infections (2nd and 3rd Manuscripts).

Each of the following three chapters contains a separate manuscript consisting of relevant background, the analytic plan, results and discussion. Then, a concluding discussion follows these three chapters.

Chapter IV. Stress Ulcer Prophylaxis utilization and overutilization in Intensive Care Units between 2008 and 2012

Introduction:

Stress ulcer prophylaxis is a standard of care in intensive care units (ICU_(s)) that is given to prevent stress-related mucosal damage (SRMD). Stress-related mucosal damage has been associated with the formation of stress ulcer that eventually may bleed and increase ICU mortality¹⁰. In the last two decades multiple guidelines came out determining which patients should receive SUP. The most common in the US are the 1999 guidelines published by the American Society of Health System Pharmacists (ASHP)¹⁶. Based on the available evidence at the time of publication, the receipt of SUP was recommended for patients with coagulopathy, mechanical ventilation for more than 48 hours, head injuries, burns that covers more than 35% of body surface area and partial hepatectomy. In addition, based on experts opinion, the guidelines recommended SUP administration to patients with renal or hepatic transplantation, multiple trauma, spinal cord injuries, history of gastrointestinal bleeding or ulceration during the 12-months period before ICU admission, or the presence of two of the following conditions: staying in the ICU for more than a week, the development of occult GI bleeding for more than 6 days, sepsis or the receipt of glucocorticoids equivalent to 250 mg hydrocortisone or more. Similarly, in 2008, the Eastern Association for the Surgery of Trauma (EAST)

recommended the administration of SUP to part of the aforementioned patient subgroups⁴⁶ (Table 4.1).

Table 4.1: Risk Factors for Stress Ulcer Related Gastrointestinal Bleeding in Intensive Care Units

Risk factors of gastrointestinal bleeding due to stress ulcer	Source
Major	
Mechanical Ventilation > 48 hrs.	ASHP & EAST
Coagulopathy	ASHP & EAST
Major Head Injuries	ASHP & EAST
Major Burns (>35% of BSA)	ASHP & EAST
Minor	
Sepsis	ASHP & EAST
Multiple Trauma Injury	ASHP & EAST
Corticosteroid Therapy > 250 mg of hydrocortisone or equivalent daily	ASHP & EAST
Spinal cord injuries or Head injuries	ASHP
Renal Failure	ASHP
Hepatic Failure	ASHP
Partial Hepatectomy	ASHP
Transplantation	ASHP
History of Gastric Ulcer or bleeding a year prior to admission	ASHP
ICU stay of > 1 week	ASHP
Occult or overt bleeding for \geq 6 days	ASHP

ASHP: American Society of Health System Pharmacists; EAST: Eastern Association for the Surgery of Trauma; BSA: Body Surface Area, ICU: Intensive Care Unit

However, since the introduction of the ASHP guidelines, many aspects in ICU practice have changed such as the introduction of proton pump inhibitors (PPIs) as one of the main SUP modalities in many ICUs nowadays. In addition, ICU care itself has changed with the introduction of more sophisticated equipment and better staff training which may reduce the need for these medications. Furthermore, the nature of ICU care that requires close monitoring and the advances in information technology created large ICU-based databases that can be used in conducting observational studies on large number of patients. Despite all these changes, the majority of the SUP-related studies focused more

on exploring the benefits and risks of SUP rather than exploring who is using these medications in real world and the degree of incongruence between the guidelines and real world. The latter is important in identifying SUP overutilization and the topics that require more investigations.

Many studies have documented overuse of SUP both in ICUs and even in hospital wards where SUP is not indicated. Percentages of overutilization varied from 19% to 92%¹⁻⁴. Studies have reported in-hospital annual cost of inappropriate use between \$11,000 and \$23,000^{3,4}. Moreover, this overuse has been associated with significant financial burden not only due to unnecessary use in ICUs but also due to continuation of use after hospital discharge. For instance, in 2010 Thomas and colleagues used a managed care organization database of 29,348 beneficiaries who were prescribed proton pump inhibitors (PPIs) in the ICU. They reported that 68.7% of the patients were inappropriately discharged on a PPI. In this study, between 2003 and 2006, the total cost associated with one month use of PPIs after hospital discharge was \$3,013,069⁵.

Thus, using this population-based study of multiple years had two main objectives: First, to describe SUP utilization which encompasses exploring the use of different SUP strategies, determining the percentage of patients who received SUP in concordance with the guidelines i.e. adherence to guidelines and determining factors associated with the receipt of SUP. This is important to determine areas where more implementation of the guidelines is needed and the areas where more research is necessary. Second, to describe SUP overutilization over the five years of the study and determine factors associated with it. We hypothesize, first, that if there was a complete overutilization then current practice

would be indifferent between patients with stress ulcer risk factors and patients without them. Second, there should be no association between the number of risk factors and the likelihood of receiving PPIs, histamine type 2 receptor antagonists, antacids or sucralfate also known as Gastric Acid Modifying Drugs or Sucralfate (GAMAS). Lastly, we explored factors associated with the SUP overutilization during study period.

Methods:

Data Source:

The data that was used in this study came from the eICU Research Institute (eRI) data repository. The eICU Research Institute is a product of the Philips Healthcare eICU Program. The eICU program provides technology solutions to enable health systems to transform critical care with an integrated, system-wide approach that allows efficient utilization of scarce critical care resources with integration of therapeutic decision support and standardization of evidence-based care throughout the enterprise¹³⁹.

The eICU Research Institute gathers information from more than 40 health systems encompassing approximately 293 ICUs across 34 states from 2008 to June of 2012. In each participating ICU, information pertaining to patients' admission and discharge, disease diagnoses, therapeutic management, laboratory results, and demographics are electronically documented with time of occurrence in minutes since ICU admission. In addition, the system contains a care plan that represents the intended daily plan for each patient. Moreover, through an automated interface that gathers information every 5-minutes interval, patient's clinical vital signs are collected and incorporated into the eRI database repository. Selection of disease diagnosis was done through a menu of discrete

diagnoses strings that are linked to the International Classification of Diseases 9th ed. (ICD-9) codes in the eRI repository. In addition, patient's health status is measured using the acute physiology and chronic health evaluation score version IV (APACHE-IV score). The APACHE-IV score methodology uses 27 variables that cover patient's age, vital signs, laboratory results and diagnoses during the first 24 to 36 hours of ICU admission to assign a severity score to the patient and predict both hospital and ICU mortality and LOS¹⁴⁰. The score is widely acceptable as a measure of severity within the ICU environment. Furthermore, clinicians' remarks and nursing charts are transferred from the health system and linked to corresponding terms in the eRI repository. All patient information that is deemed to be protected health information was not included in the database. Therefore, each patient stay is represented by a unique unit stay number, and time is indexed from admission time in minutes rather than calendar time.

Study design and inclusion and exclusion criteria:

This is a cross-sectional study that included patients who were admitted to ICUs between January 1st 2008 and June 30th 2012. Patients who were under 18 years old, not discharged from the hospital during study period (dead or alive), had invalid admission and discharge dates (e.g. admission date is after discharge date), or had missing demographics, diagnoses, or APACHE-IV score were excluded from the study cohort. In addition, to ensure complete ascertainment of medication information the cohort was restricted to ICUs that fully used the medication interface in their systems.

Measures:

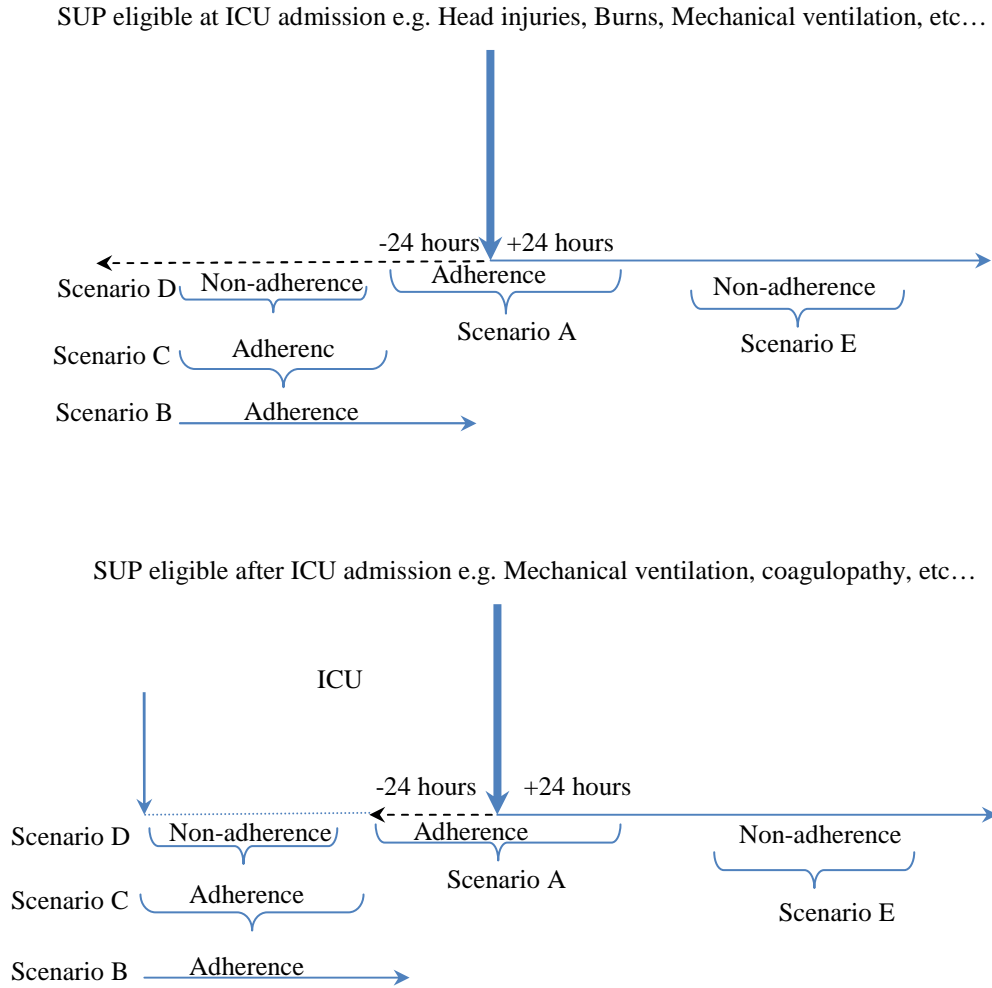
Risk factors of Stress Ulcer:

The following patient subgroups were considered at risk of developing gastrointestinal bleeding: MV > 24, coagulopathy, head injuries, multiple trauma, transplantation, major burns, sepsis, acute renal failure, hepatic failure, ICU length of stay (LOS) > 1 week, spinal injuries and corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily. Detailed description of the approach used in identifying each of these covariates is provided in Appendix 1. While mechanical ventilation, coagulopathy, major head injuries or major burns were considered major risk factors of gastrointestinal bleeding, all other factors were considered minor risk factors.

Adherence to SUP:

Proton Pump inhibitors, H2Bs, sucralfate and antacids are commonly used medications in ICU as SUP as well as treatment for many other conditions from gastric upset to peptic ulcer disease. Therefore, adherence to SUP was defined as the receipt of one of the four classes, PPIs, H2Bs, sucralfate or antacids, within 24 hours window of being at risk of stress ulcer (Scenarios A, B and C, Figure 4.1). Therefore, if a patient received one of these four classes and discontinued the drug more than 24 hours before being at-risk OR the patient received the drug after 24 hours of being at-risk then these were considered non-adherence (Scenario D and E, Figure 4.1).

Figure 4.1: Different Scenarios of Defining Adherence to SUP



In case of discontinuing the SUP drug more than 24 hours of being at risk, although PPIs have a long lasting effect that persists up to 48 hours after discontinuation of therapy¹⁴¹, the choice of 24 hours is a more conservative approach that ensures the presence of PPIs' effect at the occurrence of the risk factor. Regarding the cases who received a SUP drug after 24 hours of being at risk, 24 hours is a very long and adequate time, in the ICU settings, for receiving a SUP drug when a patient has a risk factor of stress ulcer. This ensures the concurrence of the risk factor and exposure. For instance, it

is irrational to classify a PPI or H2B that was given six days after a patient was diagnosed with a risk factor as a case of SUP adherence. Therefore, the choice of a 24-hours window increases the specificity that the intended use was SUP.

SUP Utilization:

GAMAS are not specific to stress ulcer. Therefore, patients with other conditions such esophageal or peptic ulcers end up receiving these medications. However, such patients are still benefiting from the prophylactic property of these medications against stress ulcer. Therefore, in this context, any GAMAS use is also stress ulcer prophylaxis. Consequently, to determine how the SUP medications are used in real world we explored factors associated with any use of PPIs, H2Bs, antacids or sucralfate during ICU stays. In identifying these medications we used the hierarchical ingredient code list (HICL) sequence number¹. This number identifies a list of active ingredients in a product regardless of its manufacturer¹⁴². Furthermore, the medication's name was used in addition to the HICL sequence number when the latter was not specific to the medication. Appendix 1 shows both the HICL sequence numbers and medications names used in identifying SUP medications.

Patient and ICU characteristics:

The distribution of SUP utilization was described by age, gender and race. Clinical variables are the set of variables that represented the aforementioned risk factors of stress ulcer. Gastrointestinal bleeding whether it was at admission or during ICU stay was

¹ A proprietary of First DataBank (www.fdbhealth.com)

identified using diagnosis strings from the admission and active diagnosis files. Appendix I contains a list of the diagnosis strings used in identifying gastrointestinal bleeding. The APACHE-IV score was used to measure patient's health severity. Drugs that increased the risk of gastrointestinal bleeding including anticoagulants, thrombolytics, antiplatelets and non-steroidal anti-inflammatory drugs (NSAIDs) were also identified (Appendix I). With regards to ICU characteristics, SUP utilization was described among the different types of ICUs: medical, surgical, mixed, trauma, cardiovascular and neurosciences, since both practicing patterns and patients' case-mix may differ between these ICUs.

SUP Overutilization:

Overutilization was assessed using two approaches: first, by determining if stress ulcer risk factors were associated with the use of SUP medications and whether or not there was a proportional relationship between the receipt of these medications and the number of risk factors. If there is a complete overutilization then clinicians will be indifferent between patients with these risk factors and patients without them. Therefore, one should not expect to see any association between SUP medications and these risk factors. Second, as it was mentioned earlier, the use of the SUP medications for any reason provided a prophylactic protection against stress ulcer. Therefore, to quantify SUP overutilization and determine factors associated with it, we defined overutilization as any use of these medications without appropriate indications which are the followings: having at least one risk factor of stress ulcer, duodenal ulcer, gastric ulcer, unspecified ulcer, gastritis, angiodysplasia, Dieulafoy's lesion or mucositis. For sensitivity analysis, we

excluded cases who only received antacids and re-quantified the percentages of overutilization.

Statistical Analyses:

The cohort was described using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. In addition, to assess factors associated with SUP utilization, characteristics of patients who received them were compared to those of patients who did not using chi-square and Fisher's test for categorical variables and t-test for continuous variables. Because of the dichotomous nature of the outcome i.e., the of receipt SUP medications, multivariable logistic regression was used to adjust for covariates. The estimates' standard errors were adjusted for the ICU itself to account for clustering patients with an ICU using robust variance estimator. The similar statistical approach was used to determine factors associated with SUP overutilization. Data building was mainly done using SAS, version 9.3 (SAS Institute, Cary, NC) while statistical analyses were done using STATA 11 (StataCorp.)

143,144

Results:

Sample Characteristics

A total of 572,519 patients were included in this study. The sample was almost 76% Caucasians and 54% males; the mean age was 62.4 (SD=17.4) with 58% were older than 60. Nearly one-half (48.85%) were admitted to mixed ICUs. Coronary care ICUs had the second highest percentage of patients (19.6%). Overall, there were 48,101 deaths (8.4%) among which 32,510 cases occurred in the ICU. The prevalence of gastrointestinal

bleeding was 7.3%. Out of the whole cohort, 494,703 (86.4%) of patients received at least one dose of SUP medications. Proton Pump inhibitors use was the highest (60.0%) followed by antacids (42.9%), H2Bs (30.5%) and sucralfate (2.9%). Approximately, 46% of the sample had at least one risk factor of SU. Out of the whole cohort, the most common risk factors were coagulopathy (20.5%), sepsis (11.6%), MV for more than 24 hours (11.4%), renal failure (10.0%) and ICU LOS > 7 days (8.4%). Fifteen percent of the patients had at least one major and one minor risk factor, 19.4 % had at least one major risk factor only, 10.5% had only one minor risk factor and 1.8% had two or more minor risk factors without any major risk factors. More than half of the sample (53.2%) did not receive any type of feeding during their ICU stay. Enteral nutrition was administered to 44.5% of sample while parenteral nutrition was administered to only 0.5%. The remaining 1.9% has received both enteral and parenteral nutrition during their ICU stay. The use of medications that could increase the risk GIB was prevalent in the sample: Antiplatelets (62.7%), anticoagulants (54%) and NSAIDs (42%). Only 2.1% of the whole sample had gastrointestinal-related diseases (Table 4.2)

Table 4.2: Cohort Characteristics of 572,519 patients who were admitted and discharged from the hospital between 1/1/2008 and 03/6/2012.

Characteristics	All	
	Freq.	Col %
Age		
18 to 60	242,340	42.33
61 to 70	120,927	21.12
71 to 80	114,409	19.98
80 to 90	94,843	16.57
ICU Death	32,510	5.68
Hospital Death	48,101	8.4
Gastrointestinal Bleeding	41,773	7.3
Male	306,099	53.47
Race		
Caucasian	433,761	75.76
African American	60,975	10.65
Hispanic	26,281	4.59
Native American	4,639	0.81
Asian	6,326	1.1
Other	40,537	7.08
Type of ICU		
Mixed	279,653	48.85
Cardiovascular-Surgical	52,659	9.2
Coronary Care	112,341	19.62
Trauma	3,196	0.56
Surgical	40,129	7.01
Medical	50,325	8.79
Neuroscience	34,216	5.98
Gastric Acid Modifying Drugs or Sucralfate		
Any	494,703	86.4
Proton Pump Inhibitors	343,236	60
H2Bs Antagonists	174,688	30.5
Sucralfate	16,692	2.9
Antacids	245,566	42.9
Medications		
Anticoagulants	308,901	54
Antiplatelets	358,841	62.68
Thrombolytics	55,167	9.6
Coagulating Drugs	17,890	3.12
Non-Steroidal Anti-inflammatory Drugs	240,611	42.03
Misoprostol	888	0.16
Nutrition		
No feeding	304,581	53.2
Enteral Nutrition	254,528	44.5
Parenteral Nutrition	2,788	0.5
Both Enteral Nutrition and Parenteral Nutrition	10,622	1.9
Diseases		
Any Gastrointestinal diseases	11,893	2.1
Peptic Ulcer Disease	633	0.11
Gastritis	452	0.08

Table 4.2, Continued

Characteristics	All	
	N=572,519	
	Freq.	Col %
Esophageal Disease	4,654	0.81
Duodenal Ulcer	231	0.04
Unspecified Ulcer	6,542	1.14
Angiodysplasia	0	0
Dieulafoy's Lesion	0	0
Ulcer due to mucositis	0	0
Risk factors of Stress Ulcer		
Coagulopathy	117,250	20.48
Mechanical Ventilation > 24 hours	65,092	11.37
Traumatic Brain Injury	17,825	3.11
Sepsis	66,605	11.63
Staying in ICU for more than 7 days	48,201	8.4
Hydrocortisone \geq 250 mg / day or Equivalent	10,023	1.75
Hepatic Failure	9,228	1.6
Burns covering 30% or more of Body Surface Area	56	0.01
Acute Renal Failure	57,068	9.97
Spinal Injuries	5,562	1
Multiple Trauma	4,820	0.8
Transplantation	1,038	0.2
Number of Risk Factors		
0	306,536	53.5
1	168,725	29.5
2	65,873	11.5
3	24,049	4.2
\geq 4	7,336	1.3
Types of Risk Factors		
Not at risk	306,536	53.5
Any Risk factor	265,983	46.5
Major only	110,870	19.4
Minor only	70,403	12.3
One minor	60,258	10.5
Two minors or more	10,145	1.8
Both major and minor	84,710	14.8
APACHE IV Score (mean, SD)	53	25.23

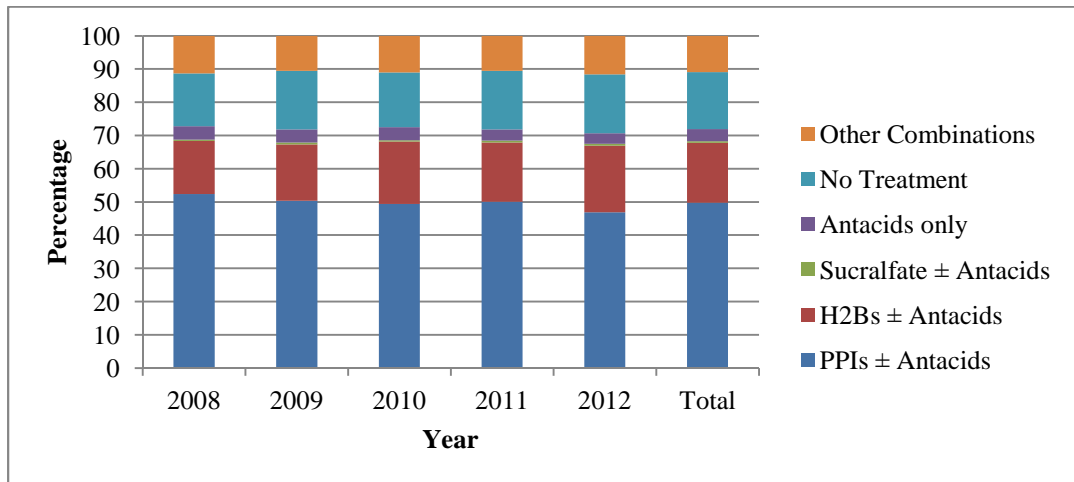
ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; SD: Standard deviation

Adherence of SUP:

Among the 265,983 who were at risk of stress ulcer, adherence of stress ulcer prophylaxis, defined as the receipt of one of the four categories within a 24-hours window of having a risk factor, was 82.87%. Since antacids use as SUP is uncommon

nowadays, we included them with one of the other three groups whenever antacids were administered with one of them (Figure 4.2). While PPIs were the highest widely used (49.80%) followed by H2Bs (17.96%), sucralfate use was the lowest (0.5%). Only 9809 patients (3.69%) of patients at risk of stress ulcer received antacids within 24 hours of being at risk without any other medications. Between the four groups, this pattern of utilization remained constant over the five years of the study. However, over the five years, there was a gradual reduction in PPIs utilization from approximately 52.4% in 2008 to 46.8% in 2012 accompanied by an increase in H2Bs utilization from 15.96% to 20.1% (Figure 4.2).

Figure 4. 2: Adherence of Stress Ulcer Prophylaxis among Patients at Risk of Stress Ulcer between 2008 and 2012 (Total=265,983)



Factors associated with SUP medications utilizations:

The bivariable analysis showed that regardless of the age group, patients above 60 were more likely to receive SUP medications than those below 60 (OR= 1.26, 99%CI: 1.23-1.28.) When compared to Caucasians, African Americans were less likely to

receive SUP medications (OR= 0.90, 99%CI: 0.87-0.92) while Native Americans were more likely to receive them (OR=1.12, 99%CI=1.01-1.26). Concerning medications, patients who received SUP medications were more likely to be on anticoagulants, antiplatelets, thrombolytics, NSAIDs and drugs used for coagulation .On the other hand, the receipt of misoprostol was inversely associated with the receipt of SUP medications (Table 4.3). Patients who experienced one of gastrointestinal-related diseases were almost 4.00 times more likely to receive SUP medications than patients who did not (99%CI: 3.53-4.51).

With regards to stress ulcer risk factors, both MV for more than 24 hours and transplantation were associated with the highest odds of receiving SUP medications comparing to not having one of these risks (OR= 17.2, 99%CI: 15.52-18.97; OR= 18.01, 99%CI: 7.61-42.67, respectively). Moreover, patients who stayed for more than 7 days in the ICU were 10.25 times more likely to receive SUP medications than those with shorter length of stay (99%CI=9.35-11.25). Other risk factors increased the odds of SUP medications receipt between 1.12 and 2.7 depending on each risk factor (Table 4.4). Furthermore, the odds of receiving these drugs increased as the number of risk factors increased from 2.17 with one risk factor to 52.23 with four or more risk factors (Table 4.4).

Table 4.3: Bivariable and Multivariable analyses of Patients who Received Gastric Acid Modifying Drugs or Sucralfate (GAMAS) compared to patients who did not receive them

Characteristics	No GAMAS n=77,816	GAMAS n=494,703	Unadjusted		Adjusted	
	Freq.	Freq.	OR	99%CI	OR	99%CI
Age						
18 to 60	36,752	205,588	Ref	Ref	Ref	
61 to 70	14,799	106,128	1.28	[1.25-1.32]	0.96	[0.92-1.00]
71 to 80	14,023	100,386	1.28	[1.25-1.32]	0.87	[0.82-0.92]
81 to 90	12,242	82,601	1.21	[1.17-1.24]	0.79	[0.73-0.85]
ICU Death	2,836	29,674	1.69	[1.6-1.78]	--	--
Hospital Death	4,404	43,697	1.62	[1.55-1.68]	--	--
Gastrointestinal Bleeding	1,423	40,350	4.77	[4.44-5.11]	5.67	[5.18-6.21]
Male	42,568	263,531	0.94	[0.93-0.96]	0.91	[0.88-0.94]
Race						
Caucasian	58,867	374,894	Ref	Ref	Ref	
African American	9,096	51,879	0.90	[0.87-0.92]	0.88	[0.79-0.98]
Hispanic	3,492	22,789	1.02	[0.98-1.08]	1.10	[0.96-1.21]
Native American	569	4,070	1.12	[1-1.26]	1.10	[0.97-1.25]
Asian	816	5,510	1.06	[0.96-1.17]	1.03	[0.85-1.25]
Other	4,976	35,561	1.12	[1.08-1.17]	1.26	[1.13-1.41]
Type of ICU						
Mixed	39,243	240,410	Ref	Ref	Ref	
Cardiovascular-Surgical	6,809	45,850	1.10	[1.06-1.14]	1.10	[0.81-1.49]
Coronary Care	16,895	95,446	0.92	[0.9-0.95]	0.92	[0.76-1.13]
Trauma	610	2,586	0.69	[0.62-0.78]	0.70	[0.47-1.04]
Surgical	4,174	35,955	1.41	[1.35-1.47]	1.38	[1.08-1.76]
Medical	5,696	44,629	1.28	[1.23-1.33]	1.24	[0.85-1.82]
Neuroscience	4,389	29,827	1.11	[1.06-1.16]	1.37	[1.02-1.83]
Medications						
Anticoagulants	32,269	276,632	1.79	[1.75-1.83]	1.27	[1.14-1.41]
Antiplatelets	41,154	317,687	1.60	[1.57-1.63]	1.45	[1.30-1.62]
Thrombolytics	4,509	50,658	1.85	[1.78-1.93]	1.22	[1.04-1.44]
Coagulating Drugs	1,081	16,809	2.50	[2.3-2.71]	1.68	[1.09-2.57]
Non-Steroidal Anti-inflammatory Drugs	20,790	219,821	2.19	[2.15-2.24]	1.78	[1.63-1.94]
Misoprostol	133	755	0.89	[0.7-1.14]	0.97	[0.76-1.25]
Nutrition						
No feeding	42,428	262,153	Ref	Ref	Ref	

Table 4.3 , Continued

Characteristics	No GAMAS n=77,816	GAMAS n=494,703	Unadjusted		Adjusted	
	Freq.	Freq.	OR	99%CI	OR	99%CI
Enteral Nutrition	34,775	219,753	1.02	[1-1.04]	0.89	[0.79-1.00]
Parenteral Nutrition	193	2,595	2.18	[1.79-2.64]	1.12	[0.92-1.35]
Both	420	10,202	3.93	[3.46-4.47]	1.13	[0.95-1.34]
Diseases						
Any Gastrointestinal diseases	459	11,434	3.99	[3.53-4.51]	1.45	[1.22,1.74]
Peptic Ulcer Disease	29	604	3.28	[2.01-5.35]	--	--
Gastritis	13	439	5.32	[2.57-10.98]	--	--
Esophageal Disease	208	4,446	3.38	[2.82-4.06]	--	--
Duodenal Ulcer	1	230	36.19	[2.74-478.13]	--	--
Unspecified Ulcer	226	6,316	4.44	[3.73-5.29]	--	--
Angiodysplasia	0	0	-	-	--	--
Dieulafoy's Lesion	0	0	-	-	--	--
Ulcer due to mucositis	0	0	-	-	--	--
Risk factors of Stress Ulcer						
Coagulopathy	7,990	109,260	2.48	[2.4-2.56]	1.99	[1.80-2.19]
Mechanical Ventilation > 24 hours	673	64,419	17.16	[15.52-18.97]	10.63	[9.23-12.25]
Traumatic Brain Injury	1,649	16,176	1.56	[1.46-1.67]	2.36	[1.88-2.95]
Sepsis	5,005	61,600	2.07	[1.99-2.15]	1.34	[1.24-1.44]
Staying in ICU for more than 7 days	796	47,405	10.25	[9.35-11.25]	2.96	[2.60-3.37]
Hydrocortisone ≥ 250 mg / day or Equivalent	730	9,293	2.02	[1.83-2.23]	1.55	[1.41-1.70]
Hepatic Failure	512	8,716	2.71	[2.41-3.05]	1.36	[1.22-1.52]
Burns covering 30% or more of Body Surface Area	4	52	2.04	[0.54-7.77]	1.24	[0.38-4.03]
Acute Renal Failure	4,358	52,710	2.01	[1.93-2.1]	1.12	[1.03-1.21]
Spinal Injuries	688	4,874	1.12	[1-1.24]	1.79	[1.53-2.10]
Multiple Trauma	410	4,410	1.70	[1.49-1.94]	1.80	[1.45-2.24]
Transplantation	9	1,029	18.01	[7.61-42.67]	13.28	[7.25-24.34]
Number of Risk factors of Stress Ulcer						
0	58,520	248,016	--	--	--	--
1	16,176	152,549	--	--	--	--

Table 4.3 , Continued

Characteristics	No GAMAS n=77,816	GAMAS n=494,703	Unadjusted		Adjusted	
	Freq.	Freq.	OR	99%CI	OR	99%CI
2	2,733	63,140	--	--	--	--
3	369	23,680	--	--	--	--
≥ 4	18	7,318	--	--	--	--
Type of Risk factors of Stress Ulcer						
Not at risk	58,520	248,016	Ref	Ref	--	--
Any Risk factor	19,296	246,687	3.02	[2.95-3.09]	--	--
Major only	8,254	102,616	2.93	[2.84-3.03]	--	--
Minor only	9,161	61,242	-	-	--	--
One minor	8,086	52,172	1.52	[1.47-1.57]	--	--
Two minors or more	1,075	9,070	1.99	[1.83-2.17]	--	--
Both major and minor	1,881	82,829	10.39	[9.77-11.05]	--	--
APACHE IV Score [mean, SD]	46	55	1.02	[1.02-1.02]	1.01	[1.01-1.02]
Observations			572,519			572,519

GAMAS: Gastric Acid Modifying Drugs or Sucralfate; OR: Odds Ratio; ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; SD: Standard deviation; Ref: Reference

Table 4.4: Association between number of risk factors and the receipt of Gastric Acid Modifying Agents or Sucralfate (N=572,519)

Number of Risk Factors	Unadjusted		*Adjusted	
	Odds Ratio	99%CI	Odds Ratio	99% CI
None (Reference)	---		---	
One	2.23	[2.17-2.28]	1.90	[1.76-2.04]
Two	5.45	[5.18-5.74]	3.71	[3.29-4.18]
Three	15.14	[13.22-17.34]	8.30	[6.72-10.27]
Four or More	95.93	[52.23-176.19]	41.77	[22.68-76.92]

* Adjusted for: Age, gender, race, ICU type, anticoagulant use, antiplatelet use, thrombolytics use, misoprostol, Non-steroidal anti-inflammatory drugs, enteral nutrition, parenteral nutrition, APACHE IV score, gastrointestinal diseases and cirrhosis

In the multivariable logistic regression, with the exception of burns, all stress ulcer risk factors were positively associated with the receipt of SUP medications. The biggest

risk factors were transplantation (OR=13.28, 99% CI: 7.247-24.34), MV for more than 24 hours (OR=10.63, 99% CI: 9.23-12.25) and prolonged ICU stay (OR=2.96, 99% CI: 2.597-3.371). The rest of the risk factors increased the odds of SUP medications receipt in a range between 1.12 and 2.35 compared to patients who did not have these risk factors (Table 4.3). Moreover, gastrointestinal-related diseases were positively associated with SUP medications use with an odds ratio of 1.45 times (99% CI: 1.22-1.74).

Interestingly, gastrointestinal bleeding predicted the use of SUP medications more than most of stress ulcer risk factors with an odds ratio of 5.67 (99% CI: 5.18-6.21). Similarly, patients who took one of the blood modifying drugs i.e. anticoagulants, antiplatelets, drugs used for coagulation or thrombolytics were more likely to be on SUP medications than patients who did not. Between these four therapeutics groups, drugs used for coagulation were associated with the biggest increase in the odds of receiving SUP medications (OR=1.68, 99% CI: 1.10-2.60) while thrombolytics were associated with the smallest increase (OR=1.22, 99% CI: 1.04-1.44). Remarkably, the receipt enteral nutrition was associated with 12% reduction in the odds of SUP medications receipt (OR=0.88, 99% CI: 0.79-1.00). On the other hand, patients who received TPN with or without enteral nutrition were positively associated with the receipt of SUP medications (Table 4.3). Compared to mixed ICU, neuroscience and surgical ICUs were more likely to prescribe SUP medications. In addition, compared to Caucasians, African Americans were less likely to receive them (OR=0.88, 99% CI: 0.79-0.98). With regards to gender, males were less likely to receive SUP medications compared to females (OR=0.91; 99% CI: 0.90-0.94). Unlike the results of bivariable analysis, regardless of the age group,

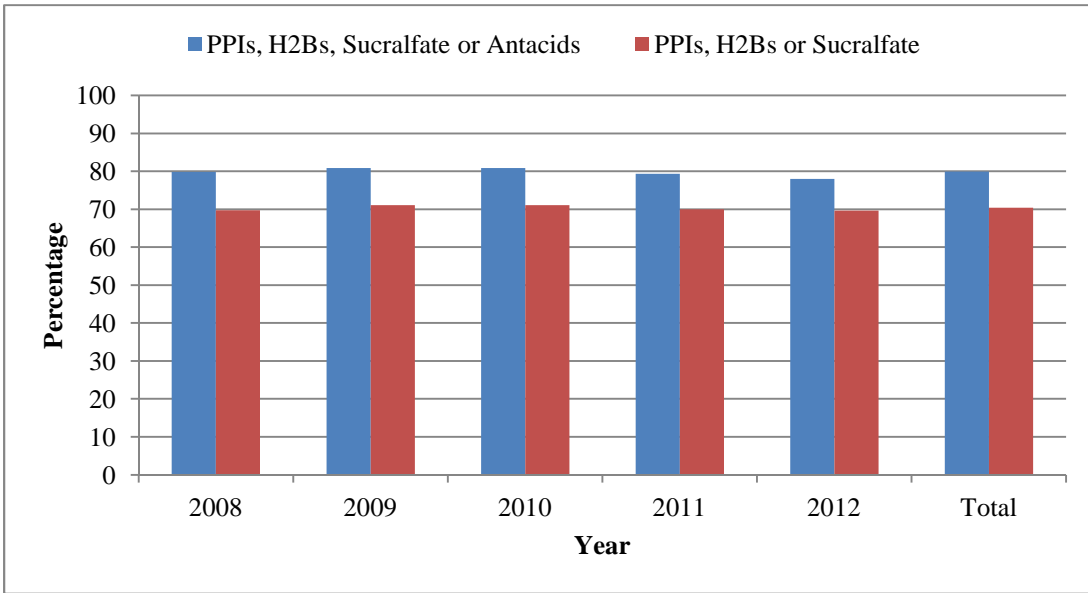
patients above 60 were less likely to receive SUP medications compared to patients less than 60.

Lastly, When the number of risk factors was used instead of the type risk of risk factors in the multivariable logistic regression, the proportional association between SUP medications receipt and the number of risk factors still existed but with lower magnitudes of estimates (Table 4.4).

Overutilization of Stress Ulcer prophylaxis:

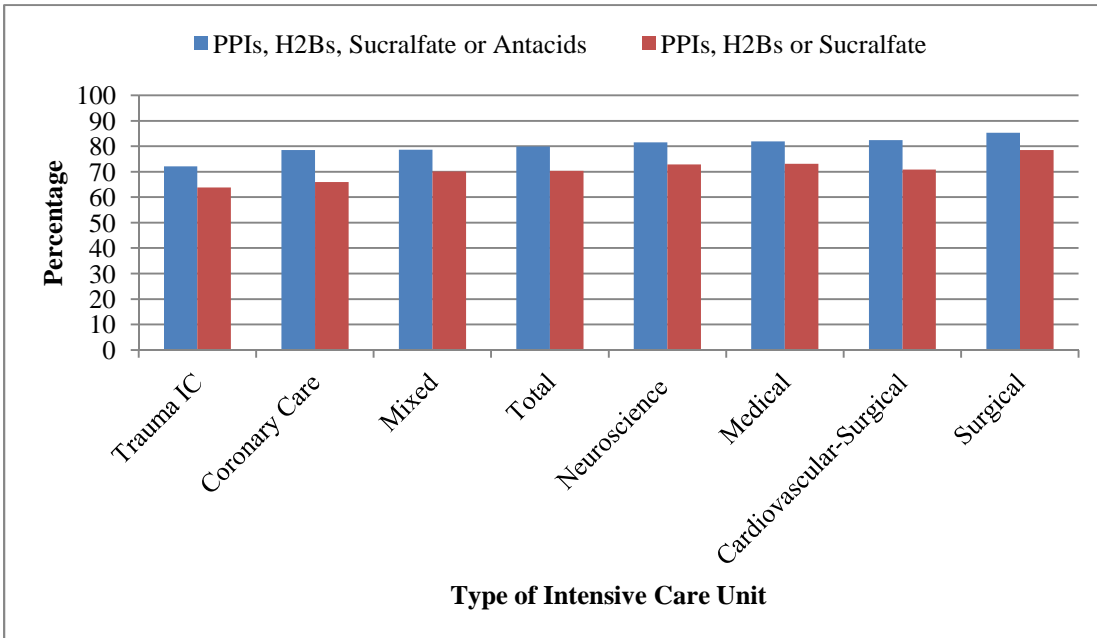
Out of the whole cohort of 572,519 patients, 285,251 (49.8%) of them did not have any known risk factors of stress ulcer, gastrointestinal-related diseases or bleeding. Almost, 80% of these patients did receive SUP during their ICU stay. Even when antacids were removed as a modality of SUP, the percentage of overutilization was 70.34%. Furthermore, from 2008 to 2012 there was no observed difference in the percentages with and without antacids use (Figure 4.3). Regardless of ICU type, more than 70% of patients who did not have stress ulcer risk factors, gastrointestinal diseases or gastrointestinal bleeding did receive SUP medications. Overutilization was the highest in surgical ICU (85.3%) and the lowest in trauma ICU (72%). The removal of antacids as a modality of SUP only reduced overutilization by 6-12% (Figure 4.4).

Figure 4.3: Percentage of Patients who did not have stress ulcer risk factors, gastrointestinal diseases or gastrointestinal bleeding who received stress ulcer prophylaxis medications by year (Total=285,251)



PPIs: Proton Pump Inhibitors; H2Bs: Histamine type-2 receptors blockers

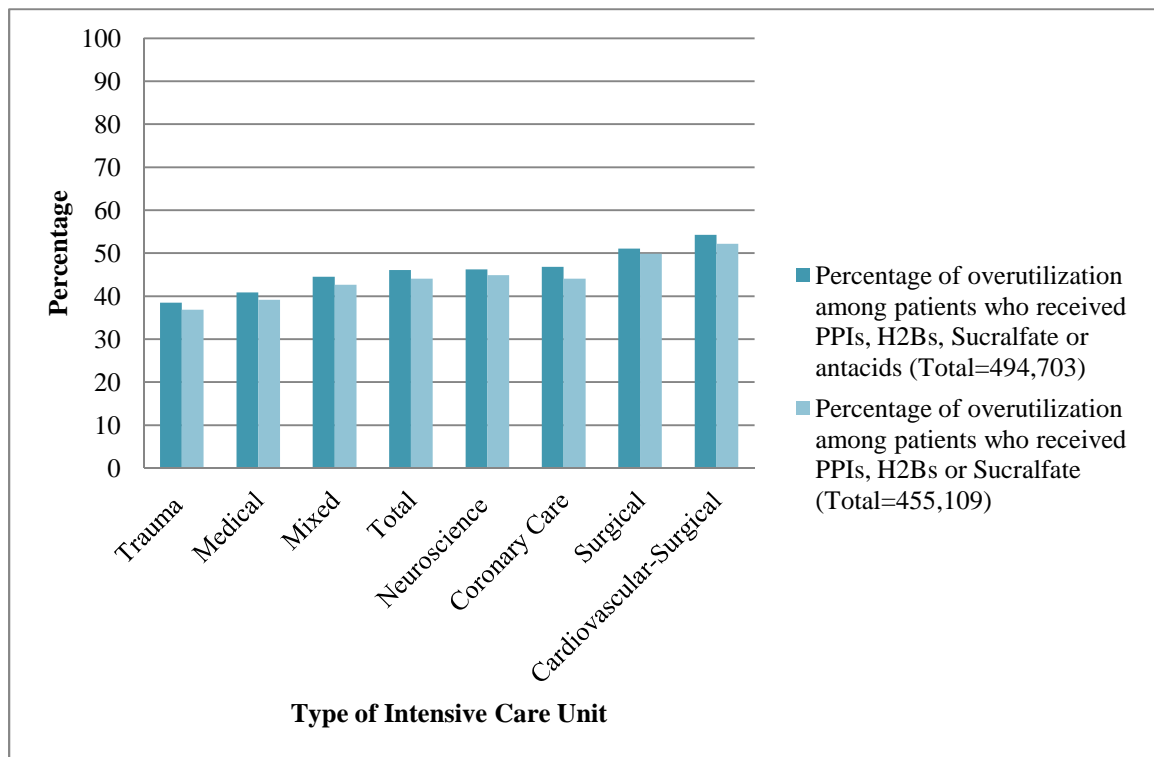
Figure 4.4: Percentage of Patients who did not have stress ulcer risk factors, gastrointestinal diseases or gastrointestinal bleeding who received stress ulcer prophylaxis by ICU Type (Total=285,251)



PPIs: Proton Pump Inhibitors; H2Bs: Histamine type-2 receptors blockers

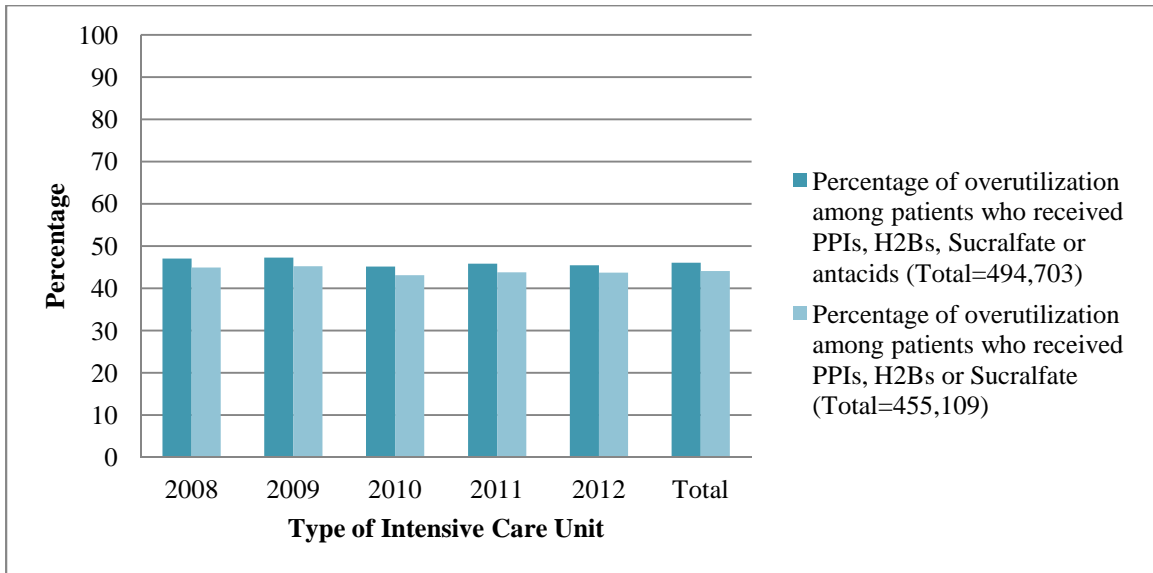
From a different angle, patients who received one of the drugs used in stress ulcer (n=494,703), 46.18 % did not have known risk factors of stress ulcer, gastrointestinal bleeding or any known diagnoses of gastrointestinal-related diseases. This percentage ranged from 38.7% to 54.3% based on the type of the ICU. Even when antacids use was excluded, the percentage of overutilization was 44.2% with a range between 37.0% and 52.2 (Figure 4.5). This percentage was approximately constant across the five years of the study (Figure 4.6). Other Univariable and bivariable analyses are provided in Appendix I, Table 4 and 5.

Figure 4.5: Percentages of overutilization among patients who received PPIs, H2Bs, Sucralfate or antacids by ICU type



PPIs: Proton Pump Inhibitors; H2Bs: Histamine type-2 receptors blockers

Figure 4.6: Percentages of overutilization among patients who received PPIs, H2Bs, Sucralfate or antacids by year



PPIs: Proton Pump Inhibitors; H2Bs: Histamine type-2 receptors blockers

Among patients who did not have known risk factors of stress ulcer, gastrointestinal diseases or gastrointestinal bleeding (n=285,251), the multivariable regression revealed that the biggest predictor of overutilization was being on MV for less than 24 hours (OR: 3.3; 99%CI: 3.04-3.59). With regards to medications use, SUP overutilization was positively associated with the use of anticoagulants (OR: 1.30; 99%CI: 1.27-1.34), NSAIDs (OR: 1.78; 99%CI: 1.73-1.83), antiplatelets (OR: 1.44; 99%CI: 1.39-1.48) and thrombolytics (OR=1.17, 99%CI: 1.11-1.24). In addition, patients above 70 were less likely to receive SUP as an overutilization compared to patients less than 60 years old. Compared to mixed ICU, coronary care ICU (OR: 0.94; 99%CI: 0.91-0.97) and trauma ICU (OR: 0.74; 99%CI: 0.63-0.87) were associated with lower SUP overutilization. In contrast, all other ICU types were associated with higher SUP overutilization compared

to mixed ICU. Lastly, there was an inverse relationship between enteral nutrition and SUP overutilization (Table 4.5).

Table 4.5: Factors associated with SUP medications overutilization among patients who did not have known risk factors of stress ulcer, gastrointestinal-related diseases or gastrointestinal bleeding between 2008 and 2012 (n=285,251).

Characteristics	OR	99% CI
Mechanical Ventilation for Less than 24 hours	3.304***	[2.472,4.415]
Age		
18 to 60	Reference	
61 to 70	0.987	[0.942,1.034]
71 to 80	0.900**	[0.844,0.960]
80 to 90	0.833***	[0.777,0.894]
Male	0.908***	[0.877,0.940]
Race		
Caucasian	Reference	
African American	0.896	[0.797,1.007]
Hispanic	1.049	[0.914,1.203]
Native American	1.044	[0.931,1.171]
Asian	1.03	[0.846,1.254]
Other	1.188**	[1.052,1.343]
Type of ICU		
Mixed	Reference	
Cardiovascular-Surgical	1.044	[0.806,1.352]
Coronary Care	0.94	[0.770,1.148]
Trauma	0.74	[0.504,1.088]
Surgical	1.406**	[1.088,1.818]
Medical	1.258	[0.857,1.847]
Neuroscience	1.426*	[1.051,1.935]
Medications		
Anticoagulants	1.304***	[1.169,1.455]
Antiplatelets	1.437***	[1.285,1.608]
Thrombolytics	1.172	[0.986,1.394]
Coagulating Drugs	1.238	[0.803,1.908]
Non-Steroidal Anti-inflammatory Drugs	1.783***	[1.641,1.938]
Misoprostol	0.882	[0.685,1.137]
Nutrition		
No feeding	Reference	
Enteral Nutrition	0.891	[0.787,1.008]
Parenteral Nutrition	1.067	[0.846,1.346]
Both	1.037	[0.839,1.281]
APACHE IV Score	1.011***	[1.009,1.013]
Observations	285,251	

OR: Odds Ratio; ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; SD: Standard deviation; Ref: Reference

* p<0.05, ** p<0.01, *** p<0.001

Discussion:

In this retrospective cohort study that included 572,519 patients the utilization of SUP medications was very prevalent (86.4%). The most common risk factors of SUP were coagulopathy, MV for more than 24 hours, long ICU stays and sepsis. Patients in ICUs are usually put on prophylactic anticoagulants to prevent deep vein thrombosis or pulmonary embolism. Therefore, patients may develop coagulopathy during their ICU stay making it the most common SUP risk factor in ICUs. In addition, due to the severity of their illnesses, many patients may end up developing sepsis or respiratory failure that requires mechanical ventilation which explains the fact these factors were the among the most common stress ulcer risk factors. Among patient who had at least one stress ulcer risk factor, almost 83% did receive a SUP medication within a 24 hours window of risk factor occurrence indicating good identification of stress ulcer risk factors, immediate plan of action in these ICUs and adherence to best practice. However, there was a huge shift in the therapeutic classes used compared to older literature. For instance, from 1999 to 2007, five surveys examined SUP utilization in ICU settings; two before 2002^{145,146} and three from 2002 until 2007¹⁴⁷⁻¹⁴⁹. In all these studies, H2Bs utilization was between 65% and 75%. On the other hand, PPIs utilization was less than 5% up to 2002. Upon the introduction of the first generic omeprazole in Nov 1, 2002¹⁵⁰, there was a shift in prescribing patterns that led to a jump in PPIs utilization to 23%^{148,149}. In our sample, regardless of the timing of the risk factor, PPIs use was the highest followed by H2Bs use. For instance, in the full cohort PPIs use was 60% while H2Bs use was 30.5%. Furthermore, PPIs that were given within 24 hours of being at risk were the most frequently used (49.8%) followed by H2Bs (17.96%). This flip in utilization between

H2Bs and PPIs is most likely due to two main reasons: first, the introduction of generic pantoprazole in 2007¹⁵¹ which reduced the cost of these medications and increased the competition with H2Bs; Second, and more importantly, the multiple meta-analyses and cost-effective studies^{71,73,74,152} that were published in the last ten years reinforced the belief that PPIs are at least as effective as and most likely cost-effective alternative for H2Bs. On the other hand, in Figure 4.2, the gradual reduction in PPIs utilization over the five years from 52.4% to 46.8% that was accompanied by a gradual increase in H2Bs utilization from 15.96% to 20.1% is most likely due the increased awareness about possible side effects of PPIs such as CDAD and NP as well as the possible interaction with clopidogrel which made H2Bs safer alternative^{106,120-122,124,153-157}. Despite the reduction in PPIs use over the five years, the fact that the reduction was modest (from: 52.4% to 46.8%; absolute reduction=5.6%; relative reduction=10.7%) indicates that despite PPIs' side effect and drug interactions the majority of clinicians perceive PPIs as a more effective SUP than H2Bs with a similar safety profile. However, since the objective of the study was not conducting a segmented time series analysis, these proposed explanations should be further investigated in future research.

SUP utilization was inversely associated with age. Compared to patients younger than 60, all other groups of old patients were less likely to receive SUP (Table 4.3). Although we have adjusted for hepatic impairment, it is possible that there was a residual variation between the different age groups in terms of the severity of the impairment. These differences may make older patients more prone to drug interactions which could make clinicians more hesitant to prescribe PPIs or cimetidine, for instance, to the elderly. An

evident example is the interaction between PPIs and clopidogrel. Clopidogrel as a prodrug needs to be activated in the liver by CYP2C19 enzyme to the active metabolite responsible for the antiplatelet effects. Proton Pump Inhibitors and cimetidine are known inhibitors for CYP2C19^{154,158,159} enzyme which with hepatic impairment may reduce the antiplatelet effectiveness of clopidogrel. Thus, clinicians may be less likely to prescribe these medications to older patients.

In our study, African Americans were 12% less likely to receive SUP than Caucasians (OR=0.88; 99%CI: 0.79-0.98). Racial disparities have been documented in both ICU practice and non-ICU practice with regards of treatment selection^{160,161}. However, this difference in SUP utilization, although it could be a true, should not be considered as a disparity without further investigation as it could also be due to unmeasured confounders that are less relevant to this study^{162,163}.

In this cohort, most of stress ulcer risk factors were associated with SUP medications utilization (Table 4.3). In particular, transplantation (OR=13.28, 99%CI: 6.88-25.66) and MV for more than 24 hours (OR=10.63, 99%CI: 9.84-11.49) were the strongest predictors of SUP medications use among these risk factors. This association between stress ulcer risk factors and SUP medications use reflects the congruence between the guidelines and current practice which is indicative of clinicians' awareness of these risk factors importance in stress ulcer etiology and, consequently, the importance of prescribing SUP. In addition, the proportional increase in the odds ratio of receiving SUP medications from 1.90 with one risk factor to 41.77 with four or more risk factors suggests that clinicians consider not only the existence of risk factors but also the number

of risk factors in their decision to prescribe SUP (Table 4.4). The latter is concordant with studies that found a proportional relationship between the number of risk factors and stress-induced bleeding¹⁶⁴. On the other hand, SUP drugs were administered to almost 80% of patients who were not at-risk of stress ulcer, did not have gastrointestinal bleeding or gastrointestinal-related diseases indicating that the issue of overutilization still exists despite the large number of studies that raised this issue in the literature^{1,2,157,165}.

In the multivariable regression models, MV >24 hours was associated with SUP use while MV <24 hours was associated with SUP overuse. This implies that clinicians identify MV as a major risk factor of stress ulcer but do not consider the duration of MV as a qualifying factor for the receipt of SUP. Based on the ASHP guidelines, patients should receive SUP if they have respiratory failure manifested by being on MV for more than 48 hours. This recommendation was based on Cook's seminal paper which found that patients with the aforementioned condition were at a greater risk of stress induced bleeding (OR = 15.6; no confidence interval reported, $p < 0.001$)¹⁰. In this paper, the choice of 48 hours was not justified. Therefore, based on the fact that stress-related mucosal damage is known to start within hours of ICU admission and occurs in almost every patient admitted to the ICU¹¹⁻¹³, many clinicians considered respiratory failure manifested by the use of MV for less than 24 hours is sufficient to prescribe SUP. This made MV for less than 24 hours the strongest predictor of SUP overutilization (OR=3.3, 99%CI: 2.5 to 4.4). In the absence of studies that determines the minimum duration of

MV required to induce stress ulcer-related bleeding, this practice pattern will continue to exist.

In Figure 4.5, out of 455,109 patients who received at least one dose of PPIs, H2Bs or sucralfate, almost 44% of them did not have any documented risk factors of stress ulcer, duodenal ulcer, gastric ulcer, unspecified ulcer, gastritis, angiodysplasia, Dieulafoy's lesion or ulcers due to mucositis. Furthermore, these percentages stayed nearly constant over the five years of the study (Figure 4.6). Hypothetically, if we consider that up to 50% of them had undocumented reasons that required the administration of one of these medications, we can safely assume that only 22% did not have a justifiable reason to receive these drugs. This is translated to 100,123 patients between 2008 and 2012. Thus, assuming equal distribution of patients over the years, 20,024 patients per year were receiving these drugs with no clinical reasons. Therefore, as a back of the envelop calculation, if we assume that the patient will receive only one dose per day and that the cost of the dose is 25 cents, \$5006 were wasted without any returned benefit and with potential exposure to side effects each year. Of course, this number is underestimated given that it does not include the number of additional doses, the total length of stay and the cost of treating a side effect.

Other factors may also have led to SUP overutilization. For instance, recent studies have reported that the fear of liability, lack of time to question the need for SUP and the perception that these medications are safe might also played a role in this pattern of practice^{166,167}.

Non-steroidal anti-inflammatory drugs have been long known to cause gastric ulcer that requires the administration of one of the SUP medications. In our definition we did not include NSAIDs because we included all types of gastric ulcers and/or gastric-related diseases. In the multivariable regression of SUP overutilization, NSAIDs were associated with SUP overutilization i.e. the use of SUP medications without an indication (OR=1.78, 99%CI: 1.64-1.94). Although NSAIDs use itself could be enough indication for SUP medications use, it is unclear if every patient on NSAIDs therapy in ICUs, where the majority of patients stay only for few days, requires SUP medications. This is a question that is still open for future research.

The use of blood modifying drugs such as antiplatelets and anticoagulants was also positively associated with overutilization i.e. the use of SUP medications without an indication (Table 4.5). Despite the fact that these patients did not have any known indications it is most likely that they had an undocumented coagulopathy. In our study, the definition of coagulopathy was based on having platelets counts less than 50,000 per/ml³, an international normalized ratio > 1.5, or a prothrombin time > 50 sec. Most of the anticoagulants' therapeutic targets are above an INR of 2^{168,169}. Therefore, by definition, these therapeutic targets will lead to coagulopathy. However, this coagulopathy may have not been documented if the medical staff did not fully use the eICU interface, did not capture it, or did not document it because the patient was about to get discharged.

Our study has limitations that should be considered when interpreting the findings. First and most important; we could not ascertain patients' past medical history of gastric

ulcer of bleeding during the twelve months before ICU admission or the presence of occult bleeding for six days in this data. These two factors are known indications for SUP. Occult bleeding is usually identified through a fecal sample that shows a positive guaiac test with no indication of overt bleeding. However, it is less likely that the test of occult bleeding is done routinely in the ICU. Consequently, the lack of ascertainment of these two factors may have led to an underestimation of the percentage of patients who received SUP medications appropriately and overestimation of the percentages of overutilization reported in this study. However, since the majority of patients (86%) have received SUP medications in our study the underestimation of SUP medications use is less of a concern. On the other hand, with regard to the overestimation of SUP overutilization, our simple calculations showed that even with the assumption that 50% of patients who received SUP medications had an undocumented indication there were around 20,024 patients per year who were exposed to these medications for no expected benefit. Second, there are factors that may affect the predictors of overutilization that we could not capture in our data such as hospital characteristics, the presence of SUP protocol, the presence of ICU pharmacists, and qualitative factors such as fear of liability or physicians' perception about the safety of these medications. Third, since the ICUs participated in this study were part of Philips eICU program, the results may not be generalizable to ICUs outside the program.

In conclusion, the practice pattern of SUP utilization has shifted toward H2Bs over PPIs between 2008 and 2012. While current practice recognizes the existence and the number of stress ulcer risk factors in the decision to prescribe SUP , the issue of SUP

overutilization was observed in almost 80% of patients who did not have any known indication. Patients are facing the danger of being exposed to the adverse effects associated with these medications such as nosocomial pneumonia, *clostridium difficile*-associated diseases and hypomagnesaemia in addition to the financial burden of unnecessary use faced by hospitals. Hospitalists and intensivists should not only be cognizant of the presence of stress ulcer risk factors but also about the lack of these risk factors to optimize patient's therapy. In addition, efforts should be exerted to develop integrated systems where pharmacists and technology can assist in detecting overutilization and evaluate the impact of these systems on both safety and effectiveness of SUP.

Chapter V. Comparative Effectiveness of Proton Pump Inhibitors vs. Histamine type-2 receptors blockers in preventing Clinically Important Gastrointestinal Bleeding in Intensive Care Units: A population-based study

Introduction:

Stress-related mucosal damage was first described in 1842 by T.B. Curling. He presented a case series of patients who developed duodenal ulceration following extensive burns ⁶. Since that time, several observational studies and randomized controlled trials (RCT_s) have shed light on the mechanisms by which stress leads to gastrointestinal bleeding (GIB) and its prophylactic modalities. After a series of studies in the 1970s and 1980s, histamine type-2 receptor blockers (H2Bs) became the cornerstone of stress ulcer prophylaxis (SUP) in intensive care units (ICU(s)), specifically, when the Food and Drug administration (FDA) approved as a SUP drug in late 1980s. Alongside the FDA approval, the ease of administration of H2Bs abated the use of sucralfate, their biggest competitor at that time, as a SUP medication. Therefore, when proton pump inhibitors (PPIs) came to the market, it was logical to compare them to H2Bs. Both therapeutic classes are known to reduce gastric acid production in the stomach. Gastric acid is an essential component in the development of stress ulcer. Its secretion is mainly stimulated by histamine, acetylcholine and gastrin. These three compounds bind to their receptors on parietal cells which are responsible for producing Hydrogen ions and maintaining gastric pH around 1.4 ⁴⁹. The binding starts a series of intracellular cascade that ends up with the activation of a Hydrogen-Potassium ATPase pump (H⁺/K⁺ pump)

that releases the hydrogen ions into the gastric lumen. Histamine receptor type-2 blockers inhibit acid production by blocking histamine receptors on parietal cells. In contrary, PPIs suppress acid production by irreversibly inhibiting the H^+/K^+ pump itself⁵⁰. This distinction in mechanism of action illustrate why tolerance develops with H2Bs but not with PPIs. When histamine receptors are blocked, acetylcholine and gastrin secretions increase as a compensatory mechanism leading to activation of H^+/K^+ pump and hydrogen ion release from parietal cells despite the blockade. To the contrary, once the H^+/K^+ pumps are inactivated by PPIs, the parietal cell itself does not produce hydrogen ions until new pump are formed. Thus, the PPIs blockade is not influenced by the compensatory release of histamine, acetylcholine and gastrin⁵¹. Both the development of tolerance to H2Bs and the irreversible action of PPIs explain the higher potency of PPIs, as acid suppressors, compared to H2Bs.

Since 1993, twelve RCT were published comparing PPIs to H2Bs. Nine of these studies were published after 2000, i.e., after the publication of the ASHP guidelines that recommended the use of H2Bs⁵⁸⁻⁶⁶. Five meta-analyses summarized the results of these RCTs⁷¹⁻⁷⁵. While four of the meta-analyses concluded that PPIs were more effective than H2Bs in preventing stress ulcer-related GIB, one meta-analysis⁷³ did not find any difference between the two therapeutic classes. Because of the biological plausibility and the results of these meta-analyses, PPIs became the most commonly used SUP in intensive care units overcoming H2Bs as a more efficacious SUP. However, many methodological flaws were reported in the RCTs that were used in these meta-analyses⁷⁴. In 2014, an observational study of 35,312 patients, among which 21,873 (61.9%)

received PPIs and 13,439 (38.1%) received H2Bs, found that PPIs were associated with higher risk of GIB compared to H2Bs (5.9% vs 2.1%). After propensity score and covariates adjustment, the investigators found that PPIs were associated with higher risk of GIB (OR=2.24, 95% CI: 1.81-2.76). This finding contradicted all previous SUP literature that suggested PPIs' higher efficacy. Therefore, the objective of this study was to determine whether PPIs were associated with lower risk of clinically important gastrointestinal bleeding (CIGIB) compared to H2Bs among patients admitted to ICUs.

Methods:

Data:

The cohort used in this study came from the Philips eICU Research Institute (eRI) data repository¹⁷⁰. The data has been previously described in the literature¹⁷¹. Briefly, the data consists of electronic medical records that contain physical examinations, laboratory results, diagnoses, treatments, physiology readings and nursing staff entries with the corresponding time flags for patients admitted to one of the participated ICUs. Selection of disease diagnoses was done through a menu of discrete diagnoses strings that are linked to the International Classification of Diseases 9th ed. (ICD-9) codes in the eRI repository. Patient's health status is measured using the acute physiology and chronic health evaluation score version IV (APACHE-IV score). All patient information that is deemed to be protected health information was not included in the database. Therefore, each patient stay is represented by a unique unit stay number, and time is indexed from admission time in minutes rather than calendar time.

Inclusion and exclusion criteria:

Intensive care units patients with at least one risk factor for stress ulcer between January 1st 2008 and June 30th 2012 were included in the study. These include patients with at least one of the following conditions: mechanical ventilation > 24 hours , coagulopathy, head injuries, major burns, sepsis, corticosteroid therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU length of stay (LOS) > 1 week. Table 5.1 contains the criteria by which these risk factors were identified.

Table 5. 1: Proposed criteria for identifying patients at risk of stress ulcer gastrointestinal bleeding

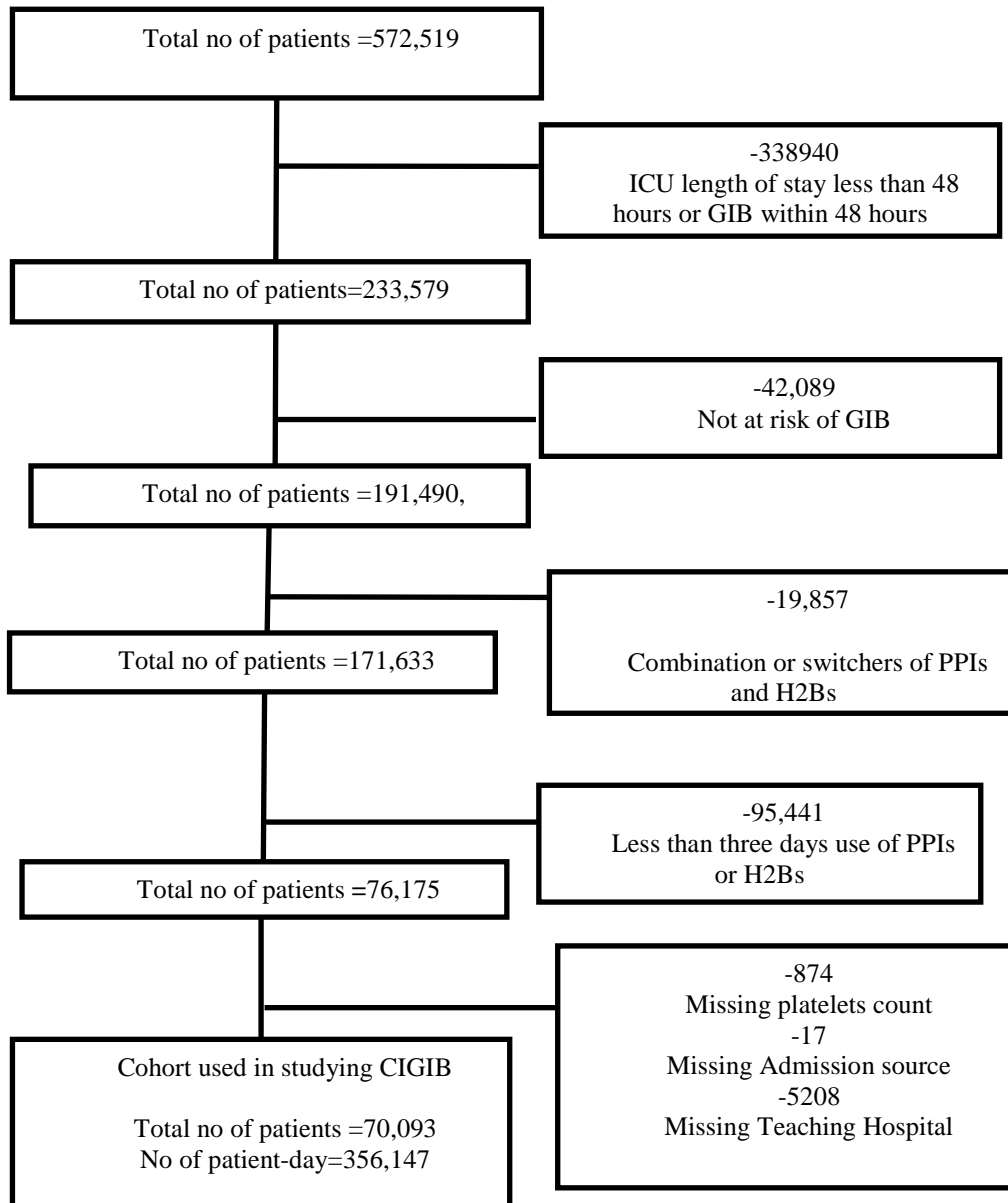
Risk factors of gastrointestinal bleeding due to stress ulcer	Selection method	Comments
Mechanical Ventilation > 24 hrs.	Continuous invasive ventilation duration in minutes	Ventilation data file
Coagulopathy	Any of the followings during an ICU stay: Platelets 50,000 per/ml ³ ; an INR > 1.5, a PT > 50 sec	Hematology or laboratory results files
Traumatic Brain Injuries	ICD-9 code: 800.0-801.9 803.0-804.9 850.0-854.1 950.1-950.3 959.01	Active diagnosis file
Major Burns	ICD-9 code: 940.*-949.*	Active diagnosis file
Sepsis	ICD-9 code: 038, 040.82, 599.0, 996.64, 998.5, 999.3	Active diagnosis file
Corticosteroid Therapy > 250 mg of hydrocortisone or equivalent daily		Medications file
Acute Renal Failure	ICD-9 code: 584.*	Active diagnosis file
Hepatic Failure	ICD-9 code: 570.*	Active diagnosis file
Transplantation	Using admission diagnosis string “operative transplant”	The APACHE admission diagnosis file
ICU stay of > 1 week	ICU length of stay variable that is available in the raw data files	APACHE Patient Results file

Table 5.1, Continued

Risk factors of gastrointestinal bleeding due to stress ulcer	Selection method	Comments
Neurological Injuries/Spinal Injuries	Using admission diagnosis string “spinal trauma”, “spinal cord decompression”, “Spinal cord only trauma”, “Spinal cord surgery, other”, “Spinal/extremity trauma”, “Spinal/face trauma”, “Abdomen/spinal trauma” Or ICD-9Code: Coma:780.01, 780.03, 850.3, 850.4, Embolic stroke:433, 434; Encephalitis: 348.1, 348.4, 348.5 Hemorrhage: 430, 431, 432, 997.02, 997.09 Spinal cord injury:806, 952	The APACHE admission diagnosis file and active diagnosis file

Patients were excluded if any of the followings existed: ICU length of stay less than 48 hours, gastrointestinal bleeding within the first 48 hours of admission or, the receipt of PPIs or H2Bs for less than three days to allow enough exposure time and establish temporality between exposure and CIGIB. In addition, patients with no risk factors for CIGIB, patients who received of PPIs and H2Bs concomitantly or consecutively, or those who had missing platelet counts, source of admission or teaching hospital status were excluded. Figure 5.1 contains the selection criteria for each of the aforementioned conditions.

Figure 5.1: Selection Criteria for the Cohort Used in Studying CIGIB



Measures

Dependent variable:

The main dependent variable in this study was CIGIB. The discriminating diagnostic tool for stress ulcer-related bleeding is gastric endoscopy which may not be done frequently in the ICU. In addition, while bleeding due to many other GI diseases has

specific international classification of diseases-ninth revision (ICD-9) codes, GIB due to stress ulcer does not have a specific ICD-9 code. Therefore, clinically important bleeding due to stress ulcer was defined by excluding other causes of bleeding and restricting on bleeding episodes that lead to hemodynamic changes. Consequently, GIB episodes were defined through ICD-9 code 578.** that encompassed hematemesis, blood in stool and unspecified bleeding. Only one entry with the aforementioned ICD-9 code was required to define a bleeding episode. This step was sensitive to capture all cases of GIB related to stress ulcer, however, not specific enough to exclude other types of GIB that also did not have a specific ICD-9 code. Therefore, diagnosis strings from the diagnoses file were used to exclude bleedings due to other causes. For example, a patient may have an ICD-9 code of 578.** but the corresponding diagnosis string was “postpartum hemorrhage” or “due to malignancy”; such bleedings were excluded. Appendix II table 1 contains the types of bleeding that were included or excluded. Clinically important bleeding episodes were defined as any episode of GIB with at least one of the following criteria occurring 24 hours before or after the bleeding: 1) an absolute reduction in systolic blood pressure by at least 20 mmHg; 2) an absolute reduction in diastolic blood pressure by at least 10 mmHg; 3) a heart rate increase by at least 20 beats/min; 4) The receipt of blood transfusion. Lastly, any bleeding episode occurred in the first 72 hours of admission was excluded to establish temporality between the exposure and the outcome and allow enough opportunity time for the medications to exert their prophylactic effects.

Independent variables:

The main independent variable was the receipt of PPIs for three days versus the receipt of H2Bs for three days. The name, time of administration and the hierarchical

ingredient code list (HICL²) sequence number¹⁴² for these therapeutic classes were recorded in the medication data file. Both the HICL sequence number and medications name were used to pull out all entries of PPIs ,omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole and pantoprazole, or H2Bs ,cimetidine, ranitidine, famotidine and nizatidine, during an ICU stay. Appendix I Table 2 shows the HICL sequence numbers as well as medications brand and generic names used in identifying the two classes and other medications included in the study. Lastly, although the onset of action of many PPIs and H2Bs is within 1 to 3 hours, the peak effect of H2Bs and PPIs requires 12 to 24 hours in order to take place, respectively. Therefore, a 24-hours lag period between the exposure and the occurrence of CIGIB was needed to establish temporality.

The following covariates were included: demographics (age, gender and race); clinical variables (mechanical ventilation > 24 hrs. , coagulopathy, head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week, cancer, human immunodeficiency virus, cirrhosis, the receipt of enteral nutrition and intubation in the first day); medications that affect the risk of bleeding including antiplatelets, anticoagulants, thrombolytics, non-steroidal anti-inflammatory drugs, sucralfate and antacids; admission source, physician specialty and type of hospital (teaching vs. non-teaching). In addition, health severity was measured by the Acute Physiology and Chronic Health Evaluation (APACHE IV)

² A proprietary of First DataBank (www.fdbhealth.com)

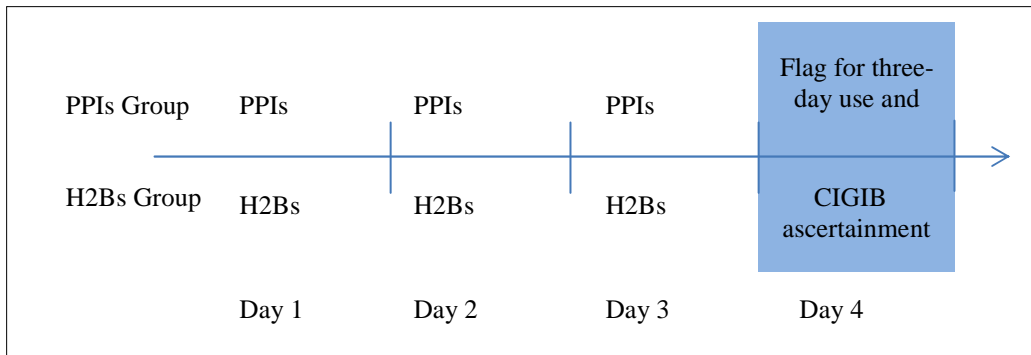
software as a sublicense from Cerner, Inc., (Kansas City, MO). The study was exempted from Institutional Review Board review (HP-00055985) at University of Maryland.

Statistical Analysis:

Univariable and bivariable analyses were done to describe the distribution of the variables and compare the two groups i.e. patients who received PPIs for three days compared to patients who received H2Bs for three days. Dichotomous variables were reported in counts and percentages while continuous variables were reported in means and standard deviations. Bivariable analyses were done using chi-squared tests for categorical variables and t-test for continuous variables.

The main issues in this analysis were the possibility of late exposure after ICU admission; avoiding reverse causality by keeping the desired lag time between the exposure and CIGIB; and reducing the unbalanced distribution of covariates between the PPIs group and the H2Bs group resulting from the absence of randomization. We used three distinct approaches that separately investigated these issues in analyzing the data. First, we used Cox-proportional hazard model with discrete time intervals. The ease of using discrete time intervals allowed not only accommodating late exposure after ICU admission but also keeping a 24-hour lag time between the exposure and outcome to avoid any reverse causality (Figure 5.3). Therefore, a person-day data file was created to allow for multiple observations per patient based on the exposure status.

Figure 5.2: The definition of three day use as a lagged variable



PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 Receptor Blockers; CIGIB: Clinically Important Gastrointestinal Bleeding

Second, since treatment allocation was not random i.e. it was determined by patient, physician and facility characteristics; propensity score matching was used to account for the observable covariates that can explain treatment selection. Third, instrumental variable (IV) analysis was used as to reduce the bias associated with confounding by indication a.k.a. treatment selection bias associated with both measured and unmeasured covariates and arising from.

Propensity Score Matching:

From the patient-day file created for previous analyses, a patient level file was created for this analysis. In a multivariable logistic regression model, the propensity scores of receiving three days of PPIs vs three days of H2Bs was determined using age, gender, race, ICU type, enteral nutrition, cancer, HIV, cirrhosis, neutropenia, platelet count, immunosuppression, risk factors of stress ulcer, the use of sucralfate, antacids, anticoagulants, antiplatelets, thrombolytics or NSAIDs, admission source, physician specialty and APACHE-IV score in the three days prior to exposure as independent variables. Model fit was assessed using C-statistic, Pearson's χ^2 and Hosmer-Lemeshow

goodness of fit tests. Next, we performed one to one matching with no replacement and a caliper of 0.00001 to create the matched group. Covariates balance before and after matching was checked using t-test, accounting for matching design, and the standardized mean difference approach¹⁷² (Appendix II). If the P-value of the t-test was less than 0.05 and the standardized mean difference was less than 10% then the covariate was considered imbalanced between the two groups and, therefore, was included in the final model. Lastly, we estimated the effect of the exposure on the instantaneous risk of CIGIB within the matched group using simple Cox proportional hazard model.

Instrumental Variable Analysis:

The instrumental variable approach utilizes an ‘instrument’ to mimic the random group assignment process that is characteristic of a RCT. The IV approach facilitates comparisons between intervention and control groups that are otherwise comparable by using an instrument to determine group assignment within a nonrandomized design. A valid IV has two characteristics: first, it must be strongly correlated with exposure; second, the IV should not be correlated with the error term of the structural equation i.e. should not be correlated with the unobserved variables that influence the outcome in the error term. When a great proportion of patients in an ICU receive PPIs, it is most likely that prescribing decision is dependent on the practice of that ICU rather than patients’ characteristics. Consequently, the preferred therapeutic class for the ICU can be used as an instrument for determining who receives either PPIs or H2Bs. Specifically, each ICU can be classified either as a PPIs ICU or a H2Bs ICU. We classified ICUs that prescribed PPIs to 90% of their patients as PPIs units. This IV is expected to be strongly correlated

with the exposure i.e. the receipt of PPIs for three days. Of course, the assumption here that being in an ICU that prescribed PPIs to 90% of patients is independent of CIGIB, except through the exposure, or any unmeasured factors that may influence CIGIB.

Instrumental variable analysis was carried out in two stages: first, in a multivariable logistic regression model, we predicted the odds of receiving three days of PPIs vs. three days of H2Bs using the aforementioned IV and the following exogenous variables: demographics (gender, race, age), stress ulcer risk factors, enteral nutrition, cancer, HIV/AIDS, immunosuppression, type of ICU, physician specialty and the teaching status of the hospital. Second, we estimated the effect of the exposure on the instantaneous risk of CIGIB using multivariable regression using Cox-proportional hazard model adjusting for stress ulcer risk factors, enteral nutrition, cancer, HIV/AIDS, immunosuppression, physician specialty, admission source, APACHE-IV score and platelets count. The two-stage least square (2SLS) method was used to calculate partial F-statistics which determines whether or not the IV has any significant addition to the model of the first stage. As a rule of thumb, if the F-test is greater than 10 then it is strongly correlated with the exposure¹⁷³. Although the 2SLS method should only be used when the exposure is a continuous variable, the partial F-statistic still provides a valid estimation for the strength of the correlation between the exposure and the IV.

Because of the binary nature of CIGIB, the two-stage residual inclusion method (2SRI) was the appropriate procedure for incorporating the information from the first stage into the second regression¹⁷⁴. This was done by simply adding the residuals from the first stage as an additional covariate in the second stage. Hypothetically, the residuals

should contain the unmeasured factor(s) that influenced treatment selection. Thus, by including the residuals from the first stage the bias introduced by the non-random treatment selection was solved. Among the different ways to calculate the residuals after running the first stage multivariable logistic regression, standardized Pearson's residuals with covariates patterns adjustment were used to account for the similar covariate pattern within a patient's observations and between patients' observations¹⁷⁵. The results of the two stages and the IV diagnostics are available in appendix II.

Sensitivity analyses:

Multiple sensitivity analyses were done to determine the robustness of the results. First, duration of use was reduced to two days of exposure to determine if shorter duration has the same effect on CIGIB and to compare the findings to studies that used two days of exposure. In this case, the cohort was expanded by including CIGIB cases that occurred on the third day.

Second, the current definition of exposure deals with any patient who was exposed to one of the two groups for three days as an exposed patient throughout the ICU stay even if the drug was discontinued later. Therefore, the analysis was confined to patients who did not discontinue treatment or discontinued treatment no more than two days before discharge to avoid overestimation of the HR.

Third, the cohort was divided into deciles based on ICU LOS. The upper decile of patients, i.e. patients with the longest ICU LOS, was excluded as these patients may not represent the whole cohort.

Fourth, since having occult bleeding for six days was a risk factor that was not captured in the study, the analysis was confined to patients who stayed in the ICU for less than 6 days, i.e. who could not develop the aforementioned risk factor, to determine whether or not the magnitude and the direction of the HR will change.

Fifth, since MacLaren's study⁷⁸ reported higher risk of bleeding with PPIs, post-PPIs thrombocytopenia was tested as a possible explanation if the study's results were similar to Maclaren's study. Multiple case reports suggested that PPIs led to thrombocytopenia in patients who did not have a history of thrombocytopenia¹⁷⁶⁻¹⁸¹. Histamine type-2 receptors blockers have been also linked to thrombocytopenia^{182,183}. Consequently, adjusting for post-treatment thrombocytopenia in the regression model should at least reduce the HR if it was indeed a mediator in the relationship of PPIs and CIGIB. Thrombocytopenia was defined as any platelet counts less 150,000 / μ L.

Lastly, history of gastric ulcer or bleeding has been identified as risk factor for stress ulcer¹⁶. Unfortunately, this variable was not available in the data. Such factor could indeed act as an unmeasured confounder and also be a factor in treatment selection since patients with these two conditions are more likely to be on PPIs than H2Bs because of both the former's higher efficacy and the latter's tachyphylaxis. Since, the validity of PSM and IVs depend on satisfying their assumptions and the possibility that this unmeasured confounder affected the results of these two techniques, a third approach was used to assess the sensitivity of the results. Lin et al¹⁸⁴ proposed a method for assessing the sensitivity of regression results by using the existing model that lacks the unmeasured confounder, i.e. history of GI ulceration or bleeding, to estimate the true effect. This is

done by adjusting the observed estimate by the prevalence of the unmeasured confounder in the PPIs group and the H2Bs group and the effect of the unmeasured confounder on CIGIB based on the following equation:

$$HR = \frac{HR^*}{A}$$

$$\text{Where } A = \frac{R_1 P_1 + (1 - P_1)}{R_0 P_0 + (1 - P_0)}$$

HR and HR* are the true hazard ratio and the existing hazard ratio, respectively; R₁ and R₀ are the hazard ratios for the effect of the unmeasured confounder among the PPIs group and the H2Bs group, respectively; and P₁ and P₀ are the prevalence of the unmeasured confounder among the PPIs group and the H2Bs group, respectively. Since there was no clear answer about the effect of history of GI ulceration or bleeding on CIGIB, HRs of 2 and 3 were chosen as most of stress ulcer risk factors estimates were between these two numbers^{23,185}. Regarding the prevalence of this unmeasured confounder among the two treatment groups, it was varied between 0.1 to 1 among the PPIs group and 0.1 to 0.5 among the H2Bs group. Similarly, The 95% confidence interval was constructed using the aforementioned approach¹⁸⁴.

All analyses accounted for the clustering effect of the ICU using robust variance estimator. Data building was done using SAS 9.3 (SAS Inc., Cary, NC, USA) while Stata 11 was used for data analyses (StataCorp LP, College Station, Texas, USA).

Results:

A total of 70,093 patients were included in this study. Approximately, 70% of the patients have received PPIs for three days. Almost 76% of the sample was Caucasian and 54% was male. Around 47% of the patients were admitted to mixed ICU followed by coronary care ICU (18%). The most common stress ulcer risk factors were mechanical ventilation (60%), ICU LOS more than 7 days (38%), renal failure (29%), hypotension (26.7%), coagulopathy (26.4%) and surgery or trauma (23.1%). There were 424 cases of CIGIB that occurred at least after three days of ICU admission. More than 50% of patients have received anticoagulants, antiplatelet or NSAIDs during their ICU stay. Furthermore, approximately half of the patients were admitted from emergency room (Table 5.2). Patients' characteristics using patient-days observations were very similar to the aforementioned results. (Appendix II, Table 2)

Table 5. 2: Characteristics of patients who received either proton pump inhibitors or histamine type-2 receptor blockers for at least three days during their intensive care unit stay.

Characteristics		Univariable Analysis	
		N= Freq.	70,093 Col %
Outcome	Clinically Important Gastrointestinal Bleeding	424	0.6
Exposure	Three Days of Proton Pump Inhibitors Use	49,576	70.7
	Three Days of Histamine-2 Receptors Blockers Use	20,517	29.3
Gender	Male	37,518	53.5
Age	18 To 60	27,153	38.7
	61 To 70	15,932	22.7
	71 To 80	15,446	22.0
	≥ 81	11,562	16.5
Race	Caucasian	53,223	75.9
	African American	7,982	11.4
	Hispanic	2,047	2.9
	Native American	517	0.7
	Asian	864	1.2
	Others	5,460	7.8
ICU Type	Mixed	33,098	47.2
	Cardiovascular-Surgical	6,024	8.6
	Coronary Care	13,046	18.6
	Trauma	320	0.5
	Surgical	5,874	8.4
	Medical	6,804	9.7
	Neuroscience	4,927	7.0
Nutrition	No Feeding	26,313	37.5
	Enteral Nutrition	39,034	55.7
	Parenteral Nutrition	722	1.0
	Both Enteral Nutrition and Parenteral Nutrition	4,024	5.7
Cancer		5,502	7.8
HIV/AIDS		167	0.2
Cirrhosis		817	1.2
Immunosuppression		2,389	3.4
Intubated in the First Day		36,499	52.1
Risk Factors	Coagulopathy	18,528	26.4
	Mechanical Ventilation > 24 Hours	42,354	60.4
	Traumatic Brain Injury	3,326	4.7
	Hepatic Failure	590	0.8
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	2,670	3.8
	Transplantation	156	0.2
	Acute Myocardial Infarction	2,244	3.2
	Sepsis	18,236	26.0
	Neurological Injuries	10,495	15.0
	Surgical And Multiple Trauma	16,184	23.1
	Hypotension	18,749	26.7
	Acute Renal Failure	20,339	29.0

Table 5.2, Continued

Characteristics	Univariable Analysis		
	N=	70,093	
	Freq.	Col %	
	Burns \geq 30% BSA	20	0.0
	ICU LOS > 7 Days	26,607	38.0
Medication	Sucralfate	1,704	2.4
	Antacids	23,984	34.2
	Anticoagulants	39,514	56.4
	Antiplatelets	43,257	61.7
	Thrombolytics	5,632	8.0
	NSAIDs	36,829	52.5
Admission Source	Chest Pain Center	270	0.4
	Direct Admission	6,184	8.8
	Emergency Room	35,352	50.4
	Floor	11,242	16.0
	Operating Room	11,587	16.5
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	5,458	7.8
Year of Admission	2008	11,291	16.1
	2009	15,378	21.9
	2010	17,278	24.7
	2011	17,645	25.2
	2012	8,501	12.1
Physician Specialty	Internal medicine	12,015	17.1
	Pulmonary	12,195	17.4
	Hospitalist	6,547	9.3
	Cardiology	5,072	7.2
	Surgery-general	4,718	6.7
	Critical care medicine	5,184	7.4
	Family practice	4,097	5.8
	Surgery-cardiac	3,412	4.9
	Others	16,853	24.0
Teaching Hospital		21,193	30.2
APACHE Score IV		68	26.9
Platelet Counts		156	83.7

ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; LOS: Length of Stay.

The patients contributed a total of 356,147 patient-days of observations. The average LOS was 9.9 days while the median was 7 days. The incidence rate of CIGIB in this cohort was 1.2 case/1000 patient-days (95%CI: 1.08-1.31). The incidence rate of CIGIB was almost doubled among patients who received PPIs 1.4 case per 1000 patient-days

(95%CI: 1.26-1.55) compared to H2Bs 0.64 case per 1000 patient-days (95%CI: 0.50-0.82).

The bivariable analyses using patient-day data showed that the risk of CIGIB was higher among patients who received PPIs for three days compared to H2Bs for three days (HR:2.19, 95%CI: 1.68-2.86). However, in the bivariable analyses, the two groups were statistically different in demographics, stress ulcer risk factors, ICU type, medications received, admission source and the specialty of the admitting physician. In addition, the APACHE-IV score in the PPIs group was slightly higher (72; SD: 27.6) compared to H2Bs group (68; SD: 27.5) (Appendix II, Table 3 and 4).

The Cox proportional hazard multivariable regression model (Table 5.3) revealed that the risk of CIGIB was almost doubled among the PPIs group compared to the H2Bs group after adjusting for potential confounders (HR:1.97, 95%CI: 1.48-2.63). Other factors that were associated with higher risk of CIGIB included: male gender (HR: 1.27, 95%CI: 1.04-1.54); acute renal failure; (HR: 1.59, 95%CI: 1.28-1.97); the receipt of sucralfate (HR: 3.247, 95%CI: 2.18-4.85); the receipt of antiplatelets (HR: 1.35, 95%CI: 1.01-1.79) and the admission to ICU during 2009 or 2010. On the contrary, having a surgery or trauma was associated with lower risk of CIGIB (HR: 0.46, 95%CI: 0.25-0.84).

Interestingly, none of the other stress ulcer risk factors were positively or negatively associated with CIGIB (Table 5.3)

Table 5. 3: Survival Analysis Using Cox-Proportional Hazard Multivariable Regression Model for the Effect of Three-Day PPIs Use Compared to Three-Day H2Bs Use on the Risk of Clinically Important Gastrointestinal Bleeding among ICU Patients.

Characteristics		HR	95%CI
Exposure	Three-day use of PPIs vs. Three-day use of H2Bs	1.969***	[1.475,2.628]
Gender	Female	Reference	
	Male	1.266*	[1.042,1.539]
Age	18 To 60	Reference	
	61 To 70	1.118	[0.865,1.446]
	71 To 80	1.098	[0.839,1.437]
	≥ 81	1.16	[0.851,1.582]
Race	Caucasian	Reference	
	African American	1.044	[0.770,1.416]
	Hispanic	1.575	[0.798,3.109]
	Native American	0.745	[0.383,1.451]
	Asian	1.052	[0.377,2.932]
	Others	1.077	[0.735,1.577]
ICU Type	Medical	Reference	
	Cardiovascular-Surgical	0.744	[0.0992,5.585]
	Coronary Care	0.858	[0.510,1.444]
	Trauma	1.304	[0.905,1.881]
	Surgical	0.962	[0.576,1.609]
	Mixed	1.263	[0.906,1.761]
	Neuroscience	0.904	[0.501,1.630]
Nutrition	No Feeding	Reference	
	Enteral Nutrition	1.171	[0.931,1.472]
	Parenteral Nutrition	1.028	[0.715,1.478]
Cancer		1.288	[0.929,1.786]
HIV		1.004	[0.237,4.257]
Cirrhosis		1.382	[0.770,2.480]
Immunosuppression		0.852	[0.511,1.422]
Intubated in the First Day		0.804	[0.619,1.045]
Risk Factors	Coagulopathy	1.19	[0.949,1.491]
	Mechanical Ventilation > 24 Hours	0.79	[0.612,1.020]
	Traumatic Brain Injury	0.638	[0.280,1.455]
	Hepatic Failure	1.255	[0.707,2.229]
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	1.098	[0.710,1.698]
	Acute Myocardial Infarction	1.372	[0.743,2.532]
	Sepsis	1.03	[0.810,1.310]
	Neurological Injuries	0.947	[0.676,1.327]
	Surgical And Multiple Trauma	0.459*	[0.251,0.841]
	Hypotension	1.199	[0.939,1.531]
	Acute Renal Failure	1.587***	[1.278,1.970]
Medication	Sucralfate	3.247***	[2.176,4.847]
	Antacids	0.93	[0.755,1.146]
	Anticoagulants	0.84	[0.642,1.100]
	Antiplatelets	1.348*	[1.013,1.793]
	Thrombolytics	0.855	[0.604,1.210]
	NSAIDs	0.972	[0.795,1.188]
Admission Source	Direct Admission	Reference	

Table 5.3, Continued

Characteristics	HR	95%CI
Chest Pain Center	0.862	[0.116,6.410]
Emergency Room	1.311	[0.898,1.913]
Floor	1.258	[0.829,1.909]
Operating Room	2.013	[0.959,4.224]
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	1.074	[0.653,1.767]
Year of Admission	Reference	
2008	Reference	
2009	1.417*	[1.018,1.972]
2010	1.483*	[1.067,2.062]
2011	1.311	[0.941,1.826]
2012	1.202	[0.802,1.799]
Physician Specialty	Reference	
Internal medicine	Reference	
Pulmonary	1.155	[0.852,1.567]
Hospitalist	1.062	[0.717,1.572]
Cardiology	0.774	[0.458,1.307]
Surgery-general	0.719	[0.381,1.357]
Critical care medicine	1.398	[0.945,2.067]
Family practice	1.276	[0.829,1.964]
Surgery-cardiac	0.823	[0.425,1.595]
Others	1.048	[0.756,1.452]
Teaching Hospital	1.155	[0.915,1.458]
Continuous Variables		
APACHE Score IV	1.004	[0.999,1.008]
Platelet Counts	0.998***	[0.997,0.999]
Observations (Patient-day)	356147	

PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 receptor Blockers; ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; LOS: Length of Stay.

In sensitivity analyses, using the survival analysis with discrete time intervals framework, the use of PPIs for at least two days was associated with higher risk of bleeding compared to H2Bs use for two days adjusting for all potential confounders (HR: 2.10, 95%CI:1.65-2.67). Moreover, PPIs were associated with higher risk of CIGIB compared to H2Bs (HR: 1.81, 95%CI: 1.35-2.43) when the analysis was confined to patients who did not discontinue treatment or discontinued treatment for no more than two days before discharge which constituted 84% of the original sample. Furthermore, when patients with the longest ICU length of stay were excluded, the hazard ratio remained in favor of H2Bs over PPIs (HR: 1.90, 95%CI: 1.4-2.6) (Table 5.4). Testing Post-PPIs thrombocytopenia

as a possible mediator for the increased risk of CIGIB revealed no significant difference in the HR between the model that excluded post-treatment thrombocytopenia (HR: 1.97, 95%CI: 1.48-2.63) and the model that included it (HR: 1.95 , 95%CI: 1.44-2.65).

With regards to the propensity score matching model, out of the 70,093 patients, only 23,176 patients were one to one matched resulting in 11,588 patients in each group (Appendix II Figure 3). The C statistic for the propensity score model was 0.73 indicating an acceptable level of predicting the receipt of PPIs compared to the receipt of H2Bs. The model passed the Pearson's χ^2 test indicating good fit as the P-value was insignificant (P-value=0.3781) but failed the Hosmer-Lemeshow test as the P-value was less than 0.0001. The groups were matched on all the included covariates in the propensity score model. The maximum percentage of standardized bias was 2.5 with a mean of 0.8 and a median of 0.7. In addition, no P-value of t-test fell below 0.05 indicating very well matched groups (Appendix II, Table 7). The risk of CIGIB was significantly higher among the PPIs group compared to the H2Bs group (HR: 1.82, 95%CI: 1.19-2.78).

Regarding the IV analysis, the partial F-statistic, adjusted for the clustering effect of the unit, was 53.54 indicating a strong correlation between the IV and the receipt of PPIs for three days. This strong association corresponded to an adjusted OR of 13.44 (95%CI: 10.92-16.54) in the first stage multivariable logistic regression model (Appendix II, Table 5). Pearson's residuals were negatively associated with risk of CIGIB with a HR of 0.96 and a 95%CI (0.928-0.983). Using the 2SRI method, PPIs were associated with higher risk of CIGIB (HR: 2.37, 95%CI: 1.61-3.5) compared to H2Bs. Table 5.4 and figure 5.3

summarize the association between PPIs, H2Bs and CIGIB using the aforementioned methods.

Figure 5.3: The Risk of Clinically Important Gastrointestinal Bleeding between Patients who Received Proton Pump Inhibitors compared to Patients who received Histamine Type-2 Receptor Blockers Using Different Analytical Methods.

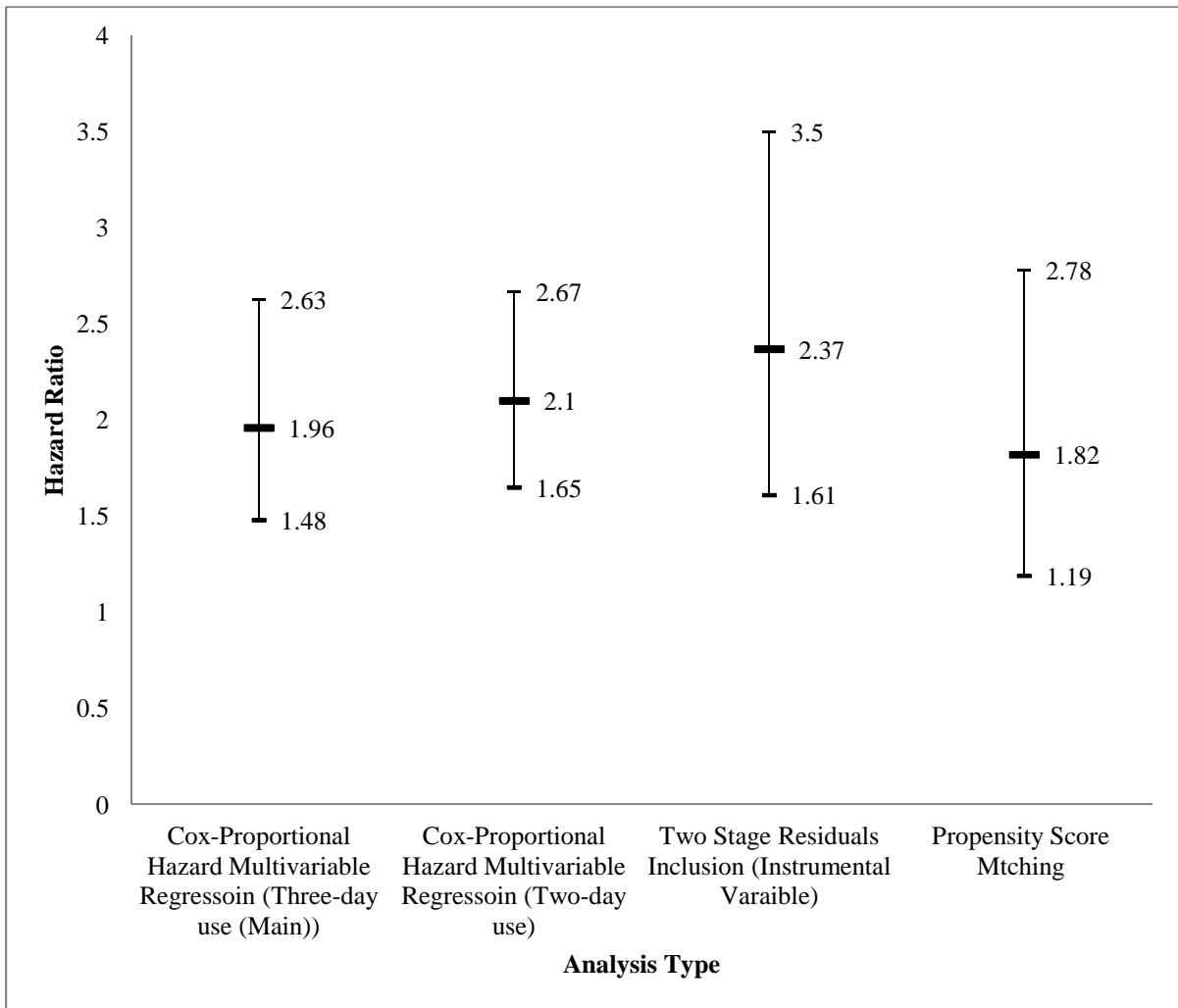


Table 5.4: Summary of analyses for studying the Risk of Clinically Important Gastrointestinal Bleeding between Patients who Received Proton Pump Inhibitors compared to Patients who received Histamine Type-2 Receptor Blockers.

Analysis	Rationale	Results
Two-day use of PPIs compared to Two-day use of H2Bs n=477,350 patient-day	To whether or not shorter duration has the same effect on the risk of CIGIB To compare the results to the a study that compared two-day use of PPIs to two-day use of H2Bs and found PPIs to be associated with higher risk of gastrointestinal bleeding.	(HR: 2.10, 95%CI: 1.65-2.67).
Limiting cohort to patients who did not discontinue treatment or discontinued treatment no more than two days before discharge (84% of the original sample) n=298,308 patient-day	The main model consider any patient who received the medications of interest for three days as exposed regardless whether or not the medications were discounted later. This may lead to estimate overestimation. Therefore, the analysis was confined to patients who continued using medications until discharge or discontinued them no more than two days before discharge.	(HR: 1.81, 95%CI: 1.35-2.43)
Removed long stayers by removing patients in the upper decile of ICU length of stay. n=287,269 patient-day	Observations with extreme length of stay may have skewed the results	(HR: 1.90 , 95%CI: 1.4-2.6)
Confined analysis to patients who stayed less than 6 days in the ICU n=114,274 patient-day	Since we could not capture one of stress ulcer risk factors which was having occult bleeding for 6 days, we confined the analysis on patients who cannot have this risk factor since they stayed for less than 6 days in the ICU.	(HR: 1.5 , 95%CI: 0.94-2.52)
Testing the hypothesis of PPIs-induced thrombocytopenia. n=356,147 patient-day	The unexpected result of higher risk of bleeding among the PPIs group compared to H2Bs could be due to PPIs induced thrombocytopenia which has been reported in few case reports. If this is the case then post treatment thrombocytopenia should be a mediator that if adjusted for will be significantly reduced the observed hazard ratio	Model1: Adjusted for baseline thrombocytopenia , baseline coagulopathy and other covariates (HR: 1.97 , 95%CI: 1.48-2.63) Model2: Adjusted for baseline thrombocytopenia , baseline coagulopathy, post-treatment thrombocytopenia and other covariates (HR: 1.95 , 95%CI: 1.44-2.65)

Table 5.4, Continued

Analysis	Rationale	Results
Propensity Score one to one Matching with no replacement n=23,176 patients	To control for possible observable treatment selection bias	(HR: 1.82, 95%CI: 1.19-2.78)
Two Stage Residual Inclusion n= 356,147 patient-day	To control for possible treatment selection bias	(HR: 2.37, 95%CI: 1.61-3.5)
Two Stage Residual Inclusion while confining the analysis to ICUs that have at least 100 patients during the year. n=233,408 patient-day	To control for possible treatment selection bias and validate the classification of an ICU as a PPI unit or not.	(HR: 2.52, 95%CI: 1.6-4.01)

PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 receptor Blockers; ICU: Intensive Care Unit; HR: Hazard Ratio

Table 5.5: Hazard ratio and 95% Confidence Intervals for the effect of Three-day use of PPIs compared to Three-day use of H2Bs adjusting for an unmeasured dichotomous confounder with a hazard ratio of 3.

P_1	P_0					
	0.0	0.1	0.2	0.3	0.4	0.5
0.0	1.97					
	(1.48,2.63)					
0.1	1.64	1.97				
	(1.23,2.19)	(1.48,2.63)				
0.2	1.41	1.69	1.97			
	(1.06,1.88)	(1.27,2.25)	(1.48,2.63)			
0.3	1.23	1.48	1.72	1.97		
	(0.93,1.64)	(1.11,1.97)	(1.3,2.3)	(1.48,2.63)		
0.4	1.09	1.31	1.53	1.75	1.97	
	(0.82,1.46)	(0.99,1.75)	(1.15,2.05)	(1.32,2.34)	(1.48,2.63)	
0.5	0.99	1.18	1.38	1.58	1.77	1.97
	(0.74,1.32)	(0.89,1.58)	(1.04,1.84)	(1.18,2.1)	(1.33,2.37)	(1.48,2.63)
0.6	0.90	1.07	1.25	1.43	1.61	1.79
	(0.67,1.2)	(0.81,1.43)	(0.94,1.67)	(1.08,1.91)	(1.21,2.15)	(1.35,2.39)
0.7	0.82	0.99	1.15	1.31	1.48	1.64
	(0.62,1.1)	(0.74,1.32)	(0.86,1.53)	(0.99,1.75)	(1.11,1.97)	(1.23,2.19)
0.8	0.76	0.91	1.06	1.21	1.36	1.52
	(0.57,1.01)	(0.68,1.21)	(0.8,1.42)	(0.91,1.62)	(1.02,1.82)	(1.14,2.02)
0.9	0.70	0.84	0.99	1.13	1.27	1.41
	(0.53,0.94)	(0.63,1.13)	(0.74,1.32)	(0.85,1.5)	(0.95,1.69)	(1.06,1.88)
1.0	0.66	0.79	0.92	1.05	1.18	1.31
	(0.53,0.94)	(0.59,1.05)	(0.69,1.23)	(0.79,1.4)	(0.89,1.58)	(0.99,1.75)

P_0 and P_1 are the prevalence of the unmeasured confounder in the H2Bs group and the PPIs group, respectively; PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 Receptors Blockers
 Red color: higher risk of CIGIB with PPIs; Green color: No difference between PPIs and H2Bs; Blue: lower risk of CIGIB with PPIs.

Lastly, the regression results sensitivity assessments using Lin’s proposed approach suggested that PPIs may be associated with a lower risk of gastrointestinal bleeding (HR: 0.7, 95%CI: 0.52-0.94) compared to H2Bs if history of GI ulceration or bleeding was associated with higher risk of CIGIB with a HR of 3 and only if the prevalence of this unmeasured confounder was 90% or 100% in the PPIs group and no patients in the H2Bs group has this unmeasured confounder (Table 5.5).

Discussion:

In this retrospective cohort study that included 70,093 patients who have received either PPIs or H2Bs for at least three days, the incidence rate of CIGIB was 1.2 cases/1000 person-day which is interpreted as 1.2 CIGIB per 1000 patients per day or as 1.2 CIGIB cases every 1000 day. The incidence rate was more than double among the PPIs group (1.4 cases/1000 person-day) compared to the H2Bs group (0.64 cases/1000 person-day). However, despite the latter result, one can conclude that in current practice stress ulcer related CIGIB is a rare outcome. Such result is multifactorial and includes not only the use of stress ulcer prophylaxis but also other improvements in current practice such as adequate hydration and blood reperfusion which reduce ischemic damage to gastric tissues, better sepsis management, early enteral nutrition and better ICU monitoring systems^{16,186-188}.

Because the inclusion criteria required both three days of exposure and a 24 hour lag between the exposure and CIGIB the minimum LOS was 4 days therefore, this cohort consisted mainly of long stayers which made both average and median LOS greater than what is reported in the literature⁷⁸.

In this cohort, all well-known stress ulcer risk factors were not associated with CIGIB except acute renal failure (HR=1.59, 95%CI: 1.28-1.97) and having surgery or trauma (HR: 0.46, 95%CI: 0.25-0.84). The lack of association between other risk factors and CIGIB is most likely because patients in this cohort have received one of the strongest therapeutic classes used as SUP which, consequently, reduced the likelihood of CIGIB. Although, acute renal failure has been previously identified as one of stress ulcer risk factor¹⁰, the observed association between having surgery or trauma, acute renal failure,

male gender and CIGIB should be interpreted with caution since the study was not designed to identify risk factors of CIGIB or the magnitude of their effects on CIGIB but only to adjust the analysis by them. This is important as other covariates pertaining to answering these questions may not have been included in this analysis. For instance, the type of interventions, treatments or care type of patients who had surgery or trauma may be different than patients who did not which may have made them less prone to CIGIB.

Our results suggested that the receipt of PPIs for at least three days was associated with higher risk of CIGIB (HR: 1.97, 95%CI: 1.48-2.63) compared to the receipt of H2Bs for the same period. The result contradicts the findings of the five meta-analyses that compared PPIs use to H2Bs during the last decade. While four of these meta-analyses^{71,72,74,75} reported 60% to 70% reduction in the odds or risk of gastrointestinal bleeding, one meta-analysis did not find any difference between the two groups⁷³. In our study, two days of exposure yielded similar results to three day exposure (HR: 2.10, 95%CI: 1.65-2.67). In February 2014, MacLaren et al found that mechanically ventilated patients who were on PPIs for two days had higher odds of GI bleeding than patients on H2Bs (OR: 2.24, 95%CI: 1.81-2.76)⁷⁸. It is known that in case of a rare outcome, such as CIGIB, both OR and HR are very similar to each other¹⁸⁹. The results of the sensitivity analyses in table 5.4 indicated very robust results under different scenarios pertaining to treatment continuation or when patients in the upper decile of ICU LOS were excluded. Furthermore, even when the analysis was confined to patients who stayed in the ICU for less than 6 days the direction of the HR stayed the same but with a wider confidence interval than the original analysis indicating the possibility of insufficient power.

The results seen in our study and MacLaren's et al. have one of two explanations: first, it could be true that PPIs were associated with higher risk of bleeding. MacLaren et al suggested that "both drug classes inhibit acid production, but Histamin-2 receptor antagonists also limit reperfusion injury in animal models, possibly reducing oxidative stress after mucosal injury". Additional studies in animals and humans on the mechanisms of injury are needed to support this conclusion. Another possible explanation was PPIs-induced thrombocytopenia. It is possible that because of the fear of H2Bs-induced thrombocytopenia, physicians preferred to prescribe PPIs to their patients, which caused thrombocytopenia and led to GIB. Thus, in essence, thrombocytopenia could be considered as the mechanism between PPIs and CIGIB. However, the adjustment for post-treatment thrombocytopenia did not have a significant impact on the HR (Table 5.4) indicating that it was not a mediator in the association between PPIs and CIGIB.

The second possible explanation for the higher risk of CIGIB seen with PPIs is confounding by indication also known as treatment selection bias resulted from non-random treatment selection. Two different approaches were used to account for confounding by indication: PSM and IV technique. Both techniques yielded similar direction to the estimate from the main analysis indicating that PPIs were associated with higher risk of CIGIB than H2Bs (Table 5.4) in a full sample and in a propensity-score matched sample. The overlapping confidence intervals in figure 5.3 indicate that the magnitude of the HR did not differ by changing the method of analysis, keeping in mind that the extent of generalizability differed across the methods of analysis. The validity of PSM and IV methods is based on fulfilling their assumptions. For instance, the

assumption of the PSM is that the propensity score model contains all variables that are confounders or variable associated with the outcome only¹⁷². With regards to IV, in addition to having a strong association between the IV and the endogenous variable i.e. the exposure to PPIs in this case, the IV should not be associated with any variable in the error term i.e. the IV should not be associated with any variable that can be confounder between the exposure and CIGIB. In our study, history of GI ulceration or bleeding was not accounted for due to unavailability of the variable in the data. This variable may violate the assumptions of both PSM and IV leading to the results seen in our study. For instance, one can assume that history of ulceration or bleeding is associated more with the receipt of PPIs compared to the receipt of H2Bs. PPIs are known to elevate gastric pH to six which is required for clot optimization and stabilization in case of gastric bleeding^{190,191}. In addition, the tachyphylaxis seen with H2Bs makes PPIs the preferred agents in case of history of GI ulceration or bleeding. Both reasons make history of GI ulceration or bleeding associated with PPIs receipt more than H2Bs. In this case, the PSM model still missed an important variable which may explain why the model did not pass the Hosmer-Lemeshow goodness of fit test. Thus, it is possible that the inability to account for this variable in the PSM model drove the PSM results (HR=1.82; 95%CI: 1.19-2.78) in the same direction as the HR of Cox regression (HR: 1.97.37, 95%CI: 1.48-2.63).

Similarly, in the IV analysis, if there was an association between being in an ICU that prescribed PPIs to at least 90% of the patients and history of GI ulceration or bleeding then the treatment effect estimated from the IV analysis (HR: 2.37, 95%CI: 1.61-3.5) will

be more biased than that estimated from the regular Cox-proportional hazard model¹⁹²(HR: 1.97.37, 95%CI: 1.48-2.63). Lin's approach provided a way to assess the robustness of the results in case of assumptions violation by evaluating the impact of the unmeasured confounder(s) on the HR directly. According to the results in table 5.5, PPIs were associated with lower risk of CIGIB compared to H2Bs only if 90% or more of the PPIs group had history of GI ulceration or bleeding, no patients in the H2Bs group had these two conditions and the HR associated with history GI ulceration or bleeding was 3. In addition, if the HR associated with history of GI ulceration or bleeding was 2 then PPIs would be as same as or worse than H2Bs in terms of CIGIB risk (Appendix II, Table 8).

Our study has its strengths and limitations. First, the use of multiple statistical approaches provided a comprehensive picture regarding the comparative effectiveness between the two the therapeutic classes. Second, the eICU data provided information that increased the precision of identifying variables needed in the study such as vital signs and transfusion episodes for identifying clinically important episodes of bleeding; and the availability of diagnosis strings and their linkage to ICD-9 codes which increased the precision of identifying and controlling for stress ulcer risk factors in the analysis. Third, the result of the study was consistent with MacLaren's study indicating the importance of exploring this question in different databases in order to determine whether or not the observed increase in the risk of CIGIB with PPIs is true. Fourth, our study proposed and tested whether or not PPIs-induced thrombocytopenia was a possible explanation for the increased risk seen with PPIs.

On the other hand, differences in institutional practices and clinician's characteristics were unavailable at the time of the analysis. Therefore, the degree by which such factors impact treatment choice and outcome occurrence is still an area for future research. In addition, despite the availability of vital signs and transfusion as well as the availability of diagnosis strings which increased the specificity of CIGIB definition, endoscopy information were unavailable to further exclude bleedings unrelated to stress ulcer which may have overestimated the already rare incidence of CIGIB. Lastly, Lin's approach depends on the assumption of independence between the unmeasured confounder and the observed confounders conditioning on treatment. Hernan et al¹⁹³, and latter VanderWeele¹⁹⁴, elaborated that this assumption is always violated. Therefore, the degree by which this violation may lead to an overestimation or underestimation of the true estimate requires cautious interpretation of the results. Nevertheless, as VanderWeele stated, Lin's approach is "perhaps best viewed as set of simplifying assumptions to obtain algebraic adjustment formulas that provide *rough guidelines* as to how substantial the influence of a confounding factor would need to be in order to eliminate or reverse the effect observed without controlling for the unmeasured confounding variable"¹⁹⁴.

In conclusion, in current practice, CIGIB is a rare outcome among patients who received SUP. Unlike previous literature, proton pump inhibitors were associated with higher risk of CIGIB compared to H2Bs. The results of PSM and IV techniques were in line with the main analysis. However, if this association is true then it is not because of post-treatment thrombocytopenia. Other possible explanation would be the presence of residual confounding that couldn't be solved by the PSM and IV techniques. However,

even in the presence of residual confounding, sensitivity analysis indicated that PPIs were superior over H2Bs only under one specific scenario. Despite the fact that we believe residual confounding is the main explanation for the observed results, future studies should not only focus on replicating the findings in different cohorts, including more relevant variables and searching for a better IV but also on exploring the possibility that PPIs may really be associated with higher risk of CIGIB compared to H2Bs. Therefore, more observational studies in different patient cohorts are needed to strengthen the signal seen with PPIs use. In addition, well-designed and well-executed randomized controlled triple blind clinical trials with no funding or reporting bias are still needed to answer this question.

Chapter VI. Comparative Safety of Proton Pump Inhibitors vs. Histamine type-2 receptors blockers in Nosocomial Pneumonia and Clostridium Difficile-Associated Diseases: A Population-Based Study

Introduction:

Stress ulcer prophylaxis has been used in intensive care units (ICUs) as a standard practice for the last thirty years. However, the use of proton pump inhibitors (PPIs) and histamine type-2 receptor blockers (H2Bs) as prophylactic therapies raised a concern that these drugs may lead to the development of nosocomial pneumonia (NP) as well as *clostridium difficile*-associated diseases (CDAD). These diseases have been linked to ICU mortality and increased lengths of stay (LOS)^{95-98,113,114,116,195}. Acid suppressants have been shown to raise the pH above four within the first 24 hours^{62,64,81}. This increase in pH allows pathogen colonization to take place in the stomach⁸². Proton pump inhibitors, in particular, have been shown to promote bacterial colonization through additional mechanisms⁸³⁻⁹². For instance, the H⁺/K⁺ pump, PPIs main action site, also was found in the laryngoesophageal tract as well as the lungs⁸³⁻⁸⁵. Therefore, at least in theory, the inhibition of these pumps also augments bacterial colonization in these areas. In addition, in vitro studies demonstrated that PPIs reduce humoral immunity through reversible inhibition of Natural Killer (NK) cells^{86,87}. Furthermore, PPIs also have been shown to reduce gastric emptying and gastric wall tension^{79,88-92} leading to an increase in stomach accommodation accompanied by relaxation of the lower esophageal sphincter^{51,93,94}. Consequently, PPIs not only enhance bacterial colonization in the stomach but also enhance tracheo-bronchial bacterial colonization and micro-aspiration of gastric

contents into the respiratory tract which can lead to the development of NP. Therefore, one should expect higher incidence of NP with PPIs when they are compared to H2Bs.

However, none of the RCTs that compared PPIs to H2Bs reported an increased risk of NP with any of the two groups (Figure 6.1). In addition, the five meta-analyses that were done using these RCTs also did not find any additional risk between the two groups. On average, the cumulative incidence of NP for each group was centered on 10% (Table 6.1).

Figure 6.1: Forrest Plot of Studies Comparing the Risk of Nosocomial Pneumonia between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in the Intensive Care Units

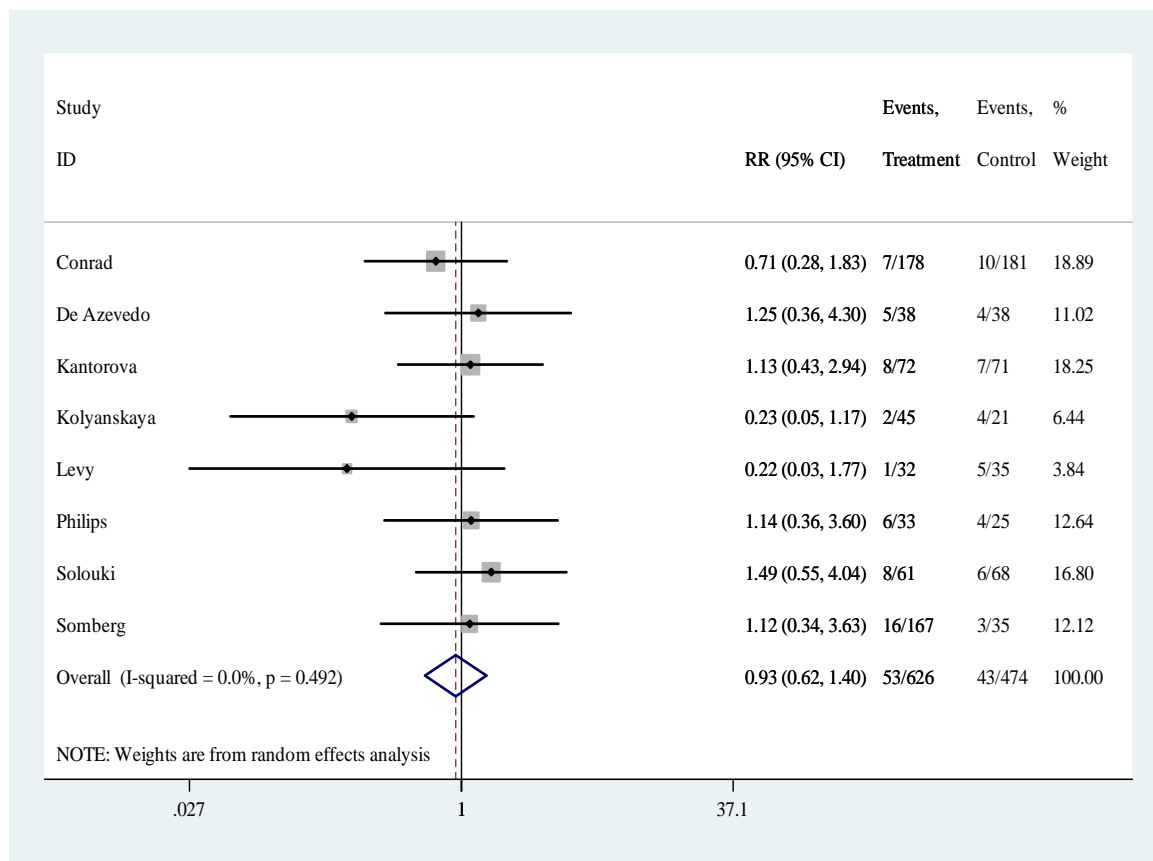


Table 6.1: Summary of Meta-Analyses that Compared the Risk of Nosocomial Pneumonia between Proton Pump Inhibitors and Histamine-2 Receptors Blockers in the Intensive Care Units

Reference	Number of nosocomial pneumonia cases among the proton pump inhibitors (PPIs) group (%)	Number of nosocomial pneumonia cases among Histamine-2 receptor blockers (H2Bs) group (%)	Point of estimate and 95% confidence interval of the risk of nosocomial pneumonia comparing PPIs to H2Bs
Pongprasobchai 2009 (n=569)	29/282 (10.3%)	29/287 (10.1%)	OR: 1.02 (95%CI: 0.59 to 1.75)
Zhou 2010 (n=771)	45/449 (10.0%)	32/322 (9.9%)	OR: 1.03 (95%CI: 0.63 to 1.70)
Lin PC 2010 (n=905)	56/520 (10.8%)	40/385 (10.4%)	RD: 0 (95%CI: -0.04 to +0.05)
Barkun AN 2012 (n=1,017)	63/610 (10.3%)	42/407 (10.3%)	OR: 1.05 (95%CI: 0.69 to 1.62)
Al-Hazzani 2013 (n=1,100)	66/626 (10.5%)	50/474 (10.6%)	RR: 1.06 (95%CI 0.73 to 1.52)

In contrast, very few observational studies compared the risk of NP among PPIs users to H2Bs users in ICUs. These studies reported higher risk of NP with PPIs by odds ratios (OR) or hazard ratios (HR) between 1.2 and 2.7^{78,104,196}. Therefore, these conflicting results between the aforementioned studies raise the question whether or not the risk of NP differs between the two most widely used classes of stress ulcer prophylaxis in intensive care. It is unknown if the lack of difference between PPIs and H2Bs in the meta-analyses was a real equivalence, a power issue or a methodological flaw due to inadequate drug exposure. In addition, the few observational studies that showed higher risk of NP with PPIs compared to H2Bs necessitate exploring this question in a different

cohort of patients to determine how robust is the result and who are the most vulnerable subgroups.

Clostridium difficile exists in two forms: vegetative cells that are acid-sensitive and acid-resistant spores¹¹¹. As previously discussed, the elevation of gastric pH promotes bacterial overgrowth and colonization inside the stomach through both forms.

Clostridium difficile bacteria produce toxin A and toxin B that cause watery diarrhea and other CDAD¹¹¹. These two toxins are discriminating markers for *C. difficile* infection that are used for diagnosis.

Studies that compared the risk of CDAD between PPIs and H2Bs are very scarce in intensive care environment. In 2014, MacLaren and colleagues reported a slight increase in the risk of CDAD among patients on PPIs compared to H2Bs (HR=1.29; 95%CI: 1.04-1.64) in a retrospective study of 35,312 ICU patients. However, the lack of RCTs that looked at the association and the limited generalizability of the results of this one observational study necessitate studying the relationship between PPIs, H2Bs and CDAD in ICUs. Therefore, the objective of this study was to compare the risk of NP and CDAD among patients who received PPIs compared to H2Bs in ICU settings.

Methods:

Data:

The data for this study came from the eICU Research Institute which gathered information from more than 40 health systems encompassing approximately 300 ICUs across 34 states from 2008 to June of 2012. In each participating ICU, information

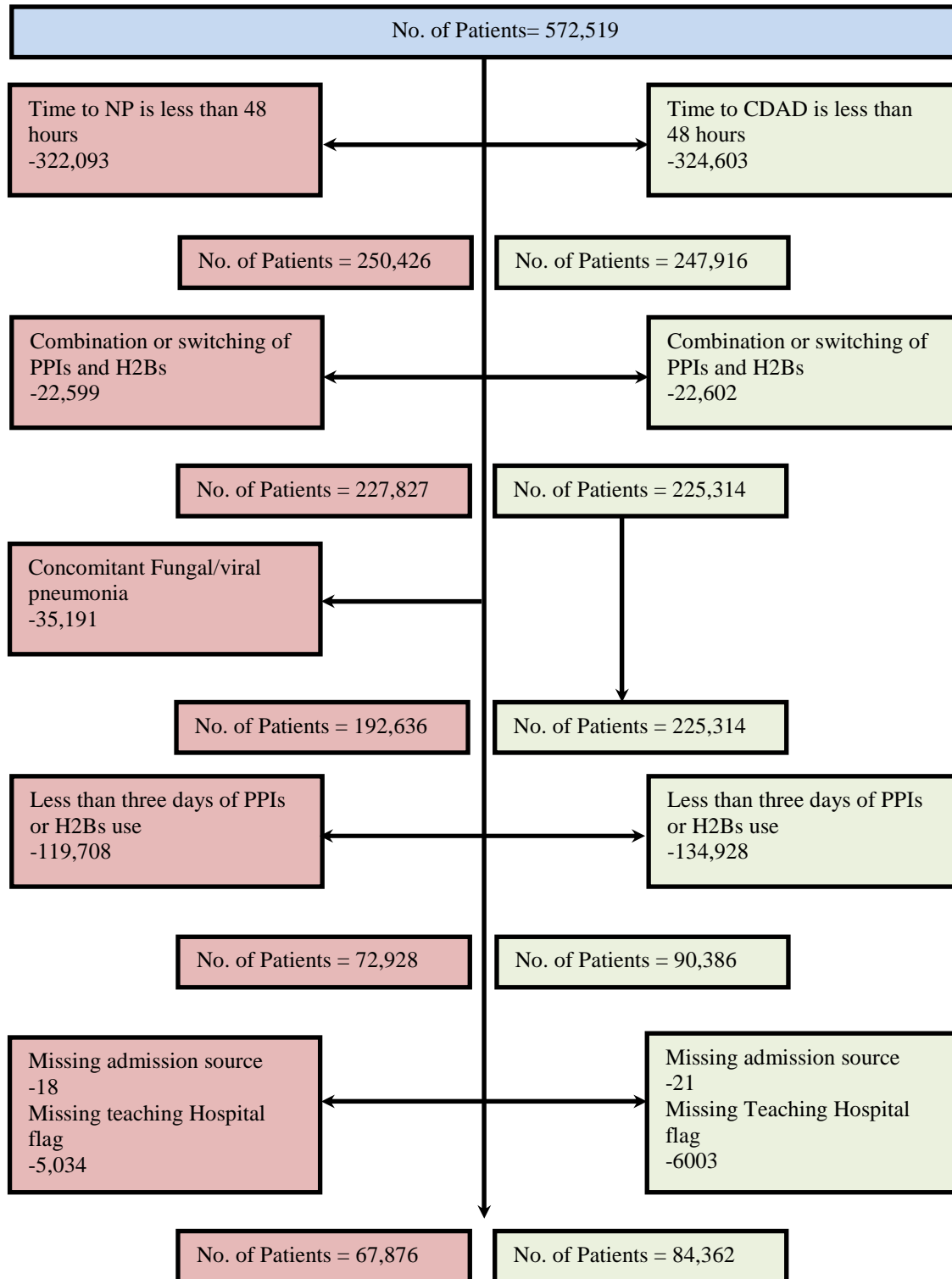
pertaining to patients' admission and discharge, disease diagnoses, therapeutic management, laboratory results, and demographics were electronically documented with time of occurrence in minutes since ICU admission. In addition, through an automated interface that gathers information every 5-minutes interval, patient's vital signs are collected and incorporated into the eRI database repository. Selection of disease diagnosis was done through a menu of discrete diagnoses strings. These diagnosis strings were eventually linked to the International Classification of Diseases 9th ed. (ICD-9) codes in the eRI repository. Thus, both diagnosis strings and ICD-9 codes were kept in the eICU repository which allowed ICD-9 codes validation. In addition, patients' health status was measured using the acute physiology and chronic health evaluation score version IV (APACHE-IV score). The data has been certified as completely de-identified by Privacert, Inc. (Pittsburgh, PA). Finally, the study was exempted from Institutional Review Board review (HP-00055985) at University of Maryland.

Inclusion and Exclusion Criteria:

The study included any patient who was admitted to ICUs between Jan 2008 and June 2012. Patients who were under 18 years old, not discharged from the hospital during study period (dead or alive), had invalid admission and discharge dates (e.g. admission date is after discharge date), or had missing demographics, diagnoses, or APACHE-IV score were excluded from the study cohort. In addition, to ensure complete ascertainment of medication information the cohort was restricted to ICUs that fully implemented the medication interface in their systems. In addition, patients were excluded if any of the followings existed: ICU length of stay less than 48 hours, an outcome (NP or CDAD) within the first 48 hours of admission, receipt of PPIs and H2Bs concomitantly or

consecutively, the receipt of PPIs or H2Bs for less than three days, and missing source of admission or teaching hospital status. In addition, for the cohort used in studying NP, patients with concomitant viral or fungal pneumonia were excluded. Figure 6.2 illustrates the selection criteria for both cohorts.

Figure 6. 2: Selection criteria for nosocomial pneumonia cohort and clostridium difficile- associated disease cohort.



Measures:

Dependent variables:

Bacterial nosocomial pneumonia was defined using both ICD-9 codes (481.**-486.** and 507) and diagnoses strings. The ICD-9 codes were based on the causative microorganism; therefore, the codes were not specific enough to exclude community-acquired pneumonia (CAP). Consequently, in addition to excluding any cases of pneumonia that occurred during the first two days of admission, diagnosis strings were used to further exclude any case of CAP. Appendix III Table 1 contains a full list of diagnoses strings that were included or excluded from the definition.

The discriminating test for CDAD is finding toxins A or toxin B in a stool sample. The two toxins are responsible for CDAD manifestations such as diarrhea and pseudomembranous enterocolitis. In addition, both toxin A and B are very specific to CDAD. An advantage of using the eICU Research Institute database is the documentation of laboratory tests and their results to the minute level during the ICU stay. Therefore, a case of CDAD was identified using both ICD-9 codes and lab results. A case of CDAD was defined as any patient who 1) has laboratory results indicating a positive toxin A, toxin B or both OR 2) received oral Vancomycin

Independent variables:

The main independent variable was the receipt of PPIs for three days versus the receipt of H2Bs for three days. The name, time of administration and the hierarchical ingredient code list (HICL) sequence number¹⁴² for these therapeutic classes were recorded in the medication data file. Both the HICL sequence number and medications

name were used to pull out all entries of PPIs ,omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole and pantoprazole, or H2Bs ,cimetidine, ranitidine, famotidine and nizatidine, during an ICU stay. Appendix I Table 2 shows both the HICL sequence numbers as well as medications' brand and generic names used in identifying the two classes and other medications included in the study. Lastly, although the onset of action of many PPIs and H2Bs is within 1 to 3 hours, the peak effect of H2Bs and PPIs requires 12 to 24 hours in order to take place, respectively. Therefore, a 24-hours lag period between the exposure and the occurrence of the outcome was needed to establish temporality.

The following covariates were included: demographics (age, gender and race); clinical variables (mechanical ventilation > 24 hrs. , head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week, cancer, human immunodeficiency virus, cirrhosis, the receipt of enteral nutrition and intubation in the first day); admission source, physician specialty and type of hospital (teaching vs. non-teaching). In addition, health severity was measured by the APACHE IV software sublicensed from Cerner, Inc., (Kansas City, MO). Lastly, medications that affect the occurrence of NP or CDAD including sucralfate, antacids, NSAIDs, aminoglycosides, cephalosporins, Flouroquinolones, Lincosamide, linezolid, macrolides, metronidazole, other b-lactams, penicillins, tetracyclines, vancomycin and miscellaneous antibiotics (tigacycline , daptomycin, nitrofurantoin, colistimethate, chloramphenicol and telavancin) were flagged. Most of aforementioned

antibiotics are either have been used in treating NP or CDAD or have been implicated in causing CDAD.

Statistical Analysis:

With the exception to the outcomes and covariates included, the approached used in analyzing the data was identical to the approach used in chapter V. The data was analyzed using Cox proportional hazard multivariable regression for survival data with time as discrete intervals, propensity score matching and instrumental variable techniques.

Results:

The cohort used in studying the effect of PPIs and H2Bs on NP consisted of 67,876 patients who contributed 285,033 patient-day observations. The incidence rate (IR) of NP in the cohort was 8.4 cases/1000 patient-days. While the IR among H2Bs users was 10.6 cases/1000 patient-days, the IR among PPIs users was 7.6 cases/1000 patient-days. Overall, the crude incidence of NP was greater among the H2Bs group (4.2%) compared to PPIs group (3.3%).

The CDAD cohort consisted of 84,362 patients who contributed 389,782 patient-day observations. Unlike NP, the IR of CDAD was much lower (1.4 cases/1000 patient-days). In addition, contrary to NP, the IR among the PPIs group was greater than IR among the H2Bs group (1.5 cases/ 1000 patient-days vs. 1.12 cases/1000 patient-days, respectively). In general, the incidence of CDAD was greater among the PPIs group (0.7%) compared to H2Bs group (0.5%).

The NP cohort was approximately 76% Caucasians and 53% males. Almost half of the patients were admitted to mixed ICU followed by coronary care ICU (18.6%). Acute respiratory distress syndrome was diagnosed in almost one third of patients while COPD was reported in 12% of patients. Almost, 50% of patients had their bed head elevated 30 degrees to prevent aspiration pneumonia. Cephalosporins, penicillins and vancomycin were the most frequent antibiotics used in this cohort. Around half of patients were admitted to the ICU from emergency room. Using the patient-day observations, patient characteristics were alike to the abovementioned results (Appendix III Table 2). In addition, the demographic characteristics of CDAD cohort were very similar to NP cohort (Table 6.2 and Appendix III Table 3).

The bivariable analysis of the association between NP and the two therapeutic classes showed that the risk of NP was lower among the PPIs group compared to the H2Bs group with HR of 0.73 and 95% CI between 0.67 and 0.79. In contrary, the risk of CDAD was greater among the PPIs group (HR: 1.36; 95%CI: 1.11-1.7) compared to H2Bs groups. However, in both cohorts PPIs and H2Bs groups were statistically different in age, gender and race, ICU type, nutrition status, diseases, stress ulcer prophylaxis risk factors, medications use, ICU admission source, physician specialty and the teaching status of the hospital. In both cohorts, the APACHE-IV score was statistically higher among the PPIs group compared to the H2Bs indicating higher severity at ICU admission among the PPIs group (Appendix III, Table 3, 4, 10, 11).

Table 6.2: Characteristics of patients who received either proton pump inhibitors or histamine type-2 receptor blockers for at least three days during their intensive care unit stay by each outcome

Characteristics		NP		CDAD	
		N=	67,876	N=	84,362
		Freq.	Col %	Freq.	Col %
Outcome	Nosocomial Pneumonia	2,393	3.5	---	---
	Clostridium-difficile associated diseases	---	---	550	0.7
Exposure	Three Days of Proton Pump Inhibitors Use	49,093	72.3	61,254	72.6
	Three Days of Histamine-2 Receptors Blockers Use	18,783	27.7	23,108	27.4
Gender	Male	36,164	53.3	45,087	53.4
Age	18 To 60	26,468	39	32,599	38.6
	61 To 70	15,414	22.7	18,923	22.4
	71 To 80	14,846	21.9	18,448	21.9
	≥ 81	11,148	16.4	14,392	17.1
Race	Caucasian	51,669	76.1	64,618	76.6
	African American	7,706	11.4	9,395	11.1
	Hispanic	1,939	2.9	2,364	2.8
	Native American	467	0.7	605	0.7
	Asian	849	1.3	1,023	1.2
	Others	5,246	7.7	6,357	7.5
ICU Type	Mixed	30,606	45.1	39,506	46.8
	Cardiovascular-Surgical	6,166	9.1	7,052	8.4
	Coronary Care	12,597	18.6	16,089	19.1
	Trauma	406	0.6	419	0.5
	Surgical	6,166	9.1	6,735	8
	Medical	6,673	9.8	8,919	10.6
	Neuroscience	5,262	7.8	5,642	6.7
Nutrition	No Feeding	28,106	41.4	33,430	39.6
	Enteral Nutrition	35,398	52.2	45,636	54.1
	Parenteral Nutrition	747	1.1	843	1
	Both Enteral Nutrition and Parenteral Nutrition	3,625	5.3	4,453	5.3
Any Gastrointestinal Diseases		1855	2.7	2,329	2.8
Cancer		4,799	7.1	---	---
HIV		88	0.1	---	---
Cirrhosis		1,026	1.5	---	---
Asthma		1648	2.4	---	---
COPD		8,061	11.9	---	---
ARDS		22488	33.1	---	---
Heart Failure		8,488	12.5	---	---
Head of Bed is 30 Degrees Up		32781	48.3	---	---
Immunosuppression		2,100	3.1	2,702	3.2
Intubated in the First Day		29,740	43.8	38,607	45.8
Risk Factors	Coagulopathy	16,289	24	20,044	23.8
	Mechanical Ventilation > 24 Hours	33973	50.1	44,444	52.7
	Traumatic Brain Injury	3,225	4.8	3,426	4.1
	Hepatic Failure	601	0.9	737	0.9
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	2,409	3.5	3,584	4.2

Table 6.2, Continued

Characteristics	NP		CDAD	
	N=		N=	
	Freq.	Col %	Freq.	Col %
Transplantation	146	0.2	156	0.2
Acute Myocardial Infarction	2,190	3.2	2,371	2.8
Sepsis	12387	18.2	18,856	22.4
Neurological Injuries	9,622	14.2	10,874	12.9
Surgical And Multiple Trauma	16103	23.7	16,706	19.8
Hypotension	14,042	20.7	19,846	23.5
Acute Renal Failure	16423	24.2	21,980	26.1
Burns \geq 30% BSA	21	0	25	0
ICU LOS > 7 Days	19992	29.5	27,837	33
Medication				
Sucralfate	1,686	2.5	1,881	2.2
Antacids	19633	28.9	23,519	27.9
Anticoagulants	30,935	45.6	39,461	46.8
Antiplatelets	35920	52.9	45,182	53.6
Thrombolytics	3,853	5.7	4,439	5.3
NSAIDs	30654	45.2	38,203	45.3
Aminoglycosides	1,937	2.9	2,685	3.2
Cephalosporins	20476	30.2	25,942	30.8
Flouroquinolones	14,536	21.4	21,643	25.7
Lincosamide	2225	3.3	3,072	3.6
Linezolid	1,499	2.2	2,535	3
Macrolides	2957	4.4	6,277	7.4
Metronidazole	5,883	8.7	6,808	8.1
Other B-lactams	5211	7.7	7,385	8.8
Penicillins	24,140	35.6	34,359	40.7
Tetracyclines	636	0.9	889	1.1
Vancomycin	19,114	28.2	28,149	33.4
Antibiotics, Others	1094	1.6	1,300	1.5
Admission Source				
Direct Admission	6,106	9	7,429	8.8
Chest Pain Center	278	0.4	---	---
Emergency Room	34,266	50.5	44,385	52.6
Floor	10,390	15.3	13,908	16.5
Operating Room	11,702	17.2	12,048	14.3
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit and chest pain center if not listed)	5,134	7.6	6,592	7.8
Year of Admission				
2008	11,098	16.4	13,588	16.1
2009	14,623	21.5	18,317	21.7
2010	16,690	24.6	20,683	24.5
2011	17,187	25.3	21,505	25.5
2012	8,278	12.2	10,269	12.2
Physician Specialty				
Internal medicine	11,980	17.6	15,345	18.2
Pulmonary	9,836	14.5	14,677	17.4
Hospitalist	6,575	9.7	8,534	10.1
Cardiology	5,506	8.1	6,061	7.2
Surgery-general	4,991	7.4	5,167	6.1
Critical care medicine (CCM)	4,030	5.9	5,937	7
Family practice	4,226	6.2	5,435	6.4

Table 6.2, Continued

Characteristics	NP		CDAD	
	N=	67,876	N=	84,362
	Freq.	Col %	Freq.	Col %
Surgery-cardiac	3,510	5.2	3,579	4.2
Others	17,222	25.4	19,627	23.3
Teaching Hospital	19,658	29	24,900	29.5
APACHE Score IV (Mean, SD)	64.95	26.53	66.31	26.6

NP: Nosocomial Pneumonia; CDAD: Clostridium-difficile associated diseases; ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; LOS: Length of Stay.

The Cox proportional hazard multivariable model showed that the adjusted hazard of NP was lower among the PPIs group compared to the H2Bs group (HR: 0.87, 95%CI: 0.78-0.97). Nosocomial pneumonia was positively associated with males (HR: 1.14, 95%CI: 1.1-1.24); being in a mixed ICUs compared to medical ICU (HR: 1.4, 95%CI: 1.11-1.7); the receipt of enteral nutrition (HR: 1.47, 95%CI: 1.27-1.7) or both enteral and parenteral nutrition (HR: 1.47, 95%CI: 1.22-1.8). In addition all respiratory related diseases including asthma, COPD or ARDS were also positively associated with NP. Furthermore, most of the antibiotics were associated with higher hazard of NP except metronidazole (Table, 6.3). Similarly, patients admitted to teaching hospital were at higher risk of NP (HR: 1.68, 95%CI: 1.42-1.99) compared to patients admitted to non-teaching hospital

Table 6.3: Discrete Time Survival Analysis Using Cox-Proportional Hazard Multivariable Regression Model for the Effect of Three-Day PPIs Use Compared to Three-Day H2Bs Use on the Risk of Nosocomial Pneumonia or Clostridium difficile-associated diseases among ICU Patients.

Characteristics		NP		CDAD	
		HR	95%CI	HR	95%CI
Exposure	Three-day use of PPIs vs. Three-day use of H2Bs	0.870*	[0.777,0.974]	1.116	[0.886,1.405]
Gender	Female	Reference		Reference	
	Male	1.143***	[1.057,1.236]	0.898	[0.751,1.074]
Age	18 To 60	Reference		Reference	
	61 To 70	0.938	[0.837,1.052]	1.010	[0.798,1.279]
	71 To 80	0.936	[0.833,1.052]	1.145	[0.925,1.418]
	≥ 81	0.944	[0.818,1.090]	1.088	[0.840,1.409]
Race	Caucasian	Reference		Reference	
	African American	0.873	[0.755,1.011]	1.325*	[1.031,1.703]
	Hispanic	0.824	[0.538,1.261]	2.064*	[1.117,3.814]
	Native American	0.717*	[0.542,0.948]	1.615*	[1.072,2.432]
	Asian	0.99	[0.705,1.390]	0.861	[0.321,2.313]
	Others	0.857	[0.702,1.046]	1.927***	[1.407,2.637]
ICU Type	Medical	Reference		Reference	
	Cardiovascular-Surgical	1.119	[0.714,1.753]	1.117	[0.364,3.423]
	Coronary Care	0.857	[0.599,1.225]	1.172	[0.800,1.715]
	Trauma	1.328	[0.991,1.779]	0.798	[0.546,1.166]
	Surgical	0.731	[0.531,1.007]	0.599*	[0.384,0.933]
	Mixed	1.399**	[1.105,1.770]	0.823	[0.610,1.111]
	Neuroscience	1.099	[0.771,1.566]	0.783	[0.477,1.287]
Nutrition	No Feeding	Reference		Reference	
	Enteral Nutrition	1.466***	[1.270,1.692]	1.439**	[1.113,1.859]
	Parenteral Nutrition	1.474***	[1.218,1.783]	1.165	[0.845,1.605]
Any Gastrointestinal Diseases		1.118	[0.919,1.360]	1.107	[0.715,1.716]
Cancer		1.056	[0.904,1.234]	---	
HIV		0.818	[0.321,2.085]	---	
Cirrhosis		1.036	[0.759,1.413]	---	
Asthma		1.446***	[1.175,1.780]	---	
COPD		1.409***	[1.251,1.588]	---	
ARDS		3.160***	[2.747,3.634]	---	
Heart Failure		1.420***	[1.267,1.591]	---	
Head of Bed is 30 Degrees Up		1.343***	[1.180,1.530]	---	
Immunosuppression		0.862	[0.676,1.099]	1.212	[0.803,1.829]
Intubated in the First Day		0.959	[0.869,1.058]	1.063	[0.853,1.326]

Table 6.3, Continued

Characteristics		NP		CDAD		
		HR	95%CI	HR	95%CI	
Risk Factors	Mechanical Ventilation > 24 Hours	0.979	[0.858,1.117]	1.505**	[1.142,1.982]	
	Traumatic Brain Injury	1.201*	[1.007,1.433]	0.623	[0.318,1.219]	
	Hepatic Failure	0.823	[0.547,1.237]	0.553	[0.213,1.438]	
	Hydrocortisone \geq 250 Mg / Day or Equivalent	1.228*	[1.039,1.452]	0.814	[0.542,1.222]	
	Transplantation	0.84	[0.331,2.129]	2.378	[0.359,15.75]	
	Acute Myocardial Infarction	0.875	[0.635,1.208]	0.977	[0.472,2.022]	
	Sepsis	1.057	[0.922,1.211]	0.987	[0.794,1.227]	
	Neurological Injuries	1.299***	[1.121,1.504]	0.648*	[0.450,0.933]	
	Surgical And Multiple Trauma	1.111	[0.950,1.299]	0.936	[0.637,1.376]	
	Hypotension	1.211***	[1.081,1.356]	0.996	[0.795,1.247]	
	Acute Renal Failure	1.152**	[1.037,1.279]	1.071	[0.883,1.300]	
	Medications	Sucralfate	1.125	[0.806,1.571]	0.818	[0.453,1.479]
		Antacids	0.899	[0.805,1.005]	1.005	[0.815,1.240]
NSAIDs		1.027	[0.919,1.148]	0.998	[0.820,1.214]	
Aminoglycosides		1.106	[0.919,1.331]	1.114	[0.821,1.512]	
Cephalosporins		1.301***	[1.175,1.440]	1.119	[0.917,1.365]	
Flouroquinolones		1.173**	[1.058,1.300]	0.854	[0.710,1.027]	
Lincosamides		1.057	[0.866,1.289]	1.383*	[1.023,1.869]	
Linezolid		1.226*	[1.004,1.496]	1.922***	[1.497,2.467]	
Macrolides		1.326***	[1.145,1.537]	1.115	[0.857,1.450]	
Metronidazole		0.860*	[0.765,0.967]	2.849***	[2.220,3.655]	
Other β -lactams		1.194**	[1.048,1.360]	1.460***	[1.187,1.795]	
Penicillins		1.579***	[1.401,1.781]	1.384**	[1.116,1.716]	
Tetracyclines		0.402***	[0.244,0.663]	0.569	[0.272,1.192]	
Vancomycin	1.827***	[1.630,2.047]	--	---		
Antibiotics, Others	0.684**	[0.527,0.889]	1.143	[0.792,1.650]		
Admission Source	Direct Admission	Reference				
	Chest Pain Center	1.989**	[1.199,3.300]	---		
	Emergency Room	1.176	[0.975,1.419]	0.922	[0.684,1.242]	
	Floor	1.019	[0.832,1.247]	1.222	[0.875,1.707]	
	Operating Room	1.174	[0.922,1.494]	1.135	[0.692,1.862]	
	Other (Other Hospital ICU, Recovery Room, Step-Down Unit or chest pain center if not listed)	1.07	[0.866,1.323]	1.116	[0.758,1.643]	
Year of Admission	2008	Reference		Reference		

Table 6.3, Continued

Characteristics		NP		CDAD	
		HR	95%CI	HR	95%CI
2009		1.014	[0.819,1.256]	1.555*	[1.109,2.179]
2010		0.959	[0.754,1.220]	1.826***	[1.309,2.548]
2011		0.811	[0.640,1.028]	1.446*	[1.007,2.076]
2012		0.745*	[0.568,0.976]	1.259	[0.845,1.877]
Physician Specialty	Internal medicine	Reference		Reference	
	Pulmonary	1.191	[0.980,1.448]	0.785	[0.575,1.072]
	Hospitalist	1.199	[0.971,1.480]	0.910	[0.634,1.305]
	Cardiology	1.152	[0.890,1.490]	0.821	[0.503,1.341]
	Surgery-general	1.053	[0.821,1.350]	1.021	[0.668,1.562]
	Critical care medicine	1.325*	[1.063,1.651]	0.962	[0.656,1.412]
	Family practice	0.889	[0.684,1.157]	0.591	[0.338,1.033]
	Surgery-cardiac	1.204	[0.885,1.638]	0.813	[0.472,1.400]
	Others	1.361***	[1.153,1.607]	0.986	[0.748,1.301]
Teaching Hospital		1.677***	[1.418,1.985]	0.692*	[0.521,0.921]
Continuous Variables	APACHE Score IV	0.998	[0.996,1.000]	1.003	[1.000,1.007]
Observations		285033		389782	

PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 receptor Blockers; ICU: Intensive Care Unit; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; APACHE score IV: Acute Physiology and Chronic Health Evaluation Score version IV; NSAIDs: Non-Steroidal Anti-inflammatory Drugs.; BSA: Body Surface Area; LOS: Length of Stay.

The results of sensitivity analyses comparing the effect of PPIs to H2Bs on NP were either favoring PPIs over H2Bs or no difference. For instance, when the minimum time of exposure was reduced to two days and the cohort was expanded to include patients who developed NP on the third day, the hazard of NP was lower among patients on PPIs compared to those on H2Bs (HR: 0.90, 95%CI: 0.81-0.99). Similarly, when patients in the upper decile of ICU length of stay were removed from the cohort PPIs still were associated with lower risk of NP compared to H2B (HR: 0.87, 95%CI: 0.77-0.97). In contrast, the result became borderline insignificant (HR: 0.89, 95%CI: 0.79-1.00) when the analysis was confined to patients who did not discontinue treatment or discontinued

treatment no more than two days before discharge. In addition, both propensity score matching and instrumental variable technique showed no difference between PPIs and H2Bs with regards to the risk of NP (HR: 0.88, 95%CI: 0.75-1.02 and (HR: 0.84, 95%CI: 0.66-1.07), respectively (Table 6.4). Appendix III contains detailed information about the models and goodness of fit tests used in propensity score matching and instrumental variables techniques

Table 6. 4: Summary of analyses used for studying the comparative safety of PPIs and H2Bs on the risk of NP and CDAD

Analysis	Rationale	Results	
		NP	CDAD
Two-day use of PPIs compared to Two-day use of H2Bs	To whether or not shorter duration has the same effect on the risk of the outcome To compare the results to the studies that compared two-day use of PPIs to two-day use of H2Bs and found PPIs	n= 412,413 patient-day (HR: 0.90, 95% CI: 0.81-0.99).	n=543,105 patient-day (HR: 1.22, 95% CI: .99-1.52).
Limiting cohort to patients who did not discontinue treatment or discontinued treatment no more than two days before discharge	The main model consider any patient who received the medications of interest for three days as exposed regardless whether or not the medications were discontinued later. This may lead to estimate overestimation. Therefore, the analysis was confined to patients who continued using medications until discharge or discontinued them no more than two days before discharge.	n= 243,882 patient-day (HR: 0.89, 95% CI: 0.79-1.00).	n=329,399 patient-day (HR:1.12, 95% CI:0.88-1.42)
Removed long stayers by removing patients in the upper decile of ICU length of stay.	Observations with extreme length of stay may have skewed the results	n=258,770 patient-day (HR: 0.87, 95% CI: 0.77-0.97).	n= 353,298 patient-day (HR:1.15, 95% CI:0.91-1.47)
Propensity Score one to one Matching with no replacement	To control for possible treatment selection bias	n=32,160 patients (HR: 0.88, 95% CI: 0.75-1.02).	n=40,648 patient (HR:1.32, 95% CI:1.03-1.695)
Two Stage Residual Inclusion	To control for possible treatment selection bias	n= 285,033 patient-day (HR: 0.84, 95% CI: 0.66-1.07).	n= 389,782 patient-day (HR: 1.50, 95% CI: 1.05-2.14)
Two Stage Residual Inclusion while confiding the analysis to ICUs that have at least 100 patients during the year.	To control for possible treatment selection bias and validate the classification of an ICU as a PPI unit or not.	n= 179,296 patient-day (HR: 0.84, 95% CI: 0.56-1.25).	n= 288,489 patient-day (HR: 1.93, 95% CI: 1.28-2.94)

PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 receptor Blockers; ICU: Intensive Care Unit; HR: Hazard Ratio

Table 6.5 showed the different scenarios that may occur if there was an unmeasured difference in care provided to patients who received PPIs compared to patients on H2Bs to reduce the likelihood of NP infection. For instance, if the unmeasured variable is associated with 23% reduction in NP then PPIs will be associated with higher risk of NP if 40% of the patients in the PPIs group have received this extra care and no one the H2Bs group has received it (HR: 1.19, 95%CI: 1.06-1.33).

Table 6. 5: Hazard ratio and 95% Confidence Intervals for the effect of Three-day use of PPIs compared to Three-day use of H2Bs adjusting for an unmeasured dichotomous confounder with a hazard ratio of 0.77.

P_1	P_0					
	0.0	0.1	0.2	0.3	0.4	0.5
0.0	0.87 (0.78,0.97)					
0.1	0.93 (0.83,1.04)	0.87 (0.78,0.97)				
0.2	1.00 (0.9,1.12)	0.94 (0.84,1.05)	0.87 (0.78,0.97)			
0.3	1.09 (0.97,1.22)	1.02 (0.91,1.14)	0.94 (0.84,1.06)	0.87 (0.78,0.97)		
0.4	1.19 (1.06,1.33)	1.11 (0.99,1.24)	1.03 (0.92,1.15)	0.95 (0.85,1.06)	0.87 (0.78,0.97)	
0.5	1.31 (1.17,1.46)	1.22 (1.09,1.37)	1.13 (1.01,1.27)	1.05 (0.93,1.17)	0.96 (0.86,1.07)	0.87 (0.78,0.97)
0.6	1.45 (1.3,1.63)	1.36 (1.21,1.52)	1.26 (1.13,1.41)	1.16 (1.04,1.3)	1.06 (0.95,1.19)	0.97 (0.86,1.08)
0.7	1.64 (1.46,1.83)	1.53 (1.37,1.71)	1.42 (1.27,1.59)	1.31 (1.17,1.47)	1.20 (1.07,1.34)	1.09 (0.97,1.22)
0.8	1.88 (1.67,2.1)	1.75 (1.56,1.96)	1.62 (1.45,1.82)	1.50 (1.34,1.68)	1.37 (1.23,1.54)	1.25 (1.11,1.4)
0.9	2.19 (1.96,2.45)	2.04 (1.83,2.29)	1.90 (1.69,2.12)	1.75 (1.56,1.96)	1.60 (1.43,1.8)	1.46 (1.3,1.63)
1.0	2.64 (2.35,2.95)	2.46 (2.2,2.75)	2.28 (2.04,2.56)	2.11 (1.88,2.36)	1.93 (1.72,2.16)	1.75 (1.57,1.96)

P_0 and P_1 are the prevalence of the unmeasured confounder in the H2Bs group and the PPIs group, respectively; PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 Receptors Blockers
 Red color: higher risk of NP with PPIs; Green color: No difference between PPIs and H2Bs; Blue: lower risk of NP with PPIs.

The adjusted hazard of *Clostridium difficile*-associated diseases did not differ between the PPIs group and the H2Bs (HR: 1.116, 95%CI: 0.89-1.41). With regards to race,

except for Asians, all other races were associated with higher hazard of CDAD compared to Caucasians. In addition, patients who received enteral nutrition during their ICU stay had 44% increase in the hazard of CDAD compared to patients who did not receive enteral nutrition. Similarly, multiple antibiotics were associated with higher hazard of CDAD including lincosamides, linezolid, metronidazole, other b-lactams and penicillins (Table 6.3). In contrary, patients in teaching hospital were less likely to develop CDAD (HR: 0.69, 95%CI: 0.52-0.92) compared to patients in non-teaching hospitals. Sensitivity analyses showed that the risk of CDAD was higher among the PPIs group compared to H2Bs although it was borderline insignificant (HR: 1.22, 95%CI: .99-1.52) when the minimum time of exposure was reduced to two days and the cohort was expanded to include patients who developed CDAD on the third day. Similarly, when the analysis was confined to patients who did not discontinue treatment or discontinued treatment no more than two days before discharge or when patients in the upper decile of ICU length of stay were removed from the cohort there was no difference between PPIs and H2Bs in the hazard of CDAD (Table 6.4). However, the propensity score matching revealed that results in a matched sample differed from the results in the full sample. The one to one propensity score matching model showed that PPIs were associated with higher hazard of CDAD (HR:1.32, 95%CI:1.03-1.695) compared to H2Bs. Moreover, PPIs were also associated with higher risk of CDAD compared to H2Bs (HR: 1.50, 95%CI: 1.05-2.14) when the IV technique was used. Appendix III contains detailed information about the models and goodness of fit tests used in propensity score matching and instrumental variables techniques.

Discussion:

Two cohorts were used to study the relationship between the administration of PPIs or H2Bs for three days and two outcomes: NP and CDAD. The overall incidence rate of NP was 8.4 cases per 1000 patients-day indicating that out of each 1000 patients admitted to the ICU in one day approximately eight patients will develop NP. The rate was higher among the H2Bs group compared the PPIs group (10.6 vs. 7.6 / 1000 patient-day, respectively).

Overall, there were 2393 (3.5%) NP cases among the cohort used for studying the relationship between the two therapeutic classes and NP. The lower incidence reported in the study compared to the 10% cumulative incidence (CI) reported in most of the previous meta-analyses is most likely due to, first, the three days treatment duration required before ascertaining the infection which excluded NP that occurred during the first three days after admission ; second, the more specific NP definition that depended on direct physician's input through the dropdown diagnoses menus which reduced the possibility of false positive due to upcoding seen in claims data¹⁹⁷; Third, the implementation of population management tools in this cohort which were used as tools for alerting clinicians about medication's adverse effects allowed setting up precautionary measures to reduce the likelihood of NP¹⁹⁸.

Previous meta-analyses of RCTs did not find any difference in the incidence of NP between the studied therapeutic classes. Contrariwise, observational studies reported higher hazard of NP with PPIs compared to H2Bs^{78,199-201}. Unlike, the aforementioned studies, in this study, the crude incidence was greater among the H2Bs group (4.2%)

compared to PPIs group (3.3%). In addition, the adjusted HR was 0.87 with a 95% confidence interval between 0.78 and 0.97 indicating that the receipt of PPIs was associated with 13% reduction in the hazard of NP when it is compared to the receipt of H2Bs. Furthermore, the results were robust when the duration of exposure was shortened to two days, patients with the highest ICU length of stay were excluded or when the analysis was confined to continuous users (Table 6.4).

In the absence of a theory supporting this finding and the presence of multiple mechanisms by which PPIs may lead to NP, it is most likely that the observed relationship is a result of confounding by indication also known as treatment selection bias. Confounding by indication occurs when an unmeasured variable directs the choice of one of the two therapeutic classes over the other i.e. treatment selection becomes deviated toward one of the two therapeutic classes due to the presence of this unmeasured variable that is observed by clinicians and not observed by the researcher. During the study period, PPIs have been put under a lot of scrutiny because of the interaction with clopidogrel, the risk of fractures with their long use and the observational studies that reported increased risk of pneumonia with them^{153,154,159,199,200,202,203}. For instance, in 2009, the journal of the American medical association published a study by Herzig et al reporting an increased risk of hospital-acquired pneumonia with PPIs compared to nothing (OR, 1.3; 95% CI, 1.1-1.4) but not with H2Bs (OR, 1.2; 95% CI, 0.98-1.4)¹⁹⁹. Therefore, clinicians might have recognized a higher risk of NP with PPIs administration than H2Bs and, hence, did more to reduce the risk. Consequently, clinicians might have directed patients with higher risk of pneumonia away from PPIs and toward H2Bs.

Although risk factors of pneumonia were included in the model, there were factors that were unavailable such as alcohol use, aspiration during intubation or swallowing problems. Another possible hypothesis is related to health severity, the PPIs groups were sicker than the H2Bs group as seen by the APACHE score in both groups (66 vs. 62, $P < 0.0001$, respectively). Therefore, overall, the sicker group may have received extra care measures, including PPIs as the most potent acids suppressant, compared to the less sicker group which eventually reduced the likelihood of developing NP in the former group. In both scenarios propensity score matching and IV techniques were used to correct for this bias given that the assumptions of each techniques were satisfied. The result of propensity score matching showed that the risk of NP did not statistically differ between PPIs and H2Bs (HR: 0.88, 95%CI: 0.75-1.02; $P = 0.09$) coinciding with what was reported in previous RCTs and meta-analyses. The large sample size of 32,160 matched pairs reduces the possibility of statistical insignificance due to insufficient power given that other studies were able to detect a difference between the two groups with smaller sample sizes^{78,201}. Thus, it is more likely that the lack of difference is real supporting the results seen in previous meta-analyses. However, one cannot also ignore the possibility of residual confounding even after propensity score matching if the propensity score model did not include all confounders or variables only associated with NP¹⁷². Instrumental variable technique showed very similar results of no statistical difference between PPIs and H2Bs in NP hazard (HR: 0.84, 95%CI: 0.66-1.07). The results of two-way sensitivity analysis in Table 6.5 provided a third approach to check the robustness of the data if the assumptions of propensity score and IV techniques were violated. The fact that it is enough for 40% of the patients in the PPIs group to receive some sort of extra care

measures such as close monitoring, implementation of care bundles or more experienced staff in order for PPIs to be associated with higher risk of NP compared to H2Bs (HR: 1.19, 95%CI: 1.06-1.33) indicates the possibility of such association to exist in reality despite that all previous RCTs and subsequent meta-analyses did not show this.

Few studies looked at the incidence rate of CDAD in intensive care unit. In this study, the incidence rate of CDAD was (1.4 cases/ 1000 patient-day) which was lower than what was reported in the literature. For instance, in 2007, Beaulieu and colleagues reported an incidence rate of 8 cases / 1000 patient-day in Quebec medical intensive care unit. However, the high incidence rate in Beaulieu's study was most likely a consequence of a CDAD outbreak that led to shutting down the medial ICU for a period of time. Similar to the incidence rate, the crude incidence in this study (0.7%) was lower than what reported in the literature between 2% to 5%¹⁰⁷. This is mainly because of the three days of exposure required in the inclusion criteria and, more importantly, the dependence on lab results or oral Vancomycin receipt in identifying CDAD cases rather than the ICD-9 code which increase the specificity of the definition and reduce the possibility of false positives.

In this cohort, the adjusted hazard of CDAD was not different between the PPIs group and the H2Bs (HR: 1.116, 95%CI: 0.89-1.41). However, although it was borderline insignificant, the risk of CDAD was higher among the PPIs group compared to H2Bs (HR: 1.22, 95%CI: .99-1.52) when the minimum time of exposure was reduced to two days and the cohort was expanded to include patients who developed CDAD on the third day. The aforementioned results indicates the presence of small effect size between PPIs

and H2Bs. MacLaren and colleagues reported a very similar estimate of CDAD risk among PPIs patient compared to H2Bs patients (OR=1.29; 95%CI: 1.04-1.64). Moreover, the results of one to one propensity score matching and the IV techniques showed that the use of PPIs for three days were associated with higher hazard of CDAD compared to H2Bs use for the same period of time (HR:1.32, 95%CI:1.03-1.695; HR: 1.50, 95%CI: 1.05-2.14, respectively). Not accounting for non-random treatment allocation may have led to the differences between results of the classical Cox regression model and PSM and IV techniques. The residuals included in the second IV stage showed a statistically significant protective effect (HR: 0.96, 95%CI: 0.93, 0.99) indicating the presence of an unmeasured variable that was associated with 4% reduction in the hazard of CDAD that needed to be included in the final model to account for treatment selection bias and achieve an unbiased estimate. As previously mentioned, the higher baseline APACHE score among the PPIs group (Appendix III Table 9, 10) may have led to differences in provided care that was captured in the residuals.

The mechanism by which PPIs are believed to cause CDAD is the elevation of gastric pH which promotes bacterial overgrowth and colonization inside the stomach. Both the vegetative cells as well as the spores of *C.difficile* are implicated in the pathogenesis of CDAD. For instance, above the pH of five which can be achieved by PPIs more than H2Bs, *C.difficile* spores germinate and produce vegetative cells that can live under this pH. In addition, inside hospital settings, the vegetative cells themselves can live up to 6 hours on moist surfaces at room temperature¹¹². Therefore, exposure to either form plays a role in the pathogenesis of CDAD among patients on acid

suppressants. In 2012, Tleyjah and colleagues conducted a meta-analysis that included any empirical study that explored the association between PPIs and CDAD. The majority of the studies included community-dwelling patients and hospitalized patients. The authors reported a 65% increase in the odds of developing CDAD with the use of PPIs compared to not receiving PPIs (OR: 1.65, 95% CI: 1.47 to 1.85), $P < 0.0001$, $I^2 = 89.9\%$.)¹³⁷. Similarly, Deshpande and colleagues conducted another meta-analysis that included 30 observational studies (n=202,965) and found that the use of PPIs was associated with higher odds of CDAD (OR: 2.15, 95% CI: 1.81 to 2.55), $P < 0.0001$, $I^2 = 87\%$.)¹³⁸.

The results of the NP and CDAD models showed that administration of enteral nutrition increased the risk of both infections approximately by 40%. Enteral nutrition has been associated with risk of gastric content aspiration into the lungs causing pneumonia²⁰⁴. In addition, patients on enteral nutrition may be at a greater risk of encountering *C.difficile* infection during manipulation of the feeding system²⁰⁵⁻²⁰⁷. The results in the NP model were consistent with the literature which showed asthma, COPD, ARDS and heart failure as risk factors for NP. Conversely, the higher risk of NP that was seen with head of bed elevation, hypotension and many of the antibiotics is most likely due reverse causality. Since the 24-hours lag time was only required between NP and the main independent variable, it is most likely that the occurrence of NP led to subsequent elevation of bed head, initiation of antibiotic therapy and hypotension in cases of concomitant sepsis. With regards to CDAD, certain antibiotics classes have been linked to CDAD such as lincosamides, penicillins which was seen in this study by the HR above 1. On the other hand, metronidazole is used to treat CDAD, therefore, it is most likely

that the observed relationship of higher risk of CDAD with metronidazole (HR: 2.85; 95% CI, 2.22-3.67) is a result of reverse causality. Finally, It is important to interpret the covariates' coefficients with caution as the purpose of including the covariates was for adjustment only. Therefore, since the intended research question was different than the question answered by each covariate, the possibility of unequal groups and missing confounders may exist.

The study has its strengths and limitations. The use of diagnosis strings and lab results along with ICD9-codes increased the specificity of outcomes definition reflecting better estimates of incidence rate and cumulative incidence than the estimates that were based only on ICD-9 code. For instance, ICD-9 codes for NP are based on the causative microorganism but do not have information about the location from which the infection was acquired. Thus, availability of diagnosis strings increased the specificity by eliminating community-acquired cases more accurately. Second, the use of different analytical methods to account for treatment selection bias and unmeasured confounding stressed the importance of using multiple methods in data analysis to provide a complete picture of the relationship between the outcomes, PPIs and H2Bs use. In contrast, patients past medical history as well as the differences in institutional practices and clinician's characteristics were unavailable at the time of the analysis. Therefore, the degree by which such factors impact treatment choice and outcome occurrence is still an area for future research.

In conclusion, each day, among each 1000 patient who received at least three days of PPIs therapy or H2Bs, around eight patients will develop NP while two patients will

develop CDAD. In this study, PPIs were associated with lower hazard of NP and higher hazard of CDAD compared to H2Bs. However, both propensity score matching and IV techniques showed that PPIs were only associated with higher risk of CDAD compared to H2Bs. Future research should focus not only on replicating these results in different cohorts and including more relevant covariates but also on exploring the effect of different outcomes definitions and different analytical methods for accounting for treatment selection bias on the robustness of the data

Chapter VII. Discussion

This concluding discussion summarizes and integrates the results of the three papers. In general, the use of stress ulcer prophylaxis was high (86.4%). Around 83% of patients have received SUP within 24 hours of stress ulcer risk factors occurrence. The positive association between SUP and most of stress ulcer risk factors indicated that clinicians are vigilant about finding these risk factors and prescribing SUP according to them. In addition, the number of risk factors was also a predictor of SUP receipt. Proton pump inhibitors were the most widely used SUP (49.8%) followed by H2Bs (17.96%). However, there was a gradual reduction in PPIs utilization over the five years from 52.4% to 46.8% that was accompanied by a gradual increase in H2Bs utilization from 15.96% to 20.1% indicating a trend toward switching toward H2Bs. While most of the stress ulcer risk factors predicted SUP receipt, mechanical ventilation for more than 24 hours (OR=10.63, 99%CI: 9.84-11.49) and transplantation (OR=13.28, 99%CI: 6.88-25.66) were the strongest predictors.

Despite that clinicians take stress ulcer risk factors in their decision to proscribe SUP, SUP drugs were administered to almost 80% of patients who did not have any documented risk factors of stress ulcer, duodenal ulcer, gastric ulcer, unspecified ulcer, gastritis, angiodysplasia, Dieulafoy's lesion or ulcers due to mucositis indicating that the issue of overutilization still exists despite the large number of studies that raised this issue in the literature. From a different angle, out of 455,109 patients who received at least one dose of PPIs, H2Bs or sucralfate, almost 44% of them did not have any of the

aforementioned conditions. This is of a great importance as this study found that each day out of 1000 patients who received PPIs or H2Bs for at least three days , around 8 patients develops NP and 2 develops CDAD. In current practice, one of the objectives is to adjust the existing therapies to maximize their benefits and minimize their risk. In this series of papers, there were 20,024 patients who received SUP medications each year without indications with the almost 90% receiving PPIs and/or H2Bs. If 8 out of 1000 patients develop NP each day, then approximately 146 cases per year can be avoided by prescribing these medications to patients who only need them. Similarly, around 40 cases per year of CDAD can be averted by avoiding over prescribing these medications. The calculations of these two numbers did not include patients who received SUP only because they were on mechanical ventilation for less than 24 hours or have received NSAIDs. With the lack of evidence, the need for SUP in the two aforementioned groups is an area where future research should be directed.

In this series, PPIs were associated with higher CIGIB compared to H2Bs regardless of the method used. In addition, PPIs were associated with lower risk of NP and no difference in CDAD compared to H2Bs when the traditional Cox proportional hazard regression was used. However, PSM and IV showed that there was no difference between the two therapeutic classes in terms of NP and higher risk of CDAD with PPIs compared to H2Bs. While observational studies represent real world practice, two of their inevitable drawbacks are residual confounding and lack of random treatment allocation. These factors may have affected estimating the true effect between exposure and the outcomes. However, the different analytical approaches such as PSM, IV and n-way sensitivity

analyses provided a comprehensive picture for estimating the true effect in the presence of such factors. One possible scenario for what is seen in this series of higher risk of CIGIB and lower risk of NP with PPIs compared to H2Bs is the following: There was an increase in the likelihood of receiving SUP as the number of stress ulcer risk factors increased. With the current trend of higher PPIs use, there is a chance that patients will receive PPIs more than H2Bs. Due to unavailability of the data, history of GI bleeding or GI ulceration were not captured. Therefore, when patients with these two conditions enter the ICU, clinicians react by prescribing PPIs and put patients on extra care measures such as close monitoring, implementation of care bundles or more experienced staff...etc to prevent PPIs-induced pneumonia. Therefore, patients on PPIs looked worse in terms of CIGIB since history of GI ulceration or bleeding was not included in CIGIB regression model and looked better in terms of NP since the extra care measures were not included in NP regression model.

The picture looks slightly different with CDAD since the evidence of PPIs-induced CDAD in intensive care units was scarce during study period. Therefore, because of the weak relationship between PPIs, H2Bs and CDAD, it is unlikely that prevention of CDAD has led to differential treatments between the PPIs group and the H2Bs group.

Future research should focus on the followings: first, better identifying patient subgroups at risk of developing stress ulcer in order to determine the eligibility of patients to SUP; Second, the development, implementation and evaluation of different approaches that can be used to reduce and eventually prevent SUP overutilization; Third, replicating the findings in different cohorts and including more relevant variables pertaining to patients

past-medical history and care measures in ICUs; Fourth, exploring the possibility of higher risk of CIGIB with PPIs compared to H2Bs through well-designed and well-executed randomized controlled triple blind clinical trials with no funding or reporting bias; Finally, exploring the effect of different outcomes definitions and different analytical methods on the robustness of the result.

APPENDIX I:

Appendix I Table 1: Definitions used in identifying risk factors of gastrointestinal bleeding.

Risk factors of gastrointestinal bleeding due to stress ulcer	Selection method	Comments
Mechanical Ventilation > 24 hrs.	Using a continuous variable: continuous invasive ventilation duration	From the ventilation data file
Coagulopathy	Any of the followings during an ICU stay: Platelets 50,000 per/ml ³ ; an INR > 1.5, a PT > 50 sec	From the hematology or laboratory results data file
Traumatic Brain Injuries	Any ICD-9 code: 800.0-801.9 803.0-804.9 850.0-854.1 950.1-950.3 959.01	From active diagnosis file
Major Burns	Any ICD-9 code: 940.*-949.*	From active diagnosis file
Sepsis	Any ICD-9 code: 038, 040.82, 599.0, 996.64, 998.5, 999.3	From active diagnosis file
Corticosteroid Therapy > 250 mg of hydrocortisone or equivalent daily		Medications file
Acute Renal Failure	Any ICD-9 code: 584.*	From active diagnosis file
Hepatic Failure	Any ICD-9 code: 570.*	From active diagnosis file
Transplantation	Using admission diagnosis string “operative transplant”	From the APACHE admission diagnosis file
ICU stay of > 1 week	From ICU length of stay variable that is available in the raw data files	From APACHE Patient Results file
Multiple Trauma	Using admission diagnosis string “multiple trauma”	From the APACHE admission diagnosis file

Appendix I Table 1, Continued

Risk factors of gastrointestinal bleeding due to stress ulcer	Selection method	Comments
Neurological Injuries/Spinal Injuries	Using admission diagnosis string “spinal trauma”, “spinal cord decompression”, “Spinal cord only trauma”, “Spinal cord surgery, other”, “Spinal/extremity trauma”, “Spinal/face trauma”, “Abdomen/spinal trauma” Or any ICD-9Code: Coma:780.01, 780.03, 850.3, 850.4, Embolic stroke:433, 434; Encephalitis: 348.1, 348.4, 348.5 Hemorrhage: 430, 431, 432, 997.02, 997.09 Spinal cord injury:806, 952	From the APACHE admission diagnosis file and active diagnosis file
Surgery/Trauma	Using admission diagnosis string “multiple trauma”	From the APACHE admission diagnosis file

(INR) International normalized ratio, (PT) prothrombin time, (aPTT) partial thromboplastin time, (ICD-9) International Classification of Diseases 9th ed. , (ICU) Intensive Care Unit, (APACHE) Acute Physiology and Chronic Health Evaluation

Appendix I Table 2: Definitions used in identifying Study Medications

Drug Category	Identification Criteria
Antacids	<p>The Following HICL Sequence Numbers: 1157 ,1168 ,2297 ,1179 ,1172 ,1173 ,34705 ,25628 ,1142 ,6046 ,589 ,1163 ,1152 ,581 ,562 , 1153 ,21088 ,22961 ,581 ,6428 ,580 ,582 ,1162 ,37124 ,1184 ,1170 ,1329 ,609,24425 ,1316 ,5859 ,1183 ,1185</p> <p>Or The Following Drug Names: FOAMING ANTACID, MAALOX TC, MG TRISILICATE/AL HYDROX/AA, RI-GEL, FOAMING ANTACID ES, MAG CARB/AL HYDROX/ALGINIC AC, MG TRISILICATE/ALH/NAHC O3/AA, RI-GEL II, FOAMING ANTACID MAX STRENGTH, MAG HYDROX/AL HYDROX/SIMETH, MI ACID, RI-MAG, GAS-X WITH MAALOX, MAG-AL, MI- ACID DS, RI-MOX, GAVISCON, MAG-AL PLUS, MI-ACID II, RI-MOX PLUS, GELUSIL, MAG-AL PLUS XS, MILANTEX, RIGINIC, GENATON, MAG-AL ULTIMATE STRENGTH, MILK OF MAGNESIA, ROLAIDS, GERI-LANTA, MAGALDRATE, MINT CREME ANTACID, ROLAIDS EXTRA STRENGTH, HEARTBURN ANTACID, MAGALDRATE/SIMETHICONE, MINTOX, RON ACID PLUS, HEARTBURN RELIEF, MAGALOX PLUS, MINTOX MAXIMUM STRENGTH, RON- ACID, HEARTBURN TABLET, MAGLOX, MINTOX PLUS, RULOX, HI-CALCIUM, MAGNESIA, MYLANTA, RULOX PLUS, HIGH POTENCY CALCIUM, MAGNESIUM CARBONATE/AL HYDROX, MYLANTA DOUBLE STRENGTH, SMOOTH ANTACID, HM ANTACID, MAGNESIUM HYDRALUMINUM HYDR, MYLANTA MAXIMUM STRENGTH, SOOTHE, HM ANTACID/ANTIGAS, MAGNESIUM HYDROXIDE, MYLANTA SUPREME ANTACID, SUPER CALCIUM, HM CALCIUM MAGNESIUM, HYDROXIDE/AL HYDROX, MYLANTA ULTRA, SUPREME ANTACID, HM CALCIUM ANTACID, MALDROXAL, MYLANTEX DOUBLE STRENGTH, TITRALAC, HM MILK OF MAGNESIA, MALDROXAL, ANTACIDANTI-GAS, NATURAL O-S CAL, TITRALAC EXTRA STRENGTH, LIQUID ANTACID, MALDROXAL PLUS,</p>

Appendix I Table 2, Continued

Drug Category	Identification Criteria
	<p>OYSCAL 500, TITRALAC PLUS, MAALOX, MASANTI, OYSCO-500, TUMS, MAALOX ADVANCED, MASANTI ANTACID, OYST-CAL-500, TUMS CALCIUM FOR LIFE, MAALOX MS, MASANTI DOUBLE STRENGTH, OYSTER SHELL, TUMS SMOOTHIES, MAALOX PLUS, MASANTI II, OYSTER SHELL CALCIUM, TUMS ULTRA, MAALOX PLUS EXTRA STRENGTH, MEDI-MILK OF MAGNESIA, PHILLIPS' MILK OF MAGNESIA, ULTRA STRENGTH ANTACID, MAALOX QUICK DISSOLVE, MEDICAL RESOURCES, REMEGEL, UNI-LAN, MAALOX RS, MG TRISILICATE/AL HYDROX, RI MAG PLUS, X-STRENGTH ANTACID</p>
Histamine-Type 2 Receptor Blockers	<p>The Following HICL Sequence Numbers: 4518 , 9793, 4517, 35085, 35107, 34357, 8965, 4522, 1232 , 4520, 4519 , 4521 Or The Drug Names: ACID REDUCER FAMOTIDINE/NACL 0.9%, RANITIDINE, ACID RELIEF FAMOTIDINE/NORMAL SALINE, RANITIDINE HCL, AXID FAMOTIDINE/PF RANITIDINE HCL/DIET.SUPP NO.17, AXID AR GABITIDINE, RANITIDINE HCL/DIET.SUPP NO.8, CIMETIDINE HEARTBURN RANITIDINE HCL/NACL 0.45%, CIMETIDINE HCL HEARTBURN 200 SENTRADINE, CIMETIDINE HCL/NACL 0.9% HEARTBURN PREVENTION, TAGAMET, CIMETIDINE IN SODIUM CHLORIDE HEARTBURN RELIEF, TAGAMET HB, COMPLETE HM ACID REDUCER, TALADINE DUAL ACTION, COMPLETE HM HEARTBURN RELIEF, WAL-ZAN 150, FAMOT/CALCIUM, CARB/MAGNESIUM NIZATIDINE, WAL-ZAN 75 FAMOTIDINE, PEPCID, ZANTAC, FAMOTIDINE IN SALINE,ISOOS/PF, PEPCID, AC ZANTAC 25, FAMOTIDINE-NS, PEPCID, COMPLETE ZANTAC 75, FAMOTIDINE/CALCIUM,CARB/MAG, PEPCID RPD</p>
Proton Pump Inhibitors	<p>The Following Hicl Sequence Numbers: 20495, 17026 , 36085 , 21607, 25968 , 8993 , 11115, 33512 , 4673 , 22008, 18847 Or The Drug Names:</p>

Appendix I Table 2, Continued

Drug Category	Identification Criteria
	ACIPHEX, NEXIUM, I.V. PREVPAC DEXLANSOPRAZOLE, OMEPRAZOLE, PRILOSEC, ESOMEPRAZOLE MAG TRIHYDRATE, OMEPRAZOLE MAGNESIUM, PRILOSEC OTC, ESOMEPRAZOLE SODIUM, OMEPRAZOLE/SODIUM BICARBONATE, PROTONIX,KAPIDEX, PANTOPRAZOLE SODIUM, PROTONIX IV, LANSOPRAZOLE, PREVACID RABEPRAZOLE SODIUM,LANSOPRAZOLE/AMOX TR/CLARITH PREVACID IV ZEGERID
Sucralfate	The Following HICL Sequence Numbers: 1186 Or The Drug Names: CARAFATE SUCRALFATE
Cephalosporins	The Following HICL Sequence Numbers: 25040 , 37021 , 33094, 26809 , 35282, 25040 ,26808 ,26809 ,18548, 35848 , 10132 , 37021, 3999 , 3984 , 35169 , 8948 , 3998 , 3979 , 33772 , 6316 , 13429 , 26488 , 26487 , 10246 , 3989 , 3988 , 3995 , 3996 , 33094 , 3992 , 3991 , 6012 , 25953 , 13908 , 3985 , 3983 , 22796 , 3976 , 3998, 3978 , 6495 , 3990 , 22796 , 22980 , 37243 Or The Drug Names: Cefaclor, Cefadroxil, Cefazolin, Cefdinir, Cefditen, Cefepime, Cefixime, Cefotaxime, Cefotetan, Cefoxitin, Cefpodoxime, Cefprozil, Ceftaroline, Ceftazidime, Ceftributen, Ceftriaxone, Cefuroxime, Cephalexin
Penicillins	The Following HICL Sequence Numbers: 3946 ,3962 ,3963 ,3953 ,3952 ,3948 ,3938 ,3960 ,17026 ,3956 ,5886 ,3957 ,6392 ,6077 ,3935 ,3940 ,3938 ,3936 ,3942 ,18813 ,3944 ,3943 ,8738 ,3941 ,3937 ,32900 ,3944 ,3966 ,3965 Or The Drug Names: Amoxicillin, Ampicillin, Piperacillin, Ticarcillin, Penicillin, Dicloxacillin, Nafcillin, Oxacillin
Other Beta Lactam	The Following HicL Sequence Numbers: 4053 ,6447 ,35075 ,23241 ,4054 ,6473 ,11254 Or The Drug Names: Aztreonam, Dipenem, Ertapenem , Imipenem, Meropenem
Flouroquinolones	The Following HICL Sequence Numbers: 13446 ,6072 ,4124 ,6071 ,12383 ,12384 ,12383 ,16487 ,25388 ,4123 Or The Drug Names: Ciprofloxacin, Gemifloxacin, Levofloxacin, Moxifloxacin, Nfloxacin, Ofloxacin
Aminoglycosides	The Following HICL Sequence Numbers:

Appendix I Table 2, Continued

Drug Category	Identification Criteria
Lincosamides	35990 ,4035 ,4032 ,4030 ,33290 ,34362 ,4028 ,4029 ,4027 ,4034 ,16926 ,4033 ,5887 The Following HICL Sequence Numbers: 19818 ,4044 ,4045 ,4046, 17263 ,4043 ,4704 Or The Drug Names: Clindamycin, Lincomycin
Linezolid	The Following HICL Sequence Numbers: 21157 Or The Drug Names: Linezolid
Vancomycin	The Following HICL Sequence Numbers: 37442 ,4042 ,10093 Or The Drug Names: Vancomycin
Macrolides	The Following HICL Sequence Numbers: ,6334 ,6228 ,4021 ,4017 ,4018 ,4020 ,4022 ,37674 Or The Drug Names: Azithromycin, Clarithromycin , Erythromycin
Metronidazole	The Following HICL Sequence Numbers: 4156, 4157, Or The Drug Names: Metronidazole, Flagyl
Miscellaneous Antibiotics	The Following HicL Sequence Numbers: ,4037 ,4050 ,4051 ,25673 ,4025 ,4089 ,4087 ,4049,32986 ,36690 Or The Drug Names: Tigecycline
Synercid	The Following HICL Sequence Numbers: 20518
Tetracyclines	The Following HICL Sequence Numbers: 4010 ,4013 ,4014 ,4012 ,33822 ,4015,4003 Or The Drug Names: DEMECLOCYCLINE, DOXYCYCLINE , MINOCYCLINE, TETRACYCLINE
Anticoagulants	The Following HICL Sequence Numbers: ,18559 ,21768 ,37946 ,5735 ,21872 ,10051 ,3682 ,35604 ,7429 ,7878 ,23233 ,33314 ,8643 ,33442 ,2808 ,2810 ,2807 ,18277 ,18682 ,537
Antiplatelets	The Following HICL Sequence Numbers: 1807 ,12474 ,1711 ,1790 ,14324 ,9655 ,1820 ,1699 ,1942 ,34574 ,168 ,4576 ,1740 ,36159 ,35915 ,37328 ,6232 ,18384 ,18386 Or The Drug Names: Aspirin, Clopidogrel
Thrombolytics	The Following HICL Sequence Numbers: 2801 ,2805 ,21292 Or The Drug Names: Alteplase, Tenecteplase, Reteplase Streptokinase
Corticosteroids	The Following HICL Sequence Numbers: ,2884 ,2860 ,389 ,2889 ,2888 ,2886 ,34381 ,2899 ,2867 ,2863 ,2865 ,2866 ,2877 ,2876 ,2875 ,2874

Appendix I Table 2, Continued

Drug Category	Identification Criteria
Immunosuppression	<p>,2870 ,38114 ,2879 ,37106 ,2894 ,2893 ,36875 ,36808</p> <p>Or The Drug Names: Betamethasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone</p> <p>The Following HICL Sequence Numbers: 14404 ,10012 ,18603 ,23167 ,10798 ,8537 ,6068 ,4528 ,6024 ,24819 ,25201 ,21367 ,8974 ,18747 ,4527 ,20519 ,34870 ,20974 ,10280</p> <p>Or “Immunosuppression” From The APACHE Admission File</p>
Non-Steroidal Anti-Inflammatory Drugs	<p>The Following HICL Sequence Numbers: ,1840 ,20420 ,8824 ,3733 ,1847 ,6089 ,3724 ,3728 ,14296 ,3723 ,3718 ,3719 ,3736 ,5175 ,3730 ,1776 ,12181 ,6311 ,36964 ,3727 ,3726 ,33195 ,3736 ,6620 ,3732 ,1845 ,3729 ,3725</p> <p>Or The Drug Names: Diclofenac, Etodolac, Fenoprofen Flurbiprofen, Ibuprofen, Indomethacin Ketoprofen, Ketolac, Meclofenamate, Mefenamic, Meloxicam, Nabumetone , Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin</p>
Misoprostol	<p>The Following HICL Sequence Numbers: 1187</p> <p>Or The Drug Names: Misoprostol</p>

Appendix I Table 3: Diagnosis Strings for Types of Bleeding Included in Defining Gastrointestinal Bleeding

Diagnosis Strings for Types of Bleeding Included
Gastrointestinal GI Bleeding / PUD
Admission Diagnosis All Diagnosis Non-Operative Diagnosis Gastrointestinal Bleeding, GI From Esophageal Varices/Portal Hypertension"
Admission Diagnosis All Diagnosis Non-Operative Diagnosis Gastrointestinal Bleeding, GI-Location Unknown"
Admission Diagnosis All Diagnosis Non-Operative Diagnosis Gastrointestinal Bleeding, Upper GI"
Admission Diagnosis All Diagnosis Operative Diagnosis Gastrointestinal Bleeding-Other GI, Surgery For"
Admission Diagnosis All Diagnosis Operative Diagnosis Gastrointestinal Bleeding-Upper GI, Surgery For"
Admission Diagnosis All Diagnosis Operative Diagnosis Gastrointestinal Bleeding-Variceal, Surgery For (Excluding Vascular Shunting-See Surgery For Portosystemic Shunt)"
Admission Diagnosis All Diagnosis Operative Diagnosis Gastrointestinal Complications Of Previous GI Surgery; Surgery For (Anastomotic Leak, Bleeding, Abscess, Infection, Dehiscence, Etc.)

Appendix I Table 4: Univariable analysis of patients who did not have known indications for receiving gastric acid modifying drugs or sucralfate (n=285,251).

All		
N=285,251		
Characteristics	Frequency	Col%
GAMAS	227,919	79.9
Mechanical Ventilation for Less than 24 hours	20,940	7.3
Age		
18 to 60	132,880	46.6
61 to 70	59,506	20.9
71 to 80	52,393	18.4
80 to 90	40,472	14.2
Male	150,649	52.8
Race		
Caucasian	216,182	75.8
African American	30,799	10.8
Hispanic	13,104	4.6
Native American	2,005	0.7
Asian	2,954	1
Other	20,207	7.1
Type of ICU		
Mixed	136,027	47.7
Cardiovascular-Surgical	30,212	10.6
Coronary Care	56,907	19.9
Trauma	1,382	0.5
Surgical	21,516	7.5
Medical	22,279	7.8
Neuroscience	16,928	5.9
Medications		
Anticoagulants	141,208	49.5
Antiplatelets	185,557	65.1
Thrombolytics	23,612	8.3
Coagulating Drugs	10,691	3.7
Non-Steroidal Anti-inflammatory Drugs	110,161	38.6
Misoprostol	563	0.2
Nutrition		
No feeding	160,212	56.2
Enteral Nutrition	122,353	42.9
Parenteral Nutrition	895	0.3
Both	1,791	0.6
APACHE IV Score (Mean, SD)	44.40	19.2

Appendix I Table 5: Bivariable analysis of patients who did not have known indications for receiving SUP medications also known as GAMAS (n=285,251).

Characteristics	No GAMAS		GAMAS		OR	99%CI
	n=	57,332	n=	227,919		
	Freq.	Col %	Freq.	Col %		
Mechanical Ventilation for Less than 24 hours	1,123	2	19,817	8.7	4.77	(3.31-6.86)
Age						
18 to 60	28,655	50	104,225	45.7	Reference	
61 to 70	10,779	18.8	48,727	21.4	1.24	(1.15-1.34)
71 to 80	9,823	17.1	42,570	18.7	1.19	(1.09-1.3)
80 to 90	8,075	14.1	32,397	14.2	1.1	(1.02-1.2)
Male	30,937	54	119,712	52.5	0.94	(0.88-1.01)
Race						
Caucasian	43,108	75.2	173,074	75.9	Reference	
African American	6,768	11.8	24,031	10.5	0.88	(0.73-1.07)
Hispanic	2,624	4.6	10,480	4.6	1	(0.83-1.2)
Native American	388	0.7	1,617	0.7	0.99	(0.82-1.2)
Asian	589	1	2,365	1	1.04	(0.76-1.41)
Other	3,855	6.7	16,352	7.2	1.06	(0.9-1.24)
Type of ICU						
Mixed	29,061	50.7	106,966	46.9	Reference	
Cardiovascular-Surgical	5,319	9.3	24,893	10.9	1.27	(0.78-2.07)
Coronary Care	12,245	21.4	44,662	19.6	0.99	(0.74-1.33)
Trauma	386	0.7	996	0.4	0.7	(0.47-1.05)
Surgical	3,162	5.5	18,354	8.1	1.58	(1.08-2.3)
Medical	4,030	7	18,249	8	1.23	(0.77-1.98)
Neuroscience	3,129	5.5	13,799	6.1	1.2	(0.76-1.88)
Medications						
Anticoagulants	22,252	38.8	118,956	52.2	1.72	(1.49-1.99)
Antiplatelets	31,001	54.1	154,556	67.8	1.79	(1.54-2.08)
Thrombolytics	3,189	5.6	20,423	9	1.67	(1.23-2.28)
Coagulating Drugs	972	1.7	9,719	4.3	2.58	(1.37-4.87)
Non-Steroidal Anti-inflammatory Drugs	14,874	25.9	95,287	41.8	2.05	(1.78-2.36)
Misoprostol	118	0.2	445	0.2	0.95	(0.6-1.51)
Nutrition						
No feeding	31,663	55.2	128,549	56.4	Reference	
Enteral Nutrition	25,304	44.1	97,049	42.6	0.94	(0.79-1.12)
Parenteral Nutrition	123	0.2	772	0.3	1.55	(1.11-2.14)
Both	242	0.4	1,549	0.7	1.58	(1.2-2.08)
APACHE IV Score (Mean, SD)	40.79	18.38	45.30	19.35	1.01	(1.01-1.02)

APPENDIX II:

Appendix II Table 1: Diagnosis Strings for Types of Bleeding that excluded and included from ICD-9 code 578. **

Types of bleeding excluded	Types of bleeding included
lower GI bleeding	GI bleeding
lower GI bleeding aorto-enteric fistula	upper GI bleeding
lower GI bleeding colonic	upper GI bleeding due to unknown etiology
lower GI bleeding diverticular	upper GI bleeding due to ulcer
lower GI bleeding due to inflammation	
lower GI bleeding due to ischemia	
lower GI bleeding due to malignancy	
lower GI bleeding post procedure	
lower GI bleeding rectal	
lower GI bleeding small intestinal	
upper GI bleeding aorto-enteric	
upper GI bleeding duodenal	
upper GI bleeding esophagitis	
upper GI bleeding hepato-biliary	
upper GI bleeding post-procedure	
upper GI bleeding tumor	
lower GI bleeding postpartum	

Appendix II Table 2: Patient-day Level Univariable Analysis of ICU patients who received PPIs or H2Bs for three days.

Characteristics		Univariable Analysis	
		N=	356,147
		Freq.	Col %
Outcome	Clinically Important Gastrointestinal Bleeding	424	0.1
Exposure	Three Days of Proton Pump Inhibitors Use	258,010	72.4
	Three Days of Histamine-2 Receptors Blockers Use	98,137	27.6
Gender	Male	194,466	54.6
Age	18 To 60	150,637	42.3
	61 To 70	82,754	23.2
	71 To 80	74,536	20.9
	≥ 81	48,220	13.5
Race	Caucasian	268,387	75.4
	African American	42,593	12
	Hispanic	10,533	3
	Native American	2,732	0.8
	Asian	4,060	1.1
	Others	27,842	7.8
ICU Type	Mixed	166,624	46.8
	Cardiovascular-Surgical	29,281	8.2
	Coronary Care	62,179	17.5
	Trauma	2,915	0.8
	Surgical	30,842	8.7
	Medical	35,010	9.8
	Neuroscience	29,296	8.2
Nutrition	No Feeding	111,734	31.4
	Enteral Nutrition	200,449	56.3
	Parenteral Nutrition	3,281	0.9
	Both Enteral Nutrition and Parenteral Nutrition	40,683	11.4
Cancer		27,240	7.6
HIV		1,027	0.3
Cirrhosis		4,268	1.2
Immunosuppression		10,274	2.9
Intubated in the First Day		211,859	59.5
Risk Factors	Coagulopathy	100,379	28.2
	Mechanical Ventilation > 24 Hours	263,892	74.1
	Traumatic Brain Injury	20,584	5.8
	Hepatic Failure	3,435	1
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	17,534	4.9
	Transplantation	629	0.2
	Acute Myocardial Infarction	7,790	2.2
	Sepsis	107,509	30.2
	Neurological Injuries	63,204	17.7
	Surgical And Multiple Trauma	78,274	22
	Hypotension	113,247	31.8
	Acute Renal Failure	115,080	32.3
	Burns ≥ 30% BSA	510	0.1
	ICU LOS > 7 Days	170,787	48

Appendix II Table 2, Continued

Characteristics		Univariable Analysis	
		N=	356,147
		Freq.	Col %
Medication	Sucralfate	9,599	2.7
	Antacids	118,703	33.3
	Anticoagulants	209,532	58.8
	Antiplatelets	220,125	61.8
	Thrombolytics	32,373	9.1
	NSAIDs	200,282	56.2
Admission Source	Chest Pain Center	1,095	0.3
	Direct Admission	33,035	9.3
	Emergency Room	175,587	49.3
	Floor	62,644	17.6
	Operating Room	51,408	14.4
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	32,378	9.1
Year of Admission	2008	62,681	17.6
	2009	80,598	22.6
	2010	86,470	24.3
	2011	87,366	24.5
	2012	39,032	11
Physician Specialty	Internal medicine	55,991	15.7
	Pulmonary	72,833	20.5
	Hospitalist	30,700	8.6
	Cardiology	22,063	6.2
	Surgery-general	24,523	6.9
	Critical care medicine (CCM)	28,667	8
	Family practice	18,665	5.2
	Surgery-cardiac	14,340	4
Others	88,365	24.8	
Teaching Hospital		114,485	32.1
Continuous Variables	APACHE Score IV	71	27.6644 9
	Platelet Counts	233	134.381 9

Appendix II Table 3: Patient-Level Bivariable Analysis Comparing Three days use of PPIs to Three days use of H2Bs among ICU patients.

Characteristics		Bivariable Analyses				P-value
		H2Bs n= Freq.	20,517 Col %	PPIs n= Freq.	49,576 Col %	
Outcome	Clinically Important Gastrointestinal Bleeding	63	0.3	361	0.7	<0.001
Gender	Male	11,127	54.2	26,391	53.2	0.007
Age	18 To 60	8,505	41.5	18,648	37.6	<0.001
	61 To 70	4,552	22.2	11,380	23	
	71 To 80	4,316	21	11,130	22.5	
	≥ 81	3,144	15.3	8,418	17	
Race	Caucasian	15,271	74.4	37,952	76.6	<0.001
	African American	1,997	9.7	5,985	12.1	
	Hispanic	586	2.9	1,461	2.9	
	Native American	112	0.5	405	0.8	
	Asian	273	1.3	591	1.2	
	Others	2,278	11.1	3,182	6.4	
ICU Type	Mixed	12,165	59.3	20,933	42.2	<0.001
	Cardiovascular-Surgical	2,020	9.8	4,004	8.1	
	Coronary Care	2,907	14.2	10,139	20.5	
	Trauma	166	0.8	154	0.3	
	Surgical	1,065	5.2	4,809	9.7	
	Medical	1,074	5.2	5,730	11.6	
	Neuroscience	1,120	5.5	3,807	7.7	
Nutrition	No Feeding	8,388	40.9	17,925	36.2	<0.001
	Enteral Nutrition	11,256	54.9	27,778	56	
	Parenteral Nutrition	144	0.7	578	1.2	
	Both Enteral Nutrition and Parenteral Nutrition	729	3.6	3,295	6.6	
Cancer		1,465	7.1	4,037	8.1	<0.001
HIV		41	0.2	126	0.3	0.154
Cirrhosis		120	0.6	697	1.4	<0.001
Immunosuppression		507	2.5	1,882	3.8	<0.001
Intubated in the First Day		11,173	54.5	25,326	51.1	<0.001
Risk Factors	Coagulopathy	4,724	23	13,804	27.8	<0.001
	Mechanical Ventilation > 24 Hours	12,686	61.8	29,668	59.8	<0.001
	Traumatic Brain Injury	1,252	6.1	2,074	4.2	<0.001
	Hepatic Failure	78	0.4	512	1	<0.001
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	758	3.7	1,912	3.9	0.536
	Transplantation	27	0.1	129	0.3	<0.001
	Acute Myocardial Infarction	835	4.1	1,409	2.8	<0.001
	Sepsis	4,422	21.6	13,814	27.9	<0.001
	Neurological Injuries	3,823	18.6	6,672	13.5	<0.001
	Surgical And Multiple Trauma	5,549	27	10,635	21.5	<0.001
	Hypotension	5,060	24.7	13,689	27.6	<0.001

Appendix II Table 3, Continued

Characteristics	Bivariable Analyses				P-value	
	H2Bs n= Freq.	20,517 Col %	PPIs n= Freq.	49,576 Col %		
	Acute Renal Failure	5,031	24.5	15,308	30.9	<0.001
	Burns ≥ 30% BSA	12	0.1	8	0	0.002
	ICU LOS > 7 Days	7,270	35.4	19,337	39	<0.001
Medication	Sucralfate	302	1.5	1,402	2.8	<0.001
	Antacids	7,237	35.3	16,747	33.8	0.001
	Anticoagulants	11,500	56.1	28,014	56.5	0.725
	Antiplatelets	12,848	62.6	30,409	61.3	0.003
	Thrombolytics	1,877	9.1	3,755	7.6	<0.001
	NSAIDs	10,805	52.7	26,024	52.5	0.034
Admission Source	Chest Pain Center	82	0.4	188	0.4	<0.001
	Direct Admission	1,980	9.7	4,204	8.5	
	Emergency Room	10,332	50.4	25,020	50.5	
	Floor	2,580	12.6	8,662	17.5	
	Operating Room	3,984	19.4	7,603	15.3	
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	1,559	7.6	3,899	7.9	
Year of Admission	2008	3,065	14.9	8,226	16.6	<0.001
	2009	4,258	20.8	11,120	22.4	
	2010	5,243	25.6	12,035	24.3	
	2011	5,111	24.9	12,534	25.3	
	2012	2,840	13.8	5,661	11.4	
Physician Specialty	Internal medicine	2,307	11.2	9,708	19.6	<0.001
	Pulmonary	4,025	19.6	8,170	16.5	
	Hospitalist	1,378	6.7	5,169	10.4	
	Cardiology	1,710	8.3	3,362	6.8	
	Surgery-general	1,477	7.2	3,241	6.5	
	Critical care medicine (CCM)	1,827	8.9	3,357	6.8	
	Family practice	959	4.7	3,138	6.3	
	Surgery-cardiac	1,370	6.7	2,042	4.1	
	Others	5,464	26.6	11,389	23	
Teaching Hospital		9,726	47.4	11,467	23.1	<0.001
APACHE Score IV (Mean, SD)		66	26.82	69	26.93	<0.001
Platelet Counts		161	78.84	154	85.57	<0.001

Appendix II Table 4: Patient-day Level Bivariable Analysis Comparing Three days use of PPIs to Three days use of H2Bs among ICU patients.

Characteristics		Bivariable Analyses				P-value
		H2Bs n= Freq.	98137 Col %	PPIs n= Freq.	258,010 Col %	
Outcome	Clinically Important					
	Gastrointestinal Bleeding	63	0.06	361	0.14	<0.001
Gender	Male	54,059	55.1	140,407	54.4	<0.001
Age	18 To 60	45,472	46.3	105,165	40.8	<0.001
	61 To 70	21,384	21.8	61,370	23.8	
	71 To 80	18,879	19.2	55,657	21.6	
	≥ 81	12,402	12.6	35,818	13.9	
Race	Caucasian	74,083	75.5	194,304	75.3	<0.001
	African American	9,534	9.7	33,059	12.8	
	Hispanic	2,676	2.7	7,857	3	
	Native American	509	0.5	2,223	0.9	
	Asian	1,105	1.1	2,955	1.1	
	Others	10,230	10.4	17,612	6.8	
ICU Type	Mixed	59,647	60.8	106,977	41.5	<0.001
	Cardiovascular-Surgical	8,388	8.5	20,893	8.1	
	Coronary Care	11,896	12.1	50,283	19.5	
	Trauma	1,531	1.6	1,384	0.5	
	Surgical	5,130	5.2	25,712	10	
	Medical	4,709	4.8	30,301	11.7	
	Neuroscience	6,836	7	22,460	8.7	
Nutrition	No Feeding	32,453	33.1	79,281	30.7	<0.001
	Enteral Nutrition	57,474	58.6	142,975	55.4	
	Parenteral Nutrition	663	0.7	2,618	1	
	Both Enteral Nutrition and Parenteral Nutrition	7,547	7.7	33,136	12.8	
Cancer		6,537	6.7	20,703	8	<0.001
HIV		284	0.3	743	0.3	0.461
Cirrhosis		514	0.5	3,754	1.5	<0.001
Immunosuppression		1,860	1.9	8,414	3.3	<0.001
Intubated in the First Day		59,566	60.7	152,293	59	<0.001
Risk Factors	Coagulopathy	22,727	23.2	77,652	30.1	<0.001
	Mechanical Ventilation > 24 Hours	72,393	73.8	191,499	74.2	<0.001
	Traumatic Brain Injury	7,839	8	12,745	4.9	<0.001
	Hepatic Failure	369	0.4	3,066	1.2	<0.001
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	4,648	4.7	12,886	5	0.122
	Transplantation	61	0.1	568	0.2	<0.001
	Acute Myocardial Infarction	2,648	2.7	5,142	2	<0.001
	Sepsis	25,057	25.5	82,452	32	<0.001
	Neurological Injuries	23,532	24	39,672	15.4	<0.001
	Surgical And Multiple Trauma	24,421	24.9	53,853	20.9	<0.001
	Hypotension	28,861	29.4	84,386	32.7	<0.001

Appendix II Table 4, Continued

Characteristics	Bivariable Analyses					
	H2Bs		PPIs		P-value	
	n=	98137	n=	258,010		
Freq.	Col %	Freq.	Col %			
	Acute Renal Failure	26,573	27.1	88,507	34.3	<0.001
	Burns ≥ 30% BSA	309	0.3	201	0.1	<0.001
	ICU LOS > 7 Days	45,158	46	125,629	48.7	<0.001
Medication	Sucralfate	1,388	1.4	8,211	3.2	<0.001
	Antacids	33,276	33.9	85,427	33.1	<0.001
	Anticoagulants	56,244	57.3	153,288	59.4	<0.001
	Antiplatelets	59,900	61	160,225	62.1	<0.001
	Thrombolytics	9,254	9.4	23,119	9	<0.001
	NSAIDs	54,467	55.5	145,815	56.5	0.123
Admission Source	Chest Pain Center	370	0.4	725	0.3	<0.001
	Direct Admission	10,102	10.3	22,933	8.9	
	Emergency Room	50,329	51.3	125,258	48.5	
	Floor	13,711	14	48,933	19	
	Operating Room	15,678	16	35,730	13.8	
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	7,947	8.1	24,431	9.5	
Year of Admission	2008	15,459	15.8	47,222	18.3	<0.001
	2009	20,750	21.1	59,848	23.2	
	2010	25,385	25.9	61,085	23.7	
	2011	23,826	24.3	63,540	24.6	
	2012	12,717	13	26,315	10.2	
Physician Specialty	Internal medicine	8,980	9.2	47,011	18.2	<0.001
	Pulmonary	22,334	22.8	50,499	19.6	
	Hospitalist	5,889	6	24,811	9.6	
	Cardiology	6,077	6.2	15,986	6.2	
	Surgery-general	7,200	7.3	17,323	6.7	
	Critical care medicine (CCM)	10,089	10.3	18,578	7.2	
	Family practice	3,784	3.9	14,881	5.8	
	Surgery-cardiac	5,025	5.1	9,315	3.6	
	Others	28,759	29.3	59,606	23.1	
Teaching Hospital		52,215	53.2	62,270	24.1	<0.001
APACHE Score IV		68	27.509	72	27.643	<0.001
Platelet Counts		248	135.72	227	133.4	<0.001

Instrumental variable analysis:

Objective: To construct an IV that is highly correlated with the receipt of PPIs for three days and uncorrelated with unmeasured factors that may influence the occurrence of CIGIB.

While the first condition can be tested, the second condition can only be supported by the literature and the logic used in constructing the IV. The chosen IV was being in a PPI unit defined as a unit that prescribed PPIs to at least 90% of patients. When at least 90% of patients receive PPIs, it is most likely that prescribing decision was related to the ICU practice rather than patients' characteristics. Therefore, such IV should suffice the two aforementioned conditions. The cutoff of 90% was chosen to reflect this logic i.e. being in a PPI unit should be highly correlated with the receipt of PPIs. In addition, it reduces the possibility that the IV is associated with any unobserved factor that may influence CIGIB. Although this assumption cannot be tested, the results from the IV analysis can be used as an affirmative approach for the main analysis. In constructing this IV, number of patients in each unit per calendar year was determined to form the denominator. Next, number of patients who received PPIs in each of these units formed the numerator which was multiplied by 100 to calculate the percentage.

The model used in the first stage:

$$\text{Logit } \{\text{Pr } (Y=1)\} = \beta_0 + \beta_1 \text{PPIUNIT90} + \beta_2 \text{DEMOG} + \beta_3 \text{SURF} + \beta_4 \text{CONDITIONS} + \beta_5 \text{ICUTYPE} + \beta_6 \text{PHYSICIAN} + \beta_7 \text{TEACHING} + \mu$$

Where:

PPIUNIT90: A dummy variable for being in an ICU that prescribed PPIs to at least 90% of the patients.

DEMOG: A vector of categorical variables for patients' demographics (gender, race, age).

SURF: A vector of dummy variables for stress ulcer risk factors (mechanical ventilation > 24 hrs. , coagulopathy, major head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week)

CONDITIONS: A vector of dummy variable for conditions that may affect treatment selection (enteral nutrition, immunosuppression)

ICUTYPE: A categorical variable for ICU type (medical, surgical, mixed, trauma, cardiovascular and neurosciences)

PHYSICIAN: A categorical variable for physician specialty (Internal medicine, pulmonary, hospitalist, cardiology, surgery-general, critical care medicine, family practice, surgery-cardiac, others)

TEACHING: A dummy variable for the teaching status of the admitting hospital.

Testing the presence of the correlation between the IV and the receipt of PPIs for three days:

The two-stage least square (2SLS) method was used to calculate partial F-statistics which determines whether or not the IV add any significant addition to the model of the first stage. As a rule of thumb, if the F-test that is greater than 10 then it is strongly correlated with the exposure. Although the 2SLS method should only be used when the exposure is a continuous variable, the partial F-statistic still provides a valid estimation for the

strength of the correlation between the exposure and the IV. In our analysis, the partial F-statistic, adjusted for the clustering effect of the unit, was 53.54 indicating a strong correlation between the IV and the receipt of PPIs for three days. This strong correlation corresponded to an adjusted OR of 13.44 (95%CI: 10.92-16.54) in the first stage multivariable logistic regression model (Appendix II Table 5).

Appendix II Table 5: : Model for predicting Three use of PPIs vs Three use of H2Bs using Instrumental variable Technique

Characteristics	OR	95%CI
IV	ICUs that prescribed to 90% of patients or more PPIs	13.44*** [10.92,16.54]
Gender	Female	Reference
	Male	0.951 [0.899,1.007]
Age	18 To 60	Reference
	61 To 70	1.198*** [1.101,1.304]
	71 To 80	1.181*** [1.084,1.288]
	≥ 81	1.121* [1.020,1.233]
Race	Caucasian	Reference
	African American	0.985 [0.851,1.141]
	Hispanic	1.035 [0.788,1.361]
	Native American	1.128 [0.886,1.435]
	Asian	1.864** [1.243,2.794]
	Others	0.673*** [0.539,0.840]
ICU Type	Mixed	Reference
	Cardiovascular-Surgical	0.341** [0.179,0.649]
	Coronary Care	0.845 [0.598,1.194]
	Trauma	0.827 [0.624,1.096]
	Surgical	0.992 [0.645,1.526]
	Medical	0.526*** [0.415,0.665]
	Neuroscience	0.975 [0.638,1.492]
Nutrition	No Feeding	Reference
	Enteral Nutrition	1.147 [0.953,1.381]
	Parenteral Nutrition	1.800*** [1.429,2.266]
Cirrhosis		2.368*** [1.691,3.314]
Immunosuppression		1.681*** [1.359,2.078]
Risk Factors	Coagulopathy	1.371*** [1.268,1.483]
	Mechanical Ventilation > 24 Hours	1.065 [0.978,1.159]
	Traumatic Brain Injury	0.931 [0.741,1.171]
	Hepatic Failure	2.770*** [1.864,4.116]
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	1.077 [0.917,1.266]
	Acute Myocardial Infarction	0.574*** [0.460,0.717]
	Sepsis	1.142** [1.044,1.248]
	Neurological Injuries	0.629*** [0.550,0.720]

Appendix II Table 5, Continued		
Characteristics	OR	95%CI
Surgical And Multiple Trauma	0.746***	[0.664,0.838]
Hypotension	0.997	[0.909,1.094]
Acute Renal Failure	1.338***	[1.240,1.444]
Medication		
Sucralfate	2.605***	[1.909,3.555]
Antacids	1.031	[0.936,1.135]
NSAIDs	1.048	[0.929,1.182]
Physician Specialty		
Internal medicine	Reference	
Pulmonary	0.492***	[0.410,0.590]
Hospitalist	0.626***	[0.523,0.750]
Cardiology	0.617***	[0.502,0.758]
Surgery-general	0.602***	[0.485,0.748]
Critical care medicine	0.477***	[0.336,0.676]
Family practice	0.701***	[0.588,0.834]
Surgery-cardiac	0.372***	[0.260,0.533]
Others	0.500***	[0.433,0.578]
Teaching Hospital Observations	0.495***	[0.406,0.603]
	356147	

* p<0.05, ** p<0.01, *** p<0.001, IV: Instrumental Variable, ICUs: Intensive Care Units, PPIs: Proton Pump Inhibitors, NSAIDs: Non-Steroidal Anti-inflammatory

The C-statistic which measures the ability of the model to discriminate patients who received PPIs for three days vs. patients who received H2Bs for three days at each time point was 0.798% indicating an acceptable level of discrimination. Even when a patient-level file was used to run the model the C-statistic showed an acceptable discrimination with a value of 0.77. The residuals calculated from the first stage were Pearson's residuals adjusted for the number of patients who shares the same covariate pattern²⁰⁸.

The model for the 2nd stage:

$$\text{Log } h(t) = \log \lambda_0(t) + \beta_1 \text{PPI} + \beta_2 \text{H2B} + \beta_3 \text{SURF} + \beta_4 \text{CONDITIONS1} + \beta_5 \text{MEDS} + \beta_6 \text{PHYSICIAN} + \beta_7 \text{ADMISSIONS} + \beta_8 \text{YEAR} + \beta_9 \text{APACHEIV} + \beta_{10} \text{PLT}$$

Where:

PPISVSH2Bs: Three days of PPIs therapy vs. Three days of H2Bs therapy.

PRESIDUALS: Pearson's Residuals adjusted for the number of patients sharing the same covariates pattern.

CONDITIONS1: A vector of dummy variables for conditions that may influence risk of CIGIB (Cancer, HIV/AIDS, cirrhosis and immunosuppression)

MEDS: A vector of dummy variables for therapeutic classes that may influence risk of CIGIB (Sucralfate, antacids, anticoagulants, anti-platelets, thrombolytics and NSAIDs)

ADMISSIONS: A categorical variable for admission source (Direct admission, chest pain center, emergency room, floor, operating room and others (other hospital or ICU, recovery room, step-down unit))

YEAR: A categorical variable for year of admission

APACHEIV: A continuous variable for APACHE-IV score

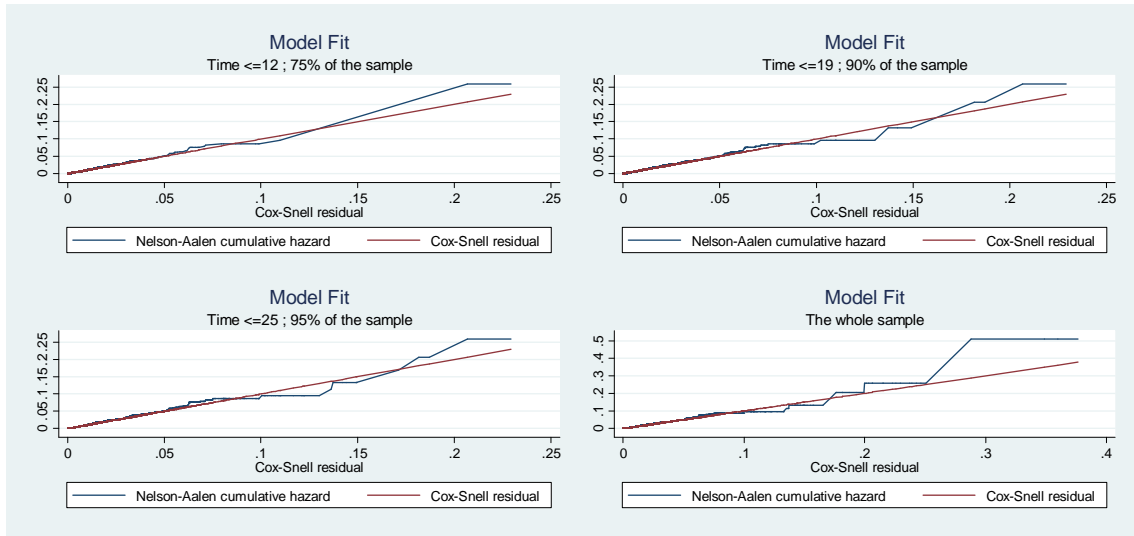
PLT: A continuous variable for platelet counts.

Model fit was assessed by comparing the concordance of Cox-Snell residuals and Nelson-Aalen cumulative hazard which indicates good model fit to the data. Based on figure (1), the model fits very well for the majority of patients with ICU length of stay less than 19 who represented 90% of the whole sample.

Appendix II Table 6: Cox Proportional Hazard model for the effect of the receipt of Three days PPIs vs. Three days H2Bs using the Two Stage Residuals inclusion Method.

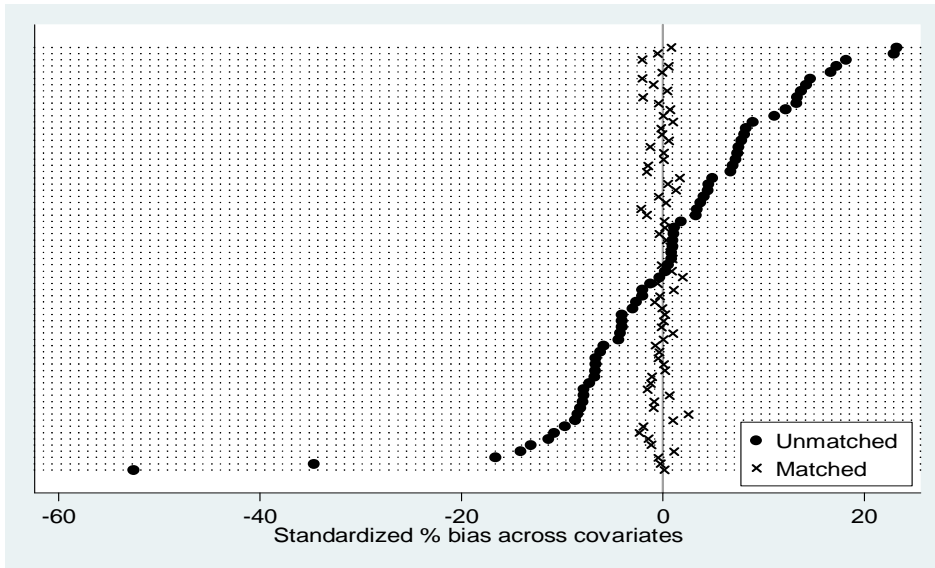
Characteristics		HR	95%CI
Exposure	Three-day use of PPIs vs. Three-day use of H2Bs	2.374***	[1.608,3.505]
Residuals	Pearson's Residual	0.955**	[0.928,0.983]
Cancer		1.299	[0.951,1.775]
HIV/AIDS		0.99	[0.234,4.183]
Cirrhosis		1.321	[0.717,2.433]
Immunosuppression		0.837	[0.509,1.377]
Intubated in the First Day		0.801	[0.613,1.045]
Risk Factors	Coagulopathy	1.168	[0.922,1.481]
	Mechanical Ventilation > 24 Hours	0.786	[0.609,1.014]
	Traumatic Brain Injury	0.644	[0.284,1.457]
	Hepatic Failure	1.215	[0.712,2.076]
	Hydrocortisone \geq 250 Mg / Day or Equivalent	1.096	[0.699,1.716]
	Acute Myocardial Infarction	1.412	[0.790,2.523]
	Sepsis	1.022	[0.799,1.308]
	Neurological Injuries	0.926	[0.675,1.270]
	Surgical And Multiple Trauma	0.460*	[0.245,0.863]
	Hypotension	1.21	[0.942,1.554]
	Acute Renal Failure	1.610***	[1.304,1.987]
Medication	Sucralfate	3.114***	[2.032,4.772]
	Antacids	0.925	[0.738,1.160]
	Anticoagulants	0.809	[0.613,1.068]
	Antiplatelets	1.393*	[1.049,1.849]
	Thrombolytics	0.889	[0.615,1.285]
	NSAIDs	0.958	[0.763,1.203]
Admission Source	Direct Admission	.	
	Chest Pain Center	1.157	[0.210,6.357]
	Emergency Room	1.381	[0.958,1.993]
	Floor	1.33	[0.876,2.018]
	Operating Room	2.077	[0.970,4.446]
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	1.135	[0.674,1.910]
Year of Admission	2008	.	
	2009	1.378	[0.971,1.954]
	2010	1.436*	[1.012,2.037]
	2011	1.269	[0.907,1.777]
	2012	1.171	[0.737,1.861]
Physician Specialty	Internal medicine	.	
	Pulmonary	1.298	[0.931,1.808]
	Hospitalist	1.095	[0.729,1.644]
	Cardiology	0.826	[0.492,1.389]
	Surgery-general	0.737	[0.407,1.336]
	Critical care medicine	1.506*	[1.015,2.234]
	Family practice	1.267	[0.782,2.053]
	Surgery-cardiac	0.85	[0.415,1.739]
	Others	1.086	[0.786,1.502]
Continuous Variables	APACHE Score IV	1.004*	[1.001,1.008]
	Platelet Counts	0.998***	[0.997,0.999]
Observations		356147	

Appendix II Figure 1: Model fit for the effect of the receipt of Three days PPIs vs. Three days H2Bs using the Two Stage Residuals inclusion Method.

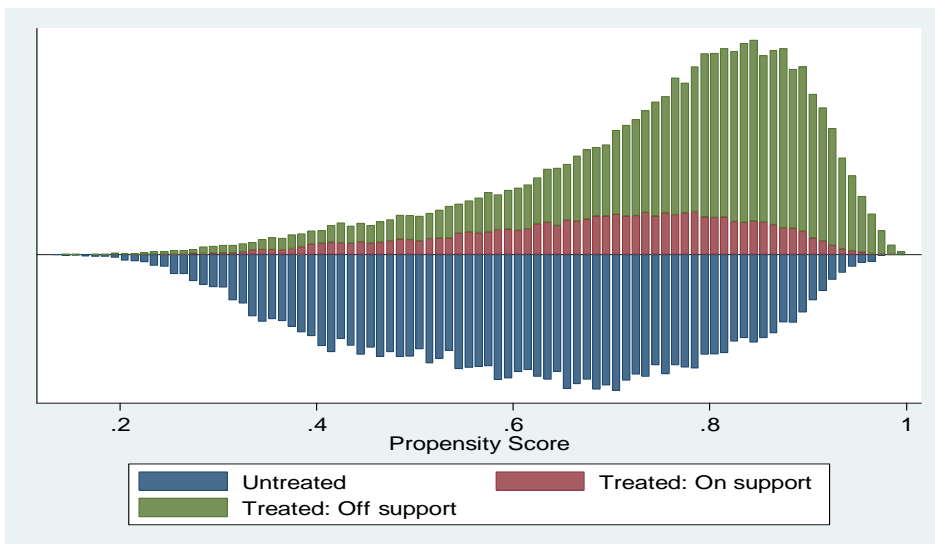


Propensity Score matching:

Appendix II Figure 1: Covariate Balance before and after Performing One to One Matching with No Replacement



Appendix II Figure 2: Propensity Score Distribution among patients who received Proton Pump Inhibitors for Three days, labeled as Treated, and patients who received Histamine Type-2 receptor Blockers for three days (labeled as untreated)



Appendix II Table 7: Covariate Distribution Before and After performing one to one matching with not replacement.

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=	n=				
			11,588	11,588				
Male	Unmatched		0.532	0.542	-2.000		-2.410	0.016
	Matched		0.534	0.536	-0.300	85.300	-0.220	0.823
Age	18 To 60	Unmatched	0.376	0.415	-7.900		-9.500	0.000
	Matched		0.383	0.380	0.700	91.200	0.530	0.598
61 To 70	Unmatched		0.230	0.222	1.800		2.210	0.027
	Matched		0.233	0.233	0.200	91.000	0.120	0.901
71 To 80	Unmatched		0.225	0.210	3.400		4.110	0.000
	Matched		0.218	0.227	-2.200	37.100	-1.630	0.104
≥ 81	Unmatched		0.170	0.153	4.500		5.380	0.000
	Matched		0.165	0.160	1.300	70.800	1.000	0.319
Race	Caucasian	Unmatched	0.766	0.744	4.900		5.980	0.000
	Matched		0.763	0.755	1.700	65.400	1.310	0.192
African American	Unmatched		0.121	0.097	7.500		8.870	0.000
	Matched		0.107	0.110	-1.200	83.400	-0.950	0.342
Hispanic	Unmatched		0.029	0.029	0.500		0.650	0.516
	Matched		0.031	0.031	-0.100	81.000	-0.080	0.940
Native American	Unmatched		0.008	0.005	3.300		3.820	0.000
	Matched		0.006	0.007	-1.600	52.200	-1.210	0.227
Asian	Unmatched		0.012	0.013	-1.200		-1.510	0.131
	Matched		0.013	0.014	-0.500	56.400	-0.400	0.689
Others	Unmatched		0.064	0.111	-16.600		-21.120	0.000
	Matched		0.080	0.082	-0.500	97.100	-0.380	0.700
ICU Type	Mixed	Unmatched	0.422	0.593	-34.600		-41.690	0.000
	Matched		0.515	0.516	-0.200	99.300	-0.180	0.854
Cardiovascular-Surgical	Unmatched		0.081	0.098	-6.200		-7.610	0.000
	Matched		0.091	0.092	-0.300	94.600	-0.250	0.802
Coronary Care	Unmatched		0.205	0.142	16.700		19.500	0.000
	Matched		0.173	0.173	-0.100	99.500	-0.070	0.945
Trauma	Unmatched		0.003	0.008	-6.700		-8.910	0.000
	Matched		0.005	0.005	0.100	98.300	0.100	0.924

Appendix II Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=11,588	n=11,588				
Surgical	Unmatched		0.097	0.052	17.200		19.660	0.000
	Matched		0.074	0.073	0.600	96.700	0.430	0.669
Medical	Unmatched		0.116	0.052	22.900		25.850	0.000
	Matched		0.072	0.073	-0.500	97.700	-0.430	0.667
Neuroscience	Unmatched		0.077	0.055	9.000		10.470	0.000
	Matched		0.070	0.067	1.000	89.100	0.730	0.467
Nutrition	No Feeding	Unmatched	0.362	0.409	-9.700		-11.770	0.000
		Matched	0.394	0.403	-1.900	80.100	-1.460	0.144
Enteral Nutrition	Unmatched		0.552	0.517	7.000		8.390	0.000
	Matched		0.523	0.530	-1.500	78.600	-1.130	0.258
Parenteral Nutrition	Unmatched		0.046	0.023	12.200		13.860	0.000
	Matched		0.031	0.030	0.700	94.200	0.570	0.566
Cancer	Unmatched		0.076	0.066	3.700		4.450	0.000
	Matched		0.071	0.070	0.300	91.900	0.230	0.817
HIV	Unmatched		0.002	0.002	1.200		1.370	0.170
	Matched		0.002	0.002	0.200	83.600	0.140	0.886
Cirrhosis	Unmatched		0.014	0.006	8.300		9.220	0.000
	Matched		0.008	0.008	-0.200	97.900	-0.150	0.881
Neutropenia	Unmatched		0.062	0.079	-6.600		-8.180	0.000
	Matched		0.064	0.065	-0.400	93.400	-0.350	0.727
Thrombocytopenia	Unmatched		0.204	0.136	18.200		21.260	0.000
	Matched		0.159	0.167	-2.100	88.700	-1.580	0.113
Immunosuppression	Unmatched		0.037	0.024	7.400		8.560	0.000
	Matched		0.031	0.031	0.100	98.600	0.080	0.939
Intubated in the First Day	Unmatched		0.511	0.545	-6.800		-8.130	0.000
	Matched		0.526	0.531	-1.100	84.100	-0.820	0.415
Risk Factors	Coagulopathy	Unmatched	0.278	0.230	11.100		13.180	0.000
		Matched	0.253	0.253	0.100	99.500	0.050	0.964
Mechanical Ventilation > 24 Hours	Unmatched		0.598	0.618	-4.100		-4.900	0.000
	Matched		0.607	0.606	0.100	98.300	0.050	0.957

Appendix II Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=	n=				
Traumatic Brain Injury	Unmatched	0.042	0.061	-8.700		-10.880	0.000	
	Matched	0.046	0.044	1.000	88.300	0.820	0.411	
Hepatic Failure	Unmatched	0.010	0.004	7.800		8.610	0.000	
	Matched	0.005	0.005	0.600	92.100	0.560	0.573	
Hydrocortisone \geq 250 Mg / Day or Equivalent	Unmatched	0.039	0.037	0.900		1.020	0.307	
	Matched	0.038	0.036	1.000	-11.700	0.730	0.464	
Acute Myocardial Infarction	Unmatched	0.028	0.041	-6.700		-8.410	0.000	
	Matched	0.038	0.037	0.200	96.500	0.170	0.863	
Sepsis	Unmatched	0.279	0.216	14.700		17.370	0.000	
	Matched	0.239	0.248	-2.100	85.900	-1.580	0.115	
Neurological Injuries	Unmatched	0.135	0.186	-14.100		-17.510	0.000	
	Matched	0.146	0.142	1.100	92.000	0.900	0.370	
Surgical And Multiple Trauma	Unmatched	0.215	0.270	-13.100		-16.020	0.000	
	Matched	0.246	0.251	-1.200	91.100	-0.880	0.378	
Hypotension	Unmatched	0.276	0.247	6.700		8.030	0.000	
	Matched	0.251	0.258	-1.600	76.000	-1.240	0.216	
Acute Renal Failure	Unmatched	0.309	0.245	14.200		16.910	0.000	
	Matched	0.270	0.274	-0.900	93.600	-0.690	0.488	
ICU los > 7 days	Unmatched	0.011	0.010	1.100		1.310	0.190	
	Matched	0.011	0.011	-0.300	69.200	-0.260	0.798	
Medications	Sucralfate	Unmatched	0.023	0.013	8.100		9.220	0.000
		Matched	0.018	0.018	-0.100	99.200	-0.050	0.960
Antacids	Unmatched	0.277	0.297	-4.400		-5.340	0.000	
	Matched	0.292	0.292	0.100	98.700	0.040	0.965	
Anticoagulants	Unmatched	0.496	0.491	1.000		1.200	0.228	
	Matched	0.495	0.493	0.400	60.300	0.300	0.763	
Antiplatelets	Unmatched	0.556	0.566	-2.000		-2.400	0.016	
	Matched	0.572	0.567	1.100	46.000	0.820	0.411	

Appendix II Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=	n=				
Thrombolytics	Unmatched	0.051	0.070	-7.800		-9.730	0.000	
	Matched	0.060	0.064	-1.600	80.100	-1.170	0.240	
NSAIDs	Unmatched	0.470	0.491	-4.000		-4.870	0.000	
	Matched	0.469	0.468	0.200	94.400	0.170	0.864	
Admission Source	Direct Admission	Unmatched	0.004	0.004	-0.300		-0.400	0.691
		Matched	0.005	0.004	1.900	-490.700	1.330	0.185
Chest Pain Center	Unmatched	0.085	0.097	-4.100		-4.970	0.000	
	Matched	0.086	0.086	-0.100	97.100	-0.090	0.925	
Emergency Room	Unmatched	0.505	0.504	0.200		0.260	0.791	
	Matched	0.498	0.493	0.900	-301.100	0.670	0.503	
Floor	Unmatched	0.175	0.126	13.700		16.110	0.000	
	Matched	0.152	0.150	0.500	96.700	0.350	0.727	
Operating Room	Unmatched	0.153	0.194	-10.800		-13.250	0.000	
	Matched	0.180	0.189	-2.300	78.400	-1.730	0.084	
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	Unmatched	0.079	0.076	1.000		1.200	0.232	
	Matched	0.080	0.078	0.700	28.700	0.540	0.591	
Year of Admission	2008	Unmatched	0.166	0.149	4.500		5.420	0.000
		Matched	0.154	0.152	0.500	89.000	0.380	0.701
2009	Unmatched	0.224	0.208	4.100		4.880	0.000	
	Matched	0.213	0.215	-0.400	90.200	-0.300	0.761	
2010	Unmatched	0.243	0.256	-3.000		-3.570	0.000	
	Matched	0.249	0.249	-0.100	98.000	-0.050	0.964	
2011	Unmatched	0.253	0.249	0.900		1.030	0.303	
	Matched	0.254	0.250	0.900	-9.200	0.710	0.477	
2012	Unmatched	0.114	0.138	-7.300		-8.950	0.000	
	Matched	0.131	0.135	-1.200	83.600	-0.890	0.373	
Physician Specialty	Internal medicine	Unmatched	0.196	0.112	23.200		26.790	0.000
		Matched	0.157	0.154	0.800	96.400	0.640	0.525
Pulmonary	Unmatched	0.165	0.196	-8.200		-9.980	0.000	

Appendix II Table 7, Continued

Characteristics		Mean		%bias	% of Bias Reduction	t-test	
		PPIs	H2Bs			t	p> t
		n=11,588	n=11,588				
Hospitalist	Matched	0.177	0.180	-0.900	89.000	-0.690	0.493
	Unmatched	0.104	0.067	13.300		15.380	0.000
Cardiology	Matched	0.084	0.085	-0.400	96.700	-0.330	0.741
	Unmatched	0.068	0.083	-5.900		-7.220	0.000
Surgery-general	Matched	0.080	0.082	-0.800	87.200	-0.550	0.580
	Unmatched	0.065	0.072	-2.600		-3.180	0.001
Critical care medicine (CCM)	Matched	0.071	0.073	-0.800	70.000	-0.580	0.560
	Unmatched	0.068	0.089	-7.900		-9.830	0.000
Family practice	Matched	0.073	0.076	-0.900	89.100	-0.670	0.500
	Unmatched	0.063	0.047	7.300		8.510	0.000
Surgery-cardiac	Matched	0.060	0.059	0.100	98.400	0.080	0.934
	Unmatched	0.041	0.067	-11.300		-14.340	0.000
Others	Matched	0.053	0.056	-1.500	87.200	-1.100	0.272
	Unmatched	0.230	0.266	-8.500		-10.320	0.000
APACHE Score IV	Matched	0.24577	0.23481	2.5	70	1.95	0.051
	Unmatched	69.267	65.672	13.400		16.100	0.000
Platelet Counts	Matched	66.982	67.519	-2.000	85.100	-1.530	0.126
	Unmatched	168.090	171.790	-4.200		-4.980	0.000
Teaching Hospital	Matched	172.160	171.260	1.000	75.900	0.760	0.448
	Unmatched	0.231	0.474	-52.500		-65.590	0.000
	Matched	0.333	0.332	0.200	99.700	0.130	0.900

Appendix II Table 8: The Hazard ratio and 95% Confidence Intervals for the effect of Three-day use of PPIs compared to Three-day use of H2Bs adjusting for an unmeasured dichotomous confounder with a hazard ratio of 2.

P_1	P_0					
	0.0	0.1	0.2	0.3	0.4	0.5
0.0	1.97 (1.46,2.63)					
0.1	1.79 (1.33,2.39)	1.97 (1.46,2.63)				
0.2	1.64 (1.22,2.19)	1.81 (1.34,2.41)	1.97 (1.46,2.63)			
0.3	1.52 (1.12,2.02)	1.67 (1.24,2.23)	1.82 (1.35,2.43)	1.97 (1.46,2.63)		
0.4	1.41 (1.04,1.88)	1.55 (1.15,2.07)	1.69 (1.25,2.25)	1.83 (1.36,2.44)	1.97 (1.46,2.63)	
0.5	1.31 (0.97,1.75)	1.44 (1.07,1.93)	1.58 (1.17,2.1)	1.71 (1.27,2.28)	1.84 (1.36,2.45)	1.97 (1.46,2.63)
0.6	1.23 (0.91,1.64)	1.35 (1.00,1.81)	1.48 (1.1,1.97)	1.60 (1.19,2.14)	1.72 (1.28,2.3)	1.85 (1.37,2.47)
0.7	1.16 (0.86,1.55)	1.27 (0.94,1.7)	1.39 (1.03,1.86)	1.51 (1.12,2.01)	1.62 (1.2,2.17)	1.74 (1.29,2.32)
0.8	1.09 (0.81,1.46)	1.20 (0.89,1.61)	1.31 (0.97,1.75)	1.42 (1.05,1.9)	1.53 (1.14,2.05)	1.64 (1.22,2.19)
0.9	1.02 (0.76,1.37)	1.14 (0.85,1.52)	1.24 (0.92,1.66)	1.35 (1.00,1.8)	1.45 (1.08,1.94)	1.56 (1.15,2.08)
1.0	0.95 (0.76,1.37)	1.08 (0.8,1.45)	1.18 (0.88,1.58)	1.28 (0.95,1.71)	1.38 (1.02,1.84)	1.48 (1.08,1.97)

P_0 and P_1 are the prevalence of the unmeasured confounder in the H2Bs group and the PPIs group, respectively; PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 Receptors Blockers
 Red color: higher risk of CIGIB with PPIs; Green color: No difference between PPIs and H2Bs; Blue: lower risk of CIGIB with PPIs.

APPENDIX III:

Nosocomial Pneumonia:

Appendix III Table 1: Diagnosis Strings for Types of pneumonia that will be excluded and included from ICD-9 code 481-486

ICD-9 code	Diagnosis strings to be excluded	ICD-9 code	Diagnosis strings to be included
481	infectious diseases chest/pulmonary infections pneumonia community-acquired bacterial pneumococcus	481	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator associated) bacterial pneumococcus
481	pulmonary pulmonary infections pneumonia community-acquired bacterial pneumococcus	481	pulmonary pulmonary infections pneumonia ventilator-associated bacterial pneumococcus
482.2	infectious diseases chest/pulmonary infections pneumonia community-acquired bacterial H influenzae	482.2	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) bacterial H influenzae
482.2	pulmonary pulmonary infections pneumonia community-acquired bacterial H influenzae	482.2	pulmonary pulmonary infections pneumonia ventilator-associated bacterial H influenzae
482.31	infectious diseases chest/pulmonary infections pneumonia community-acquired bacterial group A strep	482.31	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) bacterial group A strep
482.31	pulmonary pulmonary infections pneumonia community-acquired bacterial group A strep	482.31	pulmonary pulmonary infections pneumonia ventilator-associated bacterial group A strep
482.41	infectious diseases chest/pulmonary infections pneumonia community-acquired bacterial staph aureus	482.41	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) bacterial staph aureus
482.41	pulmonary pulmonary infections pneumonia community-acquired bacterial staph aureus	482.41	pulmonary pulmonary infections pneumonia ventilator-associated bacterial staph aureus
482.83	infectious diseases chest/pulmonary infections pneumonia community-acquired bacterial gram negative rod	482.83	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) bacterial gram negative rod
482.83	pulmonary pulmonary infections pneumonia community-acquired bacterial gram negative rod	482.83	pulmonary pulmonary infections pneumonia ventilator-associated bacterial gram negative rod
482.84	infectious diseases chest/pulmonary infections pneumonia community-acquired legionella	482.84	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) legionella
482.84	pulmonary pulmonary infections pneumonia community-acquired legionella	483.0	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) mycoplasma
483.0	infectious diseases chest/pulmonary infections pneumonia community-acquired mycoplasma	483.0	pulmonary pulmonary infections pneumonia ventilator-associated mycoplasma

Appendix III Table 1, Continued

ICD-9 code	Diagnosis strings to be excluded	ICD-9 code	Diagnosis strings to be included
483.0	pulmonary pulmonary infections pneumonia community-acquired mycoplasma	486	infectious diseases chest/pulmonary infections pneumonia
483.1	infectious diseases chest/pulmonary infections pneumonia community-acquired chlamydial	486	infectious diseases chest/pulmonary infections pneumonia hospital acquired (not ventilator-associated)
483.1	pulmonary pulmonary infections pneumonia community-acquired chlamydial	486	infectious diseases chest/pulmonary infections pneumonia opportunistic
484.1, 078.5	infectious diseases chest/pulmonary infections pneumonia opportunistic CMV	486	infectious diseases chest/pulmonary infections pneumonia ventilator-associated
484.6, 117.3	infectious diseases chest/pulmonary infections pneumonia opportunistic fungal aspergillus	486	pulmonary pulmonary infections pneumonia
484.6, 117.3	pulmonary pulmonary infections pneumonia opportunistic fungal aspergillus	486	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated)
484.7, 114.0	pulmonary pulmonary infections pneumonia opportunistic fungal coccidiomycosis	486	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) atypical organism likely
484.7, 484.7, 484.7, 484.7	infectious diseases chest/pulmonary infections pneumonia opportunistic fungal	486	pulmonary pulmonary infections pneumonia opportunistic
484.7, 484.7, 484.7, 484.7	pulmonary pulmonary infections pneumonia opportunistic fungal	486	pulmonary pulmonary infections pneumonia ventilator-associated
486	infectious diseases chest/pulmonary infections pneumonia community-acquired	486	pulmonary pulmonary infections pneumonia ventilator-associated atypical organism likely
486	infectious diseases chest/pulmonary infections pneumonia community-acquired atypical organism likely	486	pulmonary pulmonary infections pneumonia hospital acquired (not ventilator-associated) bacterial
486	infectious diseases chest/pulmonary infections pneumonia post-obstructive	486	pulmonary pulmonary infections pneumonia ventilator-associated bacterial
486	pulmonary pulmonary infections pneumonia community-acquired		
486	pulmonary pulmonary infections pneumonia community-acquired atypical organism likely		
486	pulmonary pulmonary infections pneumonia post-obstructive		
486	surgery infections pneumonia		
486	surgery infections pneumonia community-acquired		
486	surgery infections pneumonia hospital acquired (not ventilator-associated)		

Appendix III Table 1, Continued

ICD-9 code	Diagnosis strings to be excluded	ICD-9 code	Diagnosis strings to be included
486	surgery infections pneumonia ventilator-associated		
486	infectious diseases chest pulmonary infections pneumonia community-acquired bacterial		
486	pulmonary pulmonary infections pneumonia community-acquired bacterial		

Appendix III Table 2: Patient-day Level Univariable Analysis of ICU patients in Nosocomial Pneumonia cohort.

Characteristics		Univariable Analysis	
		N=	285,033
		Freq.	Col %
Outcome	Nosocomial Pneumonia	2,393	0.8
Exposure	Three Days of Proton Pump Inhibitors Use	210,111	73.7
	Three Days of Histamine-2 Receptors Blockers Use	74,922	26.3
Gender	Male	36,164	53.3
Age	18 To 60	26,468	39
	61 To 70	15,414	22.7
	71 To 80	14,846	21.9
	≥ 81	11,148	16.4
Race	Caucasian	51,669	76.1
	African American	7,706	11.4
	Hispanic	1,939	2.9
	Native American	467	0.7
	Asian	849	1.3
	Others	5,246	7.7
ICU Type	Mixed	30,606	45.1
	Cardiovascular-Surgical	6,166	9.1
	Coronary Care	12,597	18.6
	Trauma	406	0.6
	Surgical	6,166	9.1
	Medical	6,673	9.8
	Neuroscience	5,262	7.8
Nutrition	No Feeding	28,106	41.4
	Enteral Nutrition	35,398	52.2
	Parenteral Nutrition	747	1.1
	Both Enteral Nutrition and Parenteral Nutrition	3,625	5.3
Any Gastrointestinal Diseases		1,855	2.7
Cancer		4,799	7.1
HIV		88	0.1
Cirrhosis		1,026	1.5
Asthma		1,648	2.4
COPD		8,061	11.9
ARDS		22,488	33.1
Heart Failure		8,488	12.5
Head of Bed is 30 Degrees Up		32,781	48.3
Immunosuppression		2,100	3.1
Intubated in the First Day		29,740	43.8
Risk Factors	Coagulopathy	16,289	24
	Mechanical Ventilation > 24 Hours	33,973	50.1
	Traumatic Brain Injury	3,225	4.8
	Hepatic Failure	601	0.9

Appendix III Table 2, Continued

Characteristics	Univariable Analysis	
	Freq.	Col %
	N= 285,033	
Hydrocortisone \geq 250 Mg / Day or Equivalent	2,409	3.5
Transplantation	146	0.2
Acute Myocardial Infarction	2,190	3.2
Sepsis	12,387	18.2
Neurological Injuries	9,622	14.2
Surgical And Multiple Trauma	16,103	23.7
Hypotension	14,042	20.7
Acute Renal Failure	16,423	24.2
Burns \geq 30% BSA	21	0
ICU LOS > 7 Days	19,992	29.5
Medication		
Sucralfate	1,686	2.5
Antacids	19,633	28.9
Anticoagulants	30,935	45.6
Antiplatelets	35,920	52.9
Thrombolytics	3,853	5.7
NSAIDs	30,654	45.2
Aminoglycosides	1,937	2.9
Cephalosporins	20,476	30.2
Flouroquinolones	14,536	21.4
Lincosamide	2,225	3.3
Linezolid	1,499	2.2
Macrolides	2,957	4.4
Metronidazole	5,883	8.7
Other B-lactams	5,211	7.7
Penicillins	24,140	35.6
Tetracyclines	636	0.9
Vancomycin	19,114	28.2
Antibiotics, Others	1,094	1.6
Admission Source		
Direct Admission	6,106	9
Chest Pain Center	278	0.4
Emergency Room	34,266	50.5
Floor	10,390	15.3
Operating Room	11,702	17.2
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	5,134	7.6
Year of Admission		
2008	11,098	16.4
2009	14,623	21.5
2010	16,690	24.6
2011	17,187	25.3
2012	8,278	12.2
Physician Specialty		
Internal medicine	11,980	17.6
Pulmonary	9,836	14.5
Hospitalist	6,575	9.7
Cardiology	5,506	8.1
Surgery-general	4,991	7.4
Critical care medicine	4,030	5.9
Family practice	4,226	6.2
Surgery-cardiac	3,510	5.2
Others	17,222	25.4

Appendix III Table 2, Continued

Characteristics		Univariable Analysis	
		N=	285,033
		Freq.	Col %
Teaching Hospital		19,658	29
Continuous Variables	APACHE Score IV	64.95	26.53

Appendix III Table 3: Patient-Level Bivariable Analysis Comparing Three days use of PPIs to Three days use of H2Bs among ICU patients in Nosocomial Pneumonia cohort.

Characteristics		Bivariable Analyses				
		H2Bs		PPIs		P-value
		n=	18,783	n=	49,093	
		Freq.	Col %	Freq.	Col %	
Outcome	Nosocomial Pneumonia	794	4.2	1,599	3.3	< 0.001
Gender	Male	10,163	54.1	26,001	53	0.006
Age	18 To 60	7,842	41.8	18,626	37.9	< 0.001
	61 To 70	4,192	22.3	11,222	22.9	
	71 To 80	3,943	21	10,903	22.2	
	≥ 81	2,806	14.9	8,342	17	
Race	Caucasian	13,985	74.5	37,684	76.8	< 0.001
	African American	1,819	9.7	5,887	12	
	Hispanic	532	2.8	1,407	2.9	
	Native American	97	0.5	370	0.8	
	Asian	261	1.4	588	1.2	
	Others	2,089	11.1	3,157	6.4	
ICU Type	Mixed	10,530	56.1	20,076	40.9	< 0.001
	Cardiovascular-Surgical	2,046	10.9	4,120	8.4	
	Coronary Care	2,650	14.1	9,947	20.3	
	Trauma	211	1.1	195	0.4	
	Surgical	1,090	5.8	5,076	10.3	
	Medical	1,017	5.4	5,656	11.5	
	Neuroscience	1,239	6.6	4,023	8.2	
Nutrition	No Feeding	8,520	45.4	19,586	39.9	< 0.001
	Enteral Nutrition	9,538	50.8	25,860	52.7	
	Parenteral Nutrition	133	0.7	614	1.3	
	Both Enteral Nutrition and Parenteral Nutrition	592	3.2	3,033	6.2	
Any Gastrointestinal Diseases		320	1.7	1,535	3.1	< 0.001
Cancer		1,260	6.7	3,539	7.2	0.002
HIV		19	0.1	69	0.1	0.074
Cirrhosis		103	0.5	923	1.9	< 0.001
Asthma		504	2.7	1,144	2.3	0.004
COPD		1,920	10.2	6,141	12.5	< 0.001
ARDS		6,346	33.8	16,142	32.9	0.025
Heart Failure		2,039	10.9	6,449	13.1	< 0.001
Head of Bed is 30 Degrees Up		8,560	45.6	24,221	49.3	< 0.001

Appendix III Table 3 , Continued

Characteristics		Bivariable Analyses				P-value
		H2Bs		PPIs		
		n=	18,783	n=	49,093	
		Freq.	Col %	Freq.	Col %	
Immunosuppression		427	2.3	1,673	3.4	< 0.001
Intubated in the First Day		9,065	48.3	20,675	42.1	< 0.001
Risk Factors	Coagulopathy	3,898	20.8	12,391	25.2	< 0.001
	Mechanical Ventilation > 24 Hours	10,056	53.5	23,917	48.7	< 0.001
	Traumatic Brain Injury	1,190	6.3	2,035	4.1	< 0.001
	Hepatic Failure	68	0.4	533	1.1	< 0.001
	Hydrocortisone \geq 250 Mg / Day or Equivalent	707	3.8	1,702	3.5	0.018
	Transplantation	25	0.1	121	0.2	0.006
	Acute Myocardial Infarction	814	4.3	1,376	2.8	< 0.001
	Sepsis	2,808	14.9	9,579	19.5	< 0.001
	Neurological Injuries	3,485	18.6	6,137	12.5	< 0.001
	Surgical And Multiple Trauma	5,472	29.1	10,631	21.7	< 0.001
	Hypotension	3,626	19.3	10,416	21.2	< 0.001
	Acute Renal Failure	3,687	19.6	12,736	25.9	< 0.001
	Burns \geq 30% BSA	12	0.1	9	0	0.002
	ICU LOS > 7 Days	5,225	27.8	14,767	30.1	< 0.001
	Medication	Sucralfate	254	1.4	1,432	2.9
Antacids		5,872	31.3	13,761	28	< 0.001
Anticoagulants		8,902	47.4	22,033	44.9	< 0.001
Antiplatelets		10,577	56.3	25,343	51.6	< 0.001
Thrombolytics		1,373	7.3	2,480	5.1	< 0.001
NSAIDs		8,875	47.3	21,779	44.4	< 0.001
Aminoglycosides		497	2.6	1,440	2.9	0.001
Cephalosporins		6,195	33	14,281	29.1	< 0.001
Flouroquinolones		3,335	17.8	11,201	22.8	< 0.001
Lincosamide		672	3.6	1,553	3.2	0.01
Linezolid		328	1.7	1,171	2.4	< 0.001
Macrolides		748	4	2,209	4.5	< 0.001
Metronidazole		1,155	6.1	4,728	9.6	< 0.001
Other B-lactams		1,096	5.8	4,115	8.4	< 0.001
Penicillins		5,569	29.6	18,571	37.8	< 0.001
Tetracyclines	140	0.7	496	1	< 0.001	
Vancomycin	5,042	26.8	14,072	28.7	0.002	
Antibiotics, Others	235	1.3	859	1.7	< 0.001	
Admission Source	Direct Admission	1,876	10	4,230	8.6	< 0.001

Appendix III Table 3 , Continued

Characteristics		Bivariable Analyses				
		H2Bs		PPIs		P-value
		n=	18,783	n=	49,093	
		Freq.	Col %	Freq.	Col %	
	Chest Pain Center	78	0.4	200	0.4	0.807
	Emergency Room	9,214	49.1	25,052	51	< 0.001
	Floor	2,240	11.9	8,150	16.6	< 0.001
	Operating Room	3,973	21.2	7,729	15.7	< 0.001
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	1,402	7.5	3,732	7.6	0.947
Year of Admission	2008	2,820	15	8,278	16.9	< 0.001
	2009	3,795	20.2	10,828	22.1	
	2010	4,768	25.4	11,922	24.3	
	2011	4,845	25.8	12,342	25.1	
	2012	2,555	13.6	5,723	11.7	
Physician Specialty	Internal medicine	2,126	11.3	9,854	20.1	< 0.001
	Pulmonary	2,856	15.2	6,980	14.2	
	Hospitalist	1,305	6.9	5,270	10.7	
	Cardiology	1,815	9.7	3,691	7.5	
	Surgery-general	1,545	8.2	3,446	7	
	Critical care medicine	1,399	7.4	2,631	5.4	
	Family practice	915	4.9	3,311	6.7	
	Surgery-cardiac	1,397	7.4	2,113	4.3	
	Others	5,425	28.9	11,797	24	
Teaching Hospital		8,415	44.8	11,243	22.9	
Continuous Variables	APACHE Score IV (Mean, SD)	62.29	26.43	65.969	26.5	< 0.001

Appendix III Table 4: Patient-day level Bivariable Analysis Comparing Three days use of PPIs to Three days use of H2Bs among ICU patients in Nosocomial Pneumonia cohort.

Characteristics		Bivariable Analyses				
		H2Bs		PPIs		P-value
		n=	74,922	n=	210,111	
		Freq.	Col %	Freq.	Col %	
Outcome	Nosocomial Pneumonia	794	1.1	1,599	0.8	< 0.001
Gender	Male	40,649	54.3	114,506	54.5	0.042
Age	18 To 60	33,977	45.3	85,189	40.5	< 0.001
	61 To 70	16,429	21.9	50,200	23.9	
	71 To 80	14,758	19.7	45,216	21.5	
	≥ 81	9,758	13	29,506	14	
Race	Caucasian	56,412	75.3	157,661	75	< 0.001
	African American	7,243	9.7	27,576	13.1	
	Hispanic	2,050	2.7	6,069	2.9	
	Native American	389	0.5	1,560	0.7	
	Asian	885	1.2	2,407	1.1	
	Others	7,943	10.6	14,838	7.1	
ICU Type	Mixed	42,107	56.2	82,778	39.4	< 0.001
	Cardiovascular-Surgical	7,487	10	17,801	8.5	
	Coronary Care	9,004	12	39,312	18.7	
	Trauma	1,628	2.2	1,491	0.7	
	Surgical	4,664	6.2	24,350	11.6	
	Medical	3,621	4.8	23,490	11.2	
	Neuroscience	6,411	8.6	20,889	9.9	
Nutrition	No Feeding	29,254	39	72,921	34.7	< 0.001
	Enteral Nutrition	40,065	53.5	107,914	51.4	
	Parenteral Nutrition	529	0.7	2,610	1.2	
	Both Enteral Nutrition and Parenteral Nutrition	5,074	6.8	26,666	12.7	
Any Gastrointestinal Diseases		1,773	2.4	7,964	3.8	< 0.001
Cancer		4,913	6.6	15,647	7.4	< 0.001
HIV		115	0.2	335	0.2	0.315
Cirrhosis		356	0.5	4,142	2	< 0.001
Asthma		1,914	2.6	4,842	2.3	0.003
COPD		8,360	11.2	27,638	13.2	< 0.001
ARDS		34,877	46.6	99,070	47.2	< 0.001
Heart Failure		8,152	10.9	30,861	14.7	< 0.001
Head of Bed is 30 Degrees Up		37,619	50.2	120,392	57.3	< 0.001

Appendix III Table 4, Continued

Characteristics		Bivariable Analyses				P-value
		H2Bs		PPIs		
		n=	74,922	n=	210,111	
		Freq.	Col %	Freq.	Col %	
Immunosuppression		1,441	1.9	7,561	3.6	< 0.001
Intubated in the First Day		42,315	56.5	112,817	53.7	< 0.001
Risk Factors	Coagulopathy	16,460	22	61,458	29.3	< 0.001
	Mechanical Ventilation > 24 Hours	50,046	66.8	140,199	66.7	0.042
	Traumatic Brain Injury	6,292	8.4	11,231	5.3	< 0.001
	Hepatic Failure	253	0.3	2,816	1.3	< 0.001
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	3,736	5	10,290	4.9	0.036
	Transplantation	58	0.1	490	0.2	< 0.001
	Acute Myocardial Infarction	2,319	3.1	4,746	2.3	< 0.001
	Sepsis	13,683	18.3	50,933	24.2	< 0.001
	Neurological Injuries	18,809	25.1	33,385	15.9	< 0.001
	Surgical And Multiple Trauma	21,492	28.7	50,125	23.9	< 0.001
	Hypotension	17,248	23	56,980	27.1	< 0.001
	Acute Renal Failure	16,453	22	64,091	30.5	< 0.001
	Burns ≥ 30% BSA	292	0.4	225	0.1	< 0.001
	ICU LOS > 7 Days	48,826	65.2	143,529	68.3	< 0.001
	Medications	Sucralfate	1,116	1.5	7,774	3.7
Antacids		27,038	36.1	70,125	33.4	< 0.001
Anticoagulants		41,601	55.5	116,143	55.3	0.47
Antiplatelets		44,927	60	123,328	58.7	< 0.001
Thrombolytics		7,041	9.4	17,772	8.5	< 0.001
NSAIDs		39,647	52.9	113,928	54.2	< 0.001
Aminoglycosides		3,448	4.6	12,727	6.1	< 0.001
Cephalosporins		30,883	41.2	81,975	39	< 0.001
Flouroquinolones		19,764	26.4	67,435	32.1	< 0.001
Lincosamide		4,053	5.4	10,289	4.9	< 0.001
Linezolid		3,741	5	14,213	6.8	< 0.001
Macrolides		3,930	5.2	13,696	6.5	< 0.001
Metronidazole		7,908	10.6	34,013	16.2	< 0.001
Other B-lactams		7,953	10.6	34,549	16.4	< 0.001
Penicillins		32,919	43.9	109,717	52.2	< 0.001
Tetracyclines		806	1.1	3,495	1.7	< 0.001
Vancomycin		32,004	42.7	98,047	46.7	< 0.001
Antibiotics, Others	2,204	2.9	10,020	4.8	< 0.001	

Appendix III Table 4, Continued

Characteristics		Bivariable Analyses				
		H2Bs		PPIs		P-value
		n=	74,922	n=	210,111	
		Freq.	Col %	Freq.	Col %	
Admission Source	Direct Admission	8,205	11	19,405	9.2	< 0.001
	Chest Pain Center	244	0.3	642	0.3	0.321
	Emergency Room	36,748	49	99,455	47.3	< 0.001
	Floor	9,361	12.5	36,672	17.5	< 0.001
	Operating Room	14,505	19.4	34,056	16.2	< 0.001
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	5,859	7.8	19,881	9.5	< 0.001
Year of Admission	2008	11,469	15.3	38,382	18.3	< 0.001
	2009	15,322	20.5	47,048	22.4	
	2010	19,378	25.9	49,623	23.6	
	2011	18,851	25.2	52,664	25.1	
	2012	9,902	13.2	22,394	10.7	
Physician Specialty	Internal medicine	7,146	9.5	38,304	18.2	< 0.001
	Pulmonary	12,665	16.9	34,860	16.6	
	Hospitalist	4,483	6	19,622	9.3	
	Cardiology	5,584	7.5	14,745	7	
	Surgery-general	6,814	9.1	16,905	8	
	Critical care medicine	6,413	8.6	11,762	5.6	
	Family practice	2,940	3.9	12,298	5.9	
	Surgery-cardiac	4,852	6.5	8,953	4.3	
Others	24,025	32.1	52,662	25.1		
Teaching Hospital		36,505	48.7	48,615	23.1	< 0.001
Continuous Variables	APACHE Score IV (Mean, SD)	65.757	27.774	70.408	27.6768	< 0.001

Instrumental variable analysis:

Objective: To construct an IV that is highly correlated with the receipt of PPIs for three days and uncorrelated with unmeasured factors that may influence the occurrence of NP.

While the first condition can be tested, the second condition can only be supported by the literature and the logic used in constructing the IV. The chosen IV was being in a PPI unit defined as a unit that prescribed PPIs to at least 90% of patients. When at least 90% of patients receive PPIs, it is most likely that prescribing decision was related to the ICU practice rather than patients' characteristics. Therefore, such IV should suffice the two aforementioned conditions. The cutoff of 90% was chosen to reflect this logic i.e. being in a PPI unit should be highly correlated with the receipt of PPIs. In addition, it reduces the possibility that the IV is associated with any unobserved factor that may influence NP. Although this assumption cannot be tested, the results from the IV analysis can be used as an affirmative approach for the main analysis. In constructing this IV, number of patients in each unit per calendar year was determined to form the denominator. Next, number of patients who received PPIs in each of these units formed the numerator which was multiplied by 100 to calculate the percentage.

The model used in the first stage:

$$\text{Logit } \{\text{Pr } (Y=1)\} = \beta_0 + \beta_1 \text{PPIUNIT90} + \beta_2 \text{DEMOG} + \beta_3 \text{SURF} + \beta_4 \text{CONDITIONS} + \beta_5 \text{ICUTYPE} + \beta_6 \text{PHYSICIAN} + \beta_7 \text{TEACHING} + \beta_8 \text{YEAR} + \mu$$

Where:

PPIUNIT90: A dummy variable for being in an ICU that prescribed PPIs to at least 90% of the patients.

DEMOG: A vector of categorical variables for patients' demographics (gender, race, age).

SURF: A vector of dummy variables for stress ulcer risk factors (mechanical ventilation > 24 hrs. , coagulopathy, major head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week)

CONDITIONS: A vector of dummy variable for conditions that may affect treatment selection (enteral nutrition, gastrointestinal diseases, cancer, HIV, intubation in the first day)

ICUTYPE: A categorical variable for ICU type (medical, surgical, mixed, trauma, cardiovascular and neurosciences)

PHYSICIAN: A categorical variable for physician specialty (Internal medicine, pulmonary, hospitalist, cardiology, surgery-general, critical care medicine, family practice, surgery-cardiac, others)

TEACHING: A dummy variable for the teaching status of the admitting hospital.

YEAR: A set of dummy variables for Calendar years (2008,2009, 2010, 2011and 2012)

Testing the presence of the correlation between the IV and the receipt of PPIs for three days:

The two-stage least square (2SLS) method was used to calculate partial F-statistics which determines whether or not the IV add any significant addition to the model of the first stage. As a rule of thumb, if the F-test that is greater than 10 then it is strongly correlated with the exposure. Although the 2SLS method should only be used when the exposure is a continuous variable, the partial F-statistic still provides a valid estimation for the strength of the correlation between the exposure and the IV. In our analysis, the partial F-statistic, adjusted for the clustering effect of the unit, was 23.7 indicating a strong correlation between the IV and the receipt of PPIs for three days. This strong correlation corresponded to an adjusted OR of 13.66 (95%CI: 11.29-16.53) in the first stage multivariable logistic regression model (Appendix III Table 5).

Appendix III Table 5: Model for predicting three use of PPIs versus three use of H2Bs using Instrumental variable technique (outcome of interest: Nosocomial Pneumonia)

Characteristics	OR	95%CI
IV	ICUs that prescribed 90% of Patients or more PPIs	13.66*** [11.29,16.53]
Gender	Female	Reference
	Male	1.001 [0.940,1.066]
Age	18 To 60	Reference
	61 To 70	1.189*** [1.077,1.313]
	71 To 80	1.180*** [1.080,1.289]
	≥ 81	1.119* [1.007,1.244]
Race	Caucasian	Reference
	African American	1.068 [0.946,1.206]
	Hispanic	1.07 [0.840,1.363]
	Native American	1.177 [0.951,1.456]
	Asian	1.732** [1.161,2.581]
	Others	0.704** [0.564,0.878]
ICU Type	Medical	Reference
	Cardiovascular-Surgical	0.373** [0.190,0.733]
	Coronary Care	0.739 [0.532,1.027]
	Trauma	0.745* [0.565,0.981]
	Surgical	0.785 [0.524,1.178]
	Mixed	0.490*** [0.384,0.627]
	Neuroscience	1.013 [0.676,1.519]
Nutrition	No Feeding	Reference
	Enteral Nutrition	1.095 [0.939,1.277]
	Parenteral Nutrition	1.968*** [1.566,2.474]
Any Gastrointestinal Diseases		1.914** [1.252,2.926]
Cancer		0.948 [0.831,1.083]
HIV		0.676 [0.312,1.465]
Intubated in the First Day		0.928 [0.834,1.032]
Risk Factors	Coagulopathy	1.413*** [1.304,1.530]
	Mechanical Ventilation > 24 Hours	1.072 [0.963,1.194]
	Traumatic Brain Injury	0.985 [0.783,1.240]
	Hepatic Failure	3.561*** [2.383,5.321]
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	0.988 [0.839,1.164]
	Transplantation	6.347** [1.957,20.59]
	Acute Myocardial Infarction	0.586*** [0.471,0.729]
	Sepsis	1.102 [0.990,1.227]
	Neurological Injuries	0.540*** [0.467,0.625]
	Surgical And Multiple Trauma	0.714*** [0.635,0.803]
	Hypotension	1.034 [0.942,1.136]
	Acute Renal Failure	1.393*** [1.277,1.519]
Medications	Sucralfate	3.080*** [2.223,4.268]
	Antacids	1.009 [0.915,1.111]
	Anticoagulants	0.928 [0.822,1.047]
	Antiplatelets	0.851** [0.760,0.952]
	Thrombolytics	1.134 [0.982,1.309]
	NSAIDs	1.032 [0.924,1.152]

Appendix III Table 5, Continued

Characteristics		OR	95%CI
Year of Admission	2008	Reference	
	2009	0.87	[0.664,1.140]
	2010	0.79	[0.605,1.033]
	2011	0.834	[0.637,1.091]
	2012	0.647**	[0.468,0.894]
	Physician Specialty	Internal medicine	Reference
Pulmonary		0.560***	[0.468,0.671]
Hospitalist		0.729***	[0.612,0.869]
Cardiology		0.614***	[0.503,0.748]
Surgery-general		0.629***	[0.505,0.782]
Critical care medicine (CCM)		0.586***	[0.433,0.792]
Family practice		0.740**	[0.617,0.888]
Surgery-cardiac		0.378***	[0.270,0.528]
Others		0.547***	[0.476,0.628]
Teaching Hospital Observations		285033	0.572***

* p<0.05, ** p<0.01, *** p<0.001, IV: Instrumental Variable, ICUs: Intensive Care Units, PPIs: Proton Pump Inhibitors, NSAIDs: Non-Steroidal Anti-inflammatory Drugs

The C-statistic which measures the ability of the model to discriminate patients who received PPIs for three days vs. patients who received H2Bs for three days at each time point was 0.805 indicating an acceptable level of discrimination. The residuals calculated from the first stage were Pearson’s residuals adjusted for the number of patients who shares the same covariate pattern²⁰⁸.

The model for the 2nd stage:

$$\text{Log } h(t) = \log \lambda_0(t) + \beta_1 \text{PPISVSH2Bs} + \beta_2 \text{PRESIDUALS} + \beta_3 \text{SURF} + \beta_4 \text{CONDITIONS1} + \beta_5 \text{MEDS} + \beta_6 \text{PHYSICIAN} + \beta_7 \text{ADMISSIONS} + \beta_8 \text{TEACHING} + \beta_9 \text{APACHEIV}$$

Where:

PPISVSH2Bs: Three days of PPIs therapy vs. Three days of H2Bs therapy.

PRESIDUALS: Pearson's Residuals adjusted for the number of patients sharing the same covariates pattern.

SURF: A vector of dummy variables for stress ulcer risk factors (mechanical ventilation > 24 hrs., major head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week)

CONDITIONS1: A vector of dummy variables for conditions that may influence risk of NP (Gastrointestinal diseases, Cancer, HIV/AIDS, cirrhosis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, hear failure, , immunosuppression, Head of Bed is 30 Degrees Up and intubation in the first day)

MEDS: A vector of dummy variables for therapeutic classes that may influence risk of NP (Sucralfate , Antacids, NSAIDs, Aminoglycosides, Cephalosporins, Flouroquinolones, Lincosamide, Linezolid, Macrolides, Metronidazole, Other B-lactams, Penicillins, Tetracyclines, Vancomycin, Antibiotics, Others)

ADMISSIONS: A categorical variable for admission source (Direct admission, chest pain center, emergency room, floor, operating room and others (other hospital or ICU, recovery room, step-down unit))

TEACHING: A dummy variable for the teaching status of the admitting hospital.

APACHEIV: A continuous variable for APACHE-IV score

Appendix III Table 6: Cox Proportional Hazard model for the effect of the receipt of Three days PPIs vs. Three days H2Bs on the occurrence of nosocomial pneumonia using the Two Stage Residuals inclusion Method.

Characteristics		HR	95%CI
Exposure	Three-day use of PPIs vs. Three-day use of H2Bs	0.78	[0.607,1.003]
Residuals	Pearson's Residuals	1.012	[0.980,1.044]
Gender	Female	Reference	
	Male	1.139**	[1.051,1.235]
Any Gastrointestinal Diseases		1.223*	[1.018,1.470]
Cancer		1.071	[0.918,1.251]
HIV		0.823	[0.325,2.088]
Cirrhosis		1.031	[0.760,1.398]
Asthma		1.395**	[1.133,1.717]
COPD		1.432***	[1.273,1.610]
ARDS		3.304***	[2.879,3.791]
Heart Failure		1.367***	[1.220,1.531]
Head of Bed is 30 Degrees Up		1.321***	[1.155,1.511]
Immunosuppression		0.868	[0.677,1.113]
Intubated in the First Day		0.967	[0.871,1.073]
Risk Factors	Mechanical Ventilation > 24 Hours	0.979	[0.854,1.121]
	Traumatic Brain Injury	1.222*	[1.016,1.469]
	Hepatic Failure	0.869	[0.577,1.309]
	Hydrocortisone \geq 250 Mg / Day or Equivalent	1.258**	[1.068,1.483]
	Transplantation	0.945	[0.387,2.308]
	Acute Myocardial Infarction	0.85	[0.624,1.157]
	Sepsis	1.072	[0.935,1.229]
	Neurological Injuries	1.354***	[1.152,1.592]
	Surgical And Multiple Trauma	1.095	[0.937,1.279]
	Hypotension	1.229***	[1.097,1.378]
	Acute Renal Failure	1.164**	[1.045,1.296]
Medications	Sucralfate	1.033	[0.733,1.455]
	Antacids	0.884*	[0.782,1.000]
	NSAIDs	1.06	[0.939,1.196]
	Aminoglycosides	1.13	[0.939,1.359]
	Cephalosporins	1.287***	[1.161,1.426]
	Flouroquinolones	1.166**	[1.049,1.296]
	Lincosamide	1.047	[0.851,1.288]
	Linezolid	1.212	[0.989,1.486]
	Macrolides	1.348***	[1.163,1.561]
	Metronidazole	0.875*	[0.779,0.983]
	Other B-lactams	1.188*	[1.040,1.358]
	Penicillins	1.596***	[1.419,1.795]
	Tetracyclines	0.398***	[0.242,0.655]
	Vancomycin	1.811***	[1.612,2.034]
	Antibiotics, Others	0.681**	[0.523,0.887]
Admission Source	Direct Admission	Reference	
	Chest Pain Center	2.513***	[1.665,3.794]
	Emergency Room	1.225*	[1.012,1.484]
	Floor	1.065	[0.869,1.306]
	Operating Room	1.197	[0.941,1.521]
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	1.123	[0.904,1.394]

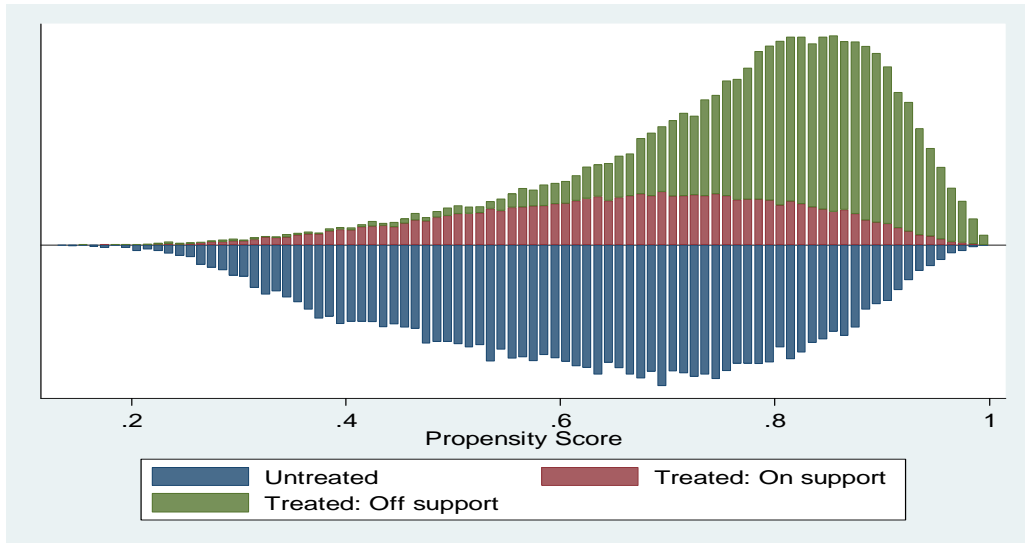
Appendix III Table 6

Characteristics	HR	95%CI
Teaching Hospital	1.853***	[1.553,2.211]
Continuous Variables APACHE Score IV	0.998*	[0.996,1.000]
Observations	285033	

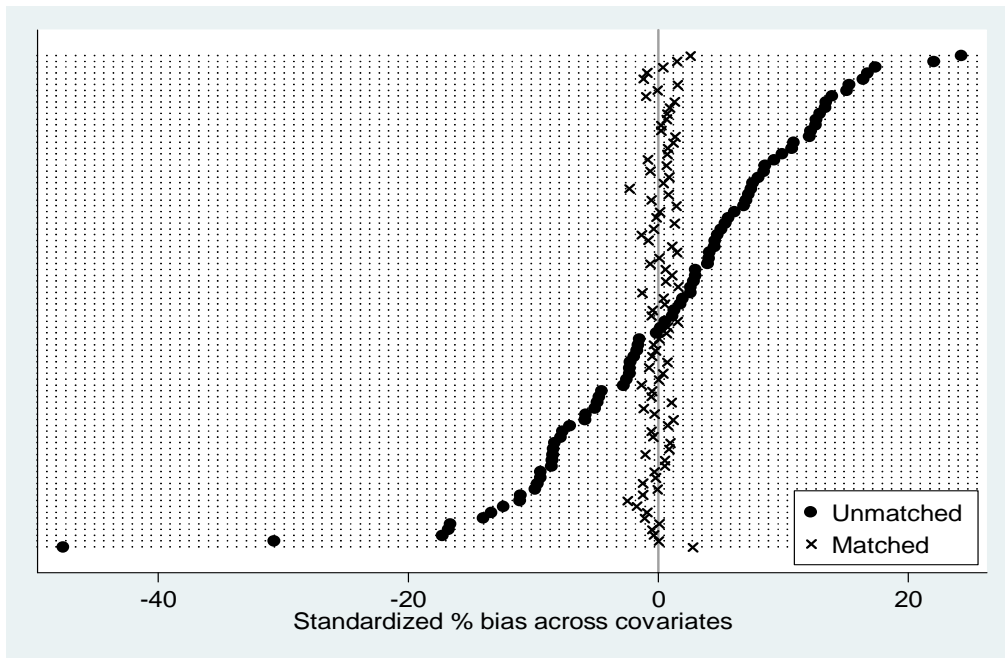
Propensity score matching:

Out of the 67,876 patients, 32,160 patients were one to one matched resulting in 16,080 patients in each group. In more details, out of the 49,093 patients who received PPIs only 16,080 had propensity scores that overlapped with those of the H2Bs group. The C statistic for the propensity score model was 0.73 indicating an acceptable level of predicting the receipt of PPIs compared to the receipt of H2Bs. The model failed the Pearson's X^2 test as the P-value was significant (P-value=0.01) as the Hosmer-Lemeshow test as the P-value was less than 0.0001 indicating the presence of residual confounding. The groups were matched on all the included covariates in the propensity score model. The maximum absolute percentage of standardized bias was 2.8 with a mean of 0.8 and a median of 0.7. In addition, only being in a teaching hospital had a P-value of t-test below 0.05 indicating very well matched groups (Appendix III, Table 8). However, since the absolute percentage of standardized bias was less than 10%, no further adjustments were needed. The risk of NP did not statistically differ between PPIs and H2Bs. (HR: 0.88, 95%CI: 0.75-1.02; P=0.09).

Appendix III Figure 1: Propensity score distribution of patients who received Proton pump inhibitors for three days (labeled Treated) and patients who received Histamine Type-2 receptors Blockers (labeled Untreated)



Appendix III Figure 2: Percentage of Standardized bias across covariates before matching and after matching



Appendix III Table 7: Covariate Distribution Before and After performing one to one matching with no replacement.

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=16,080	n=16,080				
Male	Unmatched	0.53	0.54	-2.30		-2.67	0.01	
	Matched	0.53	0.54	-0.70	67.40	-0.67	0.50	
Age	18 To 60	Unmatched	0.38	0.42	-7.80		-9.11	0.00
	Matched	0.40	0.40	-0.40	94.80	-0.36	0.72	
61 To 70	Unmatched	0.23	0.22	1.30		1.50	0.13	
	Matched	0.23	0.23	-0.50	64.30	-0.41	0.68	
71 To 80	Unmatched	0.22	0.21	3.00		3.43	0.00	
	Matched	0.22	0.22	1.10	62.70	0.98	0.33	
≥ 81	Unmatched	0.17	0.15	5.60		6.46	0.00	
	Matched	0.16	0.16	-0.20	97.00	-0.15	0.88	
Race	Caucasian	Unmatched	0.77	0.74	5.40		6.30	0.00
	Matched	0.76	0.75	1.30	76.00	1.15	0.25	
African American	Unmatched	0.12	0.10	7.40		8.48	0.00	
	Matched	0.10	0.10	-2.30	69.00	-2.14	0.03	
Hispanic	Unmatched	0.03	0.03	0.20		0.24	0.81	
	Matched	0.03	0.03	0.70	-269.70	0.65	0.51	
Native American	Unmatched	0.01	0.01	3.00		3.35	0.00	
	Matched	0.01	0.01	0.50	81.70	0.51	0.61	
Asian	Unmatched	0.01	0.01	-1.70		-2.01	0.04	
	Matched	0.01	0.01	-0.20	87.00	-0.19	0.85	
Others	Unmatched	0.06	0.11	-16.60		-20.54	0.00	
	Matched	0.10	0.10	0.10	99.60	0.06	0.96	
ICU Type	Mixed	Unmatched	0.41	0.56	-30.70		-35.86	0.00
	Matched	0.53	0.53	0.10	99.80	0.04	0.96	
Cardiovascular-Surgical	Unmatched	0.08	0.11	-8.50		-10.15	0.00	
	Matched	0.11	0.11	0.50	93.80	0.45	0.65	
Coronary Care	Unmatched	0.20	0.14	16.40		18.49	0.00	
	Matched	0.15	0.16	-1.20	92.70	-1.11	0.27	
Trauma	Unmatched	0.00	0.01	-8.40		-10.99	0.00	
	Matched	0.01	0.01	0.90	89.70	0.76	0.44	
Surgical	Unmatched	0.10	0.06	16.70		18.44	0.00	
	Matched	0.06	0.07	-0.90	94.50	-0.90	0.37	
Medical	Unmatched	0.12	0.05	22.10		24.01	0.00	

Appendix III Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=16,080	n=16,080				
	Matched	0.07	0.06	1.50	93.30	1.50	0.14	
	Unmatched	0.08	0.07	6.10		6.97	0.00	
	Matched	0.07	0.07	0.10	98.10	0.11	0.92	
Nutrition	No Feeding	Unmatched	0.40	0.45	-11.10		-12.95	0.00
	Matched	0.44	0.45	-2.50	77.70	-2.20	0.03	
	Unmatched	0.52	0.48	8.40		9.84	0.00	
	Matched	0.48	0.49	-0.60	92.30	-0.58	0.56	
	Unmatched	0.05	0.02	12.60		13.74	0.00	
	Matched	0.03	0.03	0.70	94.80	0.67	0.50	
Any Gastrointestinal Diseases	Unmatched	0.03	0.02	9.30		10.18	0.00	
	Matched	0.02	0.02	-0.90	90.80	-0.87	0.38	
Cancer	Unmatched	0.07	0.07	2.00		2.28	0.02	
	Matched	0.07	0.07	0.40	78.90	0.37	0.71	
HIV	Unmatched	0.00	0.00	1.10		1.28	0.20	
	Matched	0.00	0.00	-0.50	52.60	-0.52	0.60	
Cirrhosis	Unmatched	0.02	0.01	12.20		12.74	0.00	
	Matched	0.01	0.01	0.20	98.10	0.28	0.78	
Asthma	Unmatched	0.02	0.03	-2.30		-2.67	0.01	
	Matched	0.03	0.03	0.70	68.30	0.62	0.54	
COPD	Unmatched	0.13	0.10	7.20		8.24	0.00	
	Matched	0.11	0.11	0.80	88.60	0.75	0.46	
ARDS	Unmatched	0.33	0.34	-1.90		-2.24	0.03	
	Matched	0.33	0.33	-0.50	73.90	-0.45	0.65	
Neutropenia	Unmatched	0.05	0.06	-4.90		-5.83	0.00	
	Matched	0.06	0.05	1.10	78.10	0.95	0.34	
Heart Failure	Unmatched	0.13	0.11	7.00		8.04	0.00	
	Matched	0.12	0.12	-0.60	91.80	-0.52	0.60	
Head of Bed is 30 Degrees Up	Unmatched	0.49	0.46	7.50		8.78	0.00	
	Matched	0.48	0.47	0.40	94.20	0.39	0.70	
Thrombocytopenia	Unmatched	0.18	0.12	15.30		17.23	0.00	
	Matched	0.14	0.13	1.50	90.00	1.43	0.15	
Immunosuppression	Unmatched	0.03	0.02	6.80		7.64	0.00	
	Matched	0.03	0.03	1.50	78.60	1.35	0.18	

Appendix III Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=16,080	n=16,080				
Intubated in the First Day		Unmatched	0.42	0.48	-12.40		-14.46	0.00
		Matched	0.46	0.47	-1.70	86.00	-1.54	0.12
Risk Factors	Coagulopathy	Unmatched	0.25	0.21	10.70		12.26	0.00
		Matched	0.22	0.22	0.80	92.90	0.69	0.49
	Mechanical Ventilation > 24 Hours	Unmatched	0.49	0.54	-9.70		-11.25	0.00
		Matched	0.52	0.53	-1.20	87.10	-1.12	0.26
	Traumatic Brain Injury	Unmatched	0.04	0.06	-9.80		-12.01	0.00
		Matched	0.05	0.05	-0.10	99.10	-0.08	0.94
	Hepatic Failure	Unmatched	0.01	0.00	8.50		9.01	0.00
		Matched	0.00	0.00	0.70	92.30	0.76	0.45
	Hydrocortisone \geq 250 Mg / Day or Equivalent	Unmatched	0.03	0.04	-1.60		-1.87	0.06
		Matched	0.04	0.04	-0.40	77.00	-0.33	0.74
	Transplantation	Unmatched	0.00	0.00	2.60		2.85	0.00
		Matched	0.00	0.00	1.60	39.70	1.41	0.16
	Acute Myocardial Infarction	Unmatched	0.03	0.04	-8.30		-10.11	0.00
		Matched	0.04	0.04	0.90	88.60	0.77	0.44
	Sepsis	Unmatched	0.20	0.15	12.10		13.79	0.00
		Matched	0.16	0.16	1.40	88.70	1.26	0.21
	Neurological Injuries	Unmatched	0.13	0.19	-16.80		-20.29	0.00
		Matched	0.16	0.16	-0.50	96.90	-0.46	0.65
	Surgical And Multiple Trauma	Unmatched	0.22	0.29	-17.20		-20.55	0.00
		Matched	0.27	0.27	-0.30	98.00	-0.30	0.76
	Hypotension	Unmatched	0.21	0.19	4.80		5.50	0.00
		Matched	0.19	0.20	-1.30	72.00	-1.21	0.23
	Acute Renal Failure	Unmatched	0.26	0.20	15.10		17.22	0.00
		Matched	0.21	0.21	-0.10	99.50	-0.07	0.95
Medications	Sucralfate	Unmatched	0.03	0.01	10.80		11.73	0.00
		Matched	0.02	0.02	1.20	88.90	1.22	0.22
	Antacids	Unmatched	0.28	0.31	-7.10		-8.31	0.00
		Matched	0.31	0.30	0.70	89.40	0.67	0.51
	Anticoagulants	Unmatched	0.45	0.47	-5.00		-5.88	0.00

Appendix III Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=16,080	n=16,080				
Antiplatelets	Matched	0.47	0.47	-1.20	76.50	-1.06	0.29	
	Unmatched	0.52	0.56	-9.40		-10.96	0.00	
Thrombolytics	Matched	0.56	0.56	-0.20	97.90	-0.18	0.86	
	Unmatched	0.05	0.07	-9.40		-11.39	0.00	
NSAIDs	Matched	0.07	0.07	-0.30	96.70	-0.26	0.79	
	Unmatched	0.44	0.47	-5.80		-6.76	0.00	
Aminoglycosides	Matched	0.46	0.46	-0.30	94.40	-0.29	0.77	
	Unmatched	0.03	0.03	1.70		2.01	0.04	
Cephalosporins	Matched	0.03	0.03	0.50	69.70	0.48	0.63	
	Unmatched	0.29	0.33	-8.40		-9.89	0.00	
Flouroquinolones	Matched	0.31	0.32	-1.00	87.70	-0.93	0.36	
	Unmatched	0.23	0.18	12.60		14.40	0.00	
Lincosamide	Matched	0.19	0.19	0.20	98.00	0.23	0.82	
	Unmatched	0.03	0.04	-2.30		-2.71	0.01	
Linezolid	Matched	0.03	0.03	0.40	83.50	0.34	0.74	
	Unmatched	0.02	0.02	4.50		5.07	0.00	
Macrolides	Matched	0.02	0.02	1.10	75.70	0.99	0.32	
	Unmatched	0.05	0.04	2.60		2.95	0.00	
Metronidazole	Matched	0.04	0.04	-1.30	49.50	-1.18	0.24	
	Unmatched	0.10	0.06	12.90		14.44	0.00	
Other B-lactams	Matched	0.07	0.07	0.70	94.60	0.66	0.51	
	Unmatched	0.08	0.06	9.90		11.16	0.00	
Penicillins	Matched	0.07	0.06	0.70	92.90	0.65	0.51	
	Unmatched	0.38	0.30	17.40		19.97	0.00	
Tetracyclines	Matched	0.32	0.32	0.40	97.80	0.35	0.73	
	Unmatched	0.01	0.01	2.80		3.21	0.00	
Vancomycin	Matched	0.01	0.01	0.60	78.90	0.56	0.58	
	Unmatched	0.29	0.27	4.10		4.72	0.00	
Antibiotics, Others	Matched	0.28	0.28	0.10	98.30	0.06	0.95	
	Unmatched	0.02	0.01	4.10		4.62	0.00	
Admission Source	Matched	0.02	0.01	1.50	63.80	1.35	0.18	
	Direct Admission	Unmatched	0.004	0.004	-0.10		-0.14	0.89
Chest Pain Center	Matched	0.00	0.005	0.705	-452.50	0.57	0.57	
	Unmatched	0.09	0.10	-4.70		-5.59	0.00	
	Matched	0.09	0.10	-0.60	88.20	-0.49	0.62	

Appendix III Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=16,080	n=16,080				
Emergency Room	Unmatched	0.51	0.49	4.00		4.60	0.00	
	Matched	0.49	0.49	-0.70	83.00	-0.60	0.55	
Floor	Unmatched	0.17	0.12	13.40		15.16	0.00	
	Matched	0.14	0.13	1.30	90.20	1.22	0.22	
Operating Room	Unmatched	0.16	0.21	-14.00		-16.72	0.00	
	Matched	0.20	0.21	-1.10	92.30	-0.93	0.35	
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	Unmatched	0.08	0.07	0.50		0.61	0.54	
	Matched	0.08	0.07	1.60	-198.10	1.38	0.17	
Year of Admission	2008	Unmatched	0.17	0.15	5.10		5.83	0.00
		Matched	0.15	0.15	-0.40	92.60	-0.34	0.73
2009	Unmatched	0.22	0.20	4.50		5.25	0.00	
	Matched	0.20	0.20	-0.80	82.90	-0.71	0.48	
2010	Unmatched	0.24	0.25	-2.50		-2.98	0.00	
	Matched	0.25	0.25	0.00	98.90	0.03	0.98	
2011	Unmatched	0.25	0.26	-1.50		-1.75	0.08	
	Matched	0.26	0.26	0.10	94.30	0.08	0.94	
2012	Unmatched	0.12	0.14	-5.90		-6.93	0.00	
	Matched	0.14	0.13	1.20	79.20	1.06	0.29	
Physician Specialty	Internal medicine	Unmatched	0.20	0.11	24.20		26.90	0.00
		Matched	0.14	0.13	2.50	89.50	2.43	0.02
Pulmonary	Unmatched	0.14	0.15	-2.80		-3.27	0.00	
	Matched	0.15	0.15	-1.40	51.50	-1.20	0.23	
Hospitalist	Unmatched	0.11	0.07	13.40		14.95	0.00	
	Matched	0.08	0.08	0.90	93.10	0.88	0.38	
Cardiology	Unmatched	0.08	0.10	-7.70		-9.16	0.00	
	Matched	0.10	0.10	-0.60	92.80	-0.47	0.64	
Surgery-general	Unmatched	0.07	0.08	-4.50		-5.39	0.00	
	Matched	0.08	0.08	-0.50	89.20	-0.43	0.67	
Critical care medicine (CCM)	Unmatched	0.05	0.07	-8.50		-10.31	0.00	
	Matched	0.07	0.07	0.50	94.00	0.43	0.67	
Family practice	Unmatched	0.07	0.05	8.00		9.04	0.00	
	Matched	0.06	0.06	0.90	89.40	0.78	0.44	
Surgery-cardiac	Unmatched	0.04	0.07	-13.40		-16.53	0.00	

Appendix III Table 7, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=	n=				
			16,080	16,080				
		Matched	0.07	0.07	-0.90	93.50	-0.74	0.46
	Others	Unmatched	0.24	0.29	-11.00		-13.01	0.00
		Matched	0.26	0.27	-1.20	89.00	-1.09	0.28
	Teaching Hospital	Unmatched	0.23	0.45	-47.60		-57.63	0.00
		Matched	0.40	0.39	2.80	94.20	2.33	0.02
Continuous Variables	APACHE Score IV	Unmatched	65.97	62.29	13.90		16.19	0.00
		Matched	63.05	63.32	-1.00	92.80	-0.92	0.36

Appendix III Table 8: The Hazard ratio and 95% Confidence Intervals for the effect of Three-day use of PPIs compared to Three-day use of H2Bs adjusting for an unmeasured dichotomous confounder with a hazard ratio of 0.33.

P_1	P_0					
	0.0	0.1	0.2	0.3	0.4	0.5
0.0	0.87 (0.78,0.97)					
0.1	0.89 (0.8,1.00)	0.87 (0.78,0.97)				
0.2	0.91 (0.81,1.02)	0.89 (0.8,1.00)	0.87 (0.78,0.97)			
0.3	0.93 (0.83,1.05)	0.91 (0.82,1.02)	0.89 (0.8,1.00)	0.87 (0.78,0.97)		
0.4	0.96 (0.86,1.07)	0.94 (0.84,1.05)	0.91 (0.82,1.02)	0.89 (0.8,1.00)	0.87 (0.78,0.97)	
0.5	0.98 (0.88,1.1)	0.96 (0.86,1.08)	0.94 (0.84,1.05)	0.92 (0.82,1.02)	0.89 (0.8,1.00)	0.87 (0.78,0.97)
0.6	1.01 (0.9,1.13)	0.99 (0.88,1.1)	0.96 (0.86,1.08)	0.94 (0.84,1.05)	0.92 (0.82,1.03)	0.89 (0.8,1.00)
0.7	1.04 (0.93,1.16)	1.01 (0.9,1.13)	0.99 (0.88,1.11)	0.97 (0.86,1.08)	0.94 (0.84,1.05)	0.92 (0.82,1.03)
0.8	1.07 (0.95,1.19)	1.04 (0.93,1.17)	1.02 (0.91,1.14)	0.99 (0.89,1.11)	0.97 (0.86,1.08)	0.94 (0.84,1.06)
0.9	1.10 (0.98,1.23)	1.07 (0.96,1.2)	1.05 (0.93,1.17)	1.02 (0.91,1.14)	1.00 (0.89,1.12)	0.97 (0.87,1.09)
1.0	1.13 (0.98,1.23)	1.10 (0.99,1.24)	1.08 (0.96,1.21)	1.05 (0.94,1.18)	1.03 (0.92,1.15)	1.00 (0.89,1.12)

P_0 and P_1 are the prevalence of the unmeasured confounder in the H2Bs group and the PPIs group, respectively; PPIs: Proton Pump Inhibitors; H2Bs: Histamine Type-2 Receptors Blockers
 Red color: higher risk of NP with PPIs; Green color: No difference between PPIs and H2Bs; Blue: lower risk of NP with PPIs.

Clostridium Difficile-associated diseases:

Appendix III Table 9: Patient-day Level Univariable Analysis of ICU patients who in Clostridium-difficile associated diseases cohort.

Characteristics		Univariable Analysis	
		N=	389,782
		Freq.	Col %
Outcome	Clostridium Difficile Infection	550	0.1
Exposure	Three Days of Proton Pump Inhibitors Use	286,927	73.6
	Three Days of Histamine-2 Receptors Blockers Use	102,855	26.4
Gender	Male	213,711	54.8
Age	18 To 60	164,744	42.3
	61 To 70	89,680	23.0
	71 To 80	81,074	20.8
	≥ 81	54,284	13.9
Race	Caucasian	296,065	76.0
	African American	45,583	11.7
	Hispanic	11,121	2.9
	Native American	2,944	0.8
	Asian	4,301	1.1
	Others	29,768	7.6
ICU Type	Mixed	181,601	46.6
	Cardiovascular-Surgical	31,204	8.0
	Coronary Care	69,191	17.8
	Trauma	3,317	0.9
	Surgical	33,011	8.5
	Medical	40,278	10.3
	Neuroscience	31,180	8.0
Nutrition	No Feeding	127,765	32.8
	Enteral Nutrition	214,944	55.1
	Parenteral Nutrition	3,760	1.0
	Both Enteral Nutrition and Parenteral Nutrition	43,313	11.1
Any Gastrointestinal Diseases		13,916	3.6
Cirrhosis		5,829	1.5
Heart Failure		60,089	15.4
Immunosuppression		12,761	3.3
Intubated in the First Day		220,599	56.6
Risk Factors	Coagulopathy	105,547	27.1
	Mechanical Ventilation > 24 Hours	274,071	70.3
	Traumatic Brain Injury	20,954	5.4
	Hepatic Failure	4,404	1.1
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	23,557	6.0
	Transplantation	568	0.1
	Acute Myocardial Infarction	8,252	2.1
	Sepsis	110,298	28.3
	Neurological Injuries	64,782	16.6
	Surgical And Multiple Trauma	80,291	20.6
	Hypotension	118,344	30.4

Appendix III Table 9, Continued

Characteristics		Univariable Analysis	
		N=	389,782
		Freq.	Col %
	Acute Renal Failure	121,176	31.1
	Burns \geq 30% BSA	536	0.1
	ICU LOS > 7 Days	278,771	71.5
Medications	Anticoagulants	220,752	56.6
	Antiplatelets	233,769	60.0
	Thrombolytics	33,848	8.7
	NSAIDs	213,623	54.8
	Aminoglycosides	24,865	6.4
	Cephalosporins	157,571	40.4
	Flouroquinolones	138,340	35.5
	Lincosamide	21,375	5.5
	Linezolid	29,699	7.6
	Macrolides	40,168	10.3
	Metronidazole	55,266	14.2
	Other B-lactams	65,130	16.7
	Penicillins	215,330	55.2
	Tetracyclines	6,726	1.7
	Vancomycin	200,492	51.4
	Antibiotics, Others	15,840	4.1
Admission Source	Direct Admission	35,911	9.2
	Emergency Room	196,302	50.4
	Floor	68,527	17.6
	Operating Room	53,051	13.6
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit, Chest Pain Center)	35,991	9.2
Year of Admission	2008	68,019	17.5
	2009	87,451	22.4
	2010	93,840	24.1
	2011	97,492	25.0
	2012	42,980	11.0
Physician Specialty	Internal medicine	62,755	16.1
	Pulmonary	80,252	20.6
	Hospitalist	34,925	9.0
	Cardiology	24,108	6.2
	Surgery-general	25,745	6.6
	Critical care medicine	30,913	7.9
	Family practice	21,453	5.5
	Surgery-cardiac	14,738	3.8
	Others	94,893	24.3
Teaching Hospital		124,853	32.0
APACHE Score IV (Mean, SD)		70	27.7

Appendix III Table 10: Patient-Level Bivariable Analysis Comparing Three days use of PPIs to Three days use of H2Bs among ICU patients in Clostridium difficile-associated diseases cohort.

Characteristics		Bivariable Analyses				
		H2Bs		PPIs		P-value
		n=	23,108	n=	61,254	
		Freq.	Col %	Freq.	Col %	
Outcome	Clostridium Difficile Infection	115	0.5	435	0.7	0.001
Gender	Male	12,486	54	32,601	53.2	0.02
Age	18 To 60	9,587	41.5	23,012	37.6	< 0.001
	61 To 70	5,110	22.1	13,813	22.6	
	71 To 80	4,808	20.8	13,640	22.3	
	≥ 81	3,603	15.6	10,789	17.6	
Race	Caucasian	17,268	74.7	47,350	77.3	< 0.001
	African American	2,248	9.7	7,147	11.7	
	Hispanic	638	2.8	1,726	2.8	
	Native American	124	0.5	481	0.8	
	Asian	302	1.3	721	1.2	
	Others	2,528	10.9	3,829	6.3	
ICU Type	Mixed	13,435	58.1	26,071	42.6	< 0.001
	Cardiovascular-Surgical	2,259	9.8	4,793	7.8	
	Coronary Care	3,325	14.4	12,764	20.8	
	Trauma	213	0.9	206	0.3	
	Surgical	1,226	5.3	5,509	9	
	Medical	1,356	5.9	7,563	12.3	
	Neuroscience	1,294	5.6	4,348	7.1	
Nutrition	No Feeding	9,962	43.1	23,468	38.3	< 0.001
	Enteral Nutrition	12,238	53	33,398	54.5	
	Parenteral Nutrition	149	0.6	694	1.1	
	Both Enteral Nutrition and Parenteral Nutrition	759	3.3	3,694	6	
	Any Gastrointestinal Diseases	409	1.8	1,920	3.1	< 0.001
	Cirrhosis	129	0.6	1,074	1.8	< 0.001
	Heart Failure	2,840	12.3	8,916	14.6	< 0.001
	Immunosuppression	555	2.4	2,147	3.5	< 0.001
	Intubated in the First Day	11,433	49.5	27,174	44.4	< 0.001
Risk Factors	Coagulopathy	4,763	20.6	15,281	24.9	< 0.001
	Mechanical Ventilation > 24 Hours	12,841	55.6	31,603	51.6	< 0.001
	Traumatic Brain Injury	1,278	5.5	2,148	3.5	< 0.001
	Hepatic Failure	80	0.3	657	1.1	< 0.001
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	983	4.3	2,601	4.2	0.62
	Transplantation	27	0.1	129	0.2	0.006
	Acute Myocardial Infarction	864	3.7	1,507	2.5	< 0.001
	Sepsis	4,402	19	14,454	23.6	< 0.001
	Neurological Injuries	3,893	16.8	6,981	11.4	< 0.001
	Surgical And Multiple Trauma	5,673	24.5	11,033	18	< 0.001
	Hypotension	5,111	22.1	14,735	24.1	< 0.001
	Acute Renal Failure	5,076	22	16,904	27.6	< 0.001
	Burns ≥ 30% BSA	13	0.1	12	0	0.005

Appendix III Table 10, Continued

Characteristics		Bivariable Analyses				
		H2Bs		PPIs		P-value
		n=	23,108	n=	61,254	
	Freq.	Col %	Freq.	Col %		
	ICU LOS > 7 Days	7,309	31.6	20,528	33.5	< 0.001
Medications	Sucralfate	278	1.2	1,603	2.6	< 0.001
	Antacids	6,856	29.7	16,663	27.2	< 0.001
	Anticoagulants	11,171	48.3	28,290	46.2	< 0.001
	Antiplatelets	13,041	56.4	32,141	52.5	< 0.001
	Thrombolytics	1,544	6.7	2,895	4.7	< 0.001
	NSAIDs	10,906	47.2	27,297	44.6	< 0.001
	Aminoglycosides	690	3	1,995	3.3	0.003
	Cephalosporins	7,740	33.5	18,202	29.7	< 0.001
	Flouroquinolones	5,212	22.6	16,431	26.8	< 0.001
	Lincosamide	872	3.8	2,200	3.6	0.263
	Linezolid	596	2.6	1,939	3.2	< 0.001
	Macrolides	1,691	7.3	4,586	7.5	0.213
	Metronidazole	1,452	6.3	5,356	8.7	< 0.001
	Other B-lactams	1,634	7.1	5,751	9.4	< 0.001
	Penicillins	8,184	35.4	26,175	42.7	< 0.001
	Tetracyclines	200	0.9	689	1.1	< 0.001
	Vancomycin	7,471	32.3	20,678	33.8	0.011
	Antibiotics, Others	297	1.3	1,003	1.6	< 0.001
	Admission Source	Direct Admission	2,271	9.8	5,158	8.4
Emergency Room		11,911	51.5	32,474	53	
Floor		3,042	13.2	10,866	17.7	
Operating Room		4,083	17.7	7,965	13	
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit, Chest Pain Center)		1,801	7.8	4,791	7.8	
Year of Admission	2008	3,382	14.6	10,206	16.7	< 0.001
	2009	4,705	20.4	13,612	22.2	
	2010	5,899	25.5	14,784	24.1	
	2011	5,957	25.8	15,548	25.4	
	2012	3,165	13.7	7,104	11.6	
Physician Specialty	Internal medicine	2,759	11.9	12,586	20.5	<0.001
	Pulmonary	4,468	19.3	10,209	16.7	
	Hospitalist	1,687	7.3	6,847	11.2	
	Cardiology	1,971	8.5	4,090	6.7	
	Surgery-general	1,595	6.9	3,572	5.8	
	Critical care medicine	1,950	8.4	3,987	6.5	
	Family practice	1,186	5.1	4,249	6.9	
	Surgery-cardiac	1,429	6.2	2,150	3.5	
	Others	6,063	26.2	13,564	22.1	
Teaching Hospital		10,640	46	14,260	23.3	<0.001
Continuous Variables	APACHE Score IV (Mean, SD)	63.9	26.56	67.222	26.59	< 0.001

Appendix III Table 11: Patient-day level Bivariable Analysis Comparing Three days use of PPIs to Three days use of H2Bs among ICU patients in Clostridium difficile-associated diseases cohort.

Characteristics		Bivariable Analyses				
		H2Bs n=102,855		PPIs n=286,927		P-value
		Freq.	Col %	Freq.	Col %	
Outcome	Clostridium Difficile Infection	115	0.1	435	0.2	< 0.001
Gender	Male	56,552	55	157,159	54.8	0.006
Age	18 To 60	47,436	46.1	117,308	40.9	< 0.001
	61 To 70	22,385	21.8	67,295	23.5	
	71 To 80	19,647	19.1	61,427	21.4	
	≥ 81	13,387	13	40,897	14.3	
Race	Caucasian	77,912	75.7	218,153	76	< 0.001
	African American	9,818	9.5	35,765	12.5	
	Hispanic	2,750	2.7	8,371	2.9	
	Native American	523	0.5	2,421	0.8	
	Asian	1,153	1.1	3,148	1.1	
	Others	10,699	10.4	19,069	6.6	
ICU Type	Mixed	61,603	59.9	119,998	41.8	< 0.001
	Cardiovascular-Surgical	8,761	8.5	22,443	7.8	
	Coronary Care	12,752	12.4	56,439	19.7	
	Trauma	1,648	1.6	1,669	0.6	
	Surgical	5,592	5.4	27,419	9.6	
	Medical	5,317	5.2	34,961	12.2	
	Neuroscience	7,182	7	23,998	8.4	
Nutrition	No Feeding	35,673	34.7	92,092	32.1	< 0.001
	Enteral Nutrition	58,853	57.2	156,091	54.4	
	Parenteral Nutrition	692	0.7	3,068	1.1	
	Both Enteral Nutrition and Parenteral Nutrition	7,637	7.4	35,676	12.4	
Any Gastrointestinal Diseases		2,690	2.6	11,226	3.9	< 0.001
Cirrhosis		536	0.5	5,293	1.8	< 0.001
Heart Failure		13,265	12.9	46,824	16.3	< 0.001
Immunosuppression		2,190	2.1	10,571	3.7	< 0.001
Intubated in the First Day		60,078	58.4	160,521	55.9	< 0.001
Risk Factors	Coagulopathy	22,573	21.9	82,974	28.9	< 0.001
	Mechanical Ventilation > 24 Hours	72,717	70.7	201,354	70.2	< 0.001
	Traumatic Brain Injury	7,962	7.7	12,992	4.5	< 0.001
	Hepatic Failure	376	0.4	4,028	1.4	< 0.001
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	6,154	6	17,403	6.1	0.018

Appendix III Table 11, Continued

Characteristics	Bivariable Analyses					P-value
	H2Bs n=102,855		PPIs n=286,927		P-value	
	Freq.	Col %	Freq.	Col %		
Transplantation	61	0.1	507	0.2	0.006	
Acute Myocardial Infarction	2,726	2.7	5,526	1.9	< 0.001	
Sepsis	24,679	24	85,619	29.8	< 0.001	
Neurological Injuries	23,685	23	41,097	14.3	< 0.001	
Surgical And Multiple Trauma	24,872	24.2	55,419	19.3	< 0.001	
Hypotension	28,919	28.1	89,425	31.2	< 0.001	
Acute Renal Failure	26,637	25.9	94,539	32.9	< 0.001	
Burns \geq 30% BSA	315	0.3	221	0.1	0.002	
ICU LOS > 7 Days	72,107	70.1	206,664	72	< 0.001	
Medications						
Anticoagulants	58,107	56.5	162,645	56.7	< 0.001	
Antiplatelets	62,397	60.7	171,372	59.7	< 0.001	
Thrombolytics	9,532	9.3	24,316	8.5	< 0.001	
NSAIDs	55,894	54.3	157,729	55	< 0.001	
Aminoglycosides	5,597	5.4	19,268	6.7	0.001	
Cephalosporins	43,974	42.8	113,597	39.6	< 0.001	
Flouroquinolones	33,151	32.2	105,189	36.7	< 0.001	
Lincosamide	5,828	5.7	15,547	5.4	0.01	
Linezolid	6,707	6.5	22,992	8	< 0.001	
Macrolides	10,172	9.9	29,996	10.5	< 0.001	
Metronidazole	12,121	11.8	43,145	15	< 0.001	
Other B-lactams	13,314	12.9	51,816	18.1	< 0.001	
Penicillins	52,171	50.7	163,159	56.9	< 0.001	
Tetracyclines	1,334	1.3	5,392	1.9	< 0.001	
Vancomycin	51,409	50	149,083	52	0.002	
Antibiotics, Others	3,005	2.9	12,835	4.5	< 0.001	
Admission Source						
Direct Admission	10,604	10.3	25,307	8.8	< 0.001	
Emergency Room	53,088	51.6	143,214	49.9		
Floor	14,447	14	54,080	18.8		
Operating Room	16,133	15.7	36,918	12.9		
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit, Chest Pain Center)	8,583	8.3	27,408	9.6		
Year of Admission						
2008	16,046	15.6	51,973	18.1	< 0.001	
2009	21,560	21	65,891	23		
2010	26,430	25.7	67,410	23.5		
2011	25,615	24.9	71,877	25.1		
2012	13,204	12.8	29,776	10.4		

Appendix III Table 11, Continued

Characteristics		Bivariable Analyses				P-value
		H2Bs n=102,855		PPIs n=286,927		
		Freq.	Col %	Freq.	Col %	
Physician Specialty	Internal medicine	9,711	9.4	53,044	18.5	< 0.001
	Pulmonary	23,090	22.4	57,162	19.9	
	Hospitalist	6,472	6.3	28,453	9.9	
	Cardiology	6,619	6.4	17,489	6.1	
	Surgery-general	7,485	7.3	18,260	6.4	
	Critical care medicine	10,193	9.9	20,720	7.2	
	Family practice	4,182	4.1	17,271	6	
	Surgery-cardiac	5,128	5	9,610	3.3	
	Others	29,975	29.1	64,918	22.6	
Teaching Hospital		53,605	52.1	71,248	24.8	< 0.001
Continuous Variables	APACHE Score IV (Mean, SD)	67	27.592	72	27.639	< 0.001

Instrumental variable analysis:

Objective: To construct an IV that is highly correlated with the receipt of PPIs for three days and uncorrelated with unmeasured factors that may influence the occurrence of CDAD.

While the first condition can be tested, the second condition can only be supported by the literature and the logic used in constructing the IV. The chosen IV was being in a PPI unit defined as a unit that prescribed PPIs to at least 90% of patients. When at least 90% of patients receive PPIs, it is most likely that prescribing decision was related to the ICU practice rather than patients' characteristics. Therefore, such IV should suffice the two aforementioned conditions. The cutoff of 90% was chosen to reflect this logic i.e. being in a PPI unit should be highly correlated with the receipt of PPIs. In addition, it reduces the possibility that the IV is associated with any unobserved factor that may influence CDAD. Although this assumption cannot be tested, the results from the IV analysis can be used as an affirmative approach for the main analysis. In constructing this IV, number of patients in each unit per calendar year was determined to form the denominator. Next, number of patients who received PPIs in each of these units formed the numerator which was multiplied by 100 to calculate the percentage.

The model used in the first stage:

$$\text{Logit } \{\text{Pr } (Y=1)\} = \beta_0 + \beta_1 \text{PPIUNIT90} + \beta_2 \text{DEMOG} + \beta_3 \text{SURF} + \beta_4 \text{CONDITIONS} + \beta_5 \text{ICUTYPE} + \beta_6 \text{PHYSICIAN} + \beta_7 \text{TEACHING} + \beta_8 \text{YEAR} + \mu$$

Where:

PPIUNIT90: A dummy variable for being in an ICU that prescribed PPIs to at least 90% of the patients.

DEMOG: A vector of categorical variables for patients' demographics (gender, race, age).

SURF: A vector of dummy variables for stress ulcer risk factors (mechanical ventilation > 24 hrs. , coagulopathy, major head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week)

CONDITIONS: A vector of dummy variable for conditions that may affect treatment selection (enteral nutrition, gastrointestinal diseases, cancer, HIV, intubation in the first day)

ICUTYPE: A categorical variable for ICU type (medical, surgical, mixed, trauma, cardiovascular and neurosciences)

PHYSICIAN: A categorical variable for physician specialty (Internal medicine, pulmonary, hospitalist, cardiology, surgery-general, critical care medicine, family practice, surgery-cardiac, others)

TEACHING: A dummy variable for the teaching status of the admitting hospital.

YEAR: A set of dummy variables for Calendar years (2008, 2009, 2010, 2011 and 2012)

Testing the presence of the correlation between the IV and the receipt of PPIs for three days:

The two-stage least square (2SLS) method was used to calculate partial F-statistics which determines whether or not the IV add any significant addition to the model of the first stage. As a rule of thumb, if the F-test that is greater than 10 then it is strongly correlated with the exposure. Although the 2SLS method should only be used when the exposure is a continuous variable, the partial F-statistic still provides a valid estimation for the strength of the correlation between the exposure and the IV. In our analysis, the partial F-statistic, adjusted for the clustering effect of the unit, was 25.6 indicating a strong correlation between the IV and the receipt of PPIs for three days. This strong correlation corresponded to an adjusted OR of 12.84 (95%CI: 10.67-15.46) in the first stage multivariable logistic regression model (Appendix III Table 12).

Appendix III Table 12: Model for predicting three use of PPIs versus three use of H2Bs using Instrumental variable technique

Characteristics		OR	95%CI
IV	ICUs that prescribed 90% of Patients or more PPIs	12.84***	[10.67,15.46]
Gender	Female	Reference	
	Male	0.975	[0.923,1.028]
Age	18 To 60	Reference	
	61 To 70	1.180***	[1.083,1.287]
	71 To 80	1.189***	[1.093,1.294]
	≥ 81	1.122*	[1.026,1.226]
Race	Caucasian	Reference	
	African American	1.003	[0.879,1.145]
	Hispanic	1.037	[0.783,1.373]
	Native American	1.141	[0.917,1.420]
	Asian	1.906**	[1.265,2.872]
	Others	0.669***	[0.540,0.829]
ICU Type	Mixed	Reference	
	Cardiovascular-Surgical	0.411*	[0.205,0.824]
	Coronary Care	0.765	[0.561,1.044]
	Trauma	0.690**	[0.526,0.906]
	Surgical	0.841	[0.573,1.235]
	Medical	0.482***	[0.384,0.606]
	Neuroscience	0.993	[0.670,1.473]
Nutrition	No Feeding	Reference	
	Enteral Nutrition	1.128	[0.956,1.330]
	Parenteral Nutrition	1.848***	[1.487,2.298]
Any Gastrointestinal Diseases		1.917**	[1.239,2.966]
Cancer		1.022	[0.905,1.153]
HIV		0.659	[0.398,1.091]
Intubated in the First Day		0.974	[0.888,1.068]
Risk Factors	Coagulopathy	1.425***	[1.325,1.532]
	Mechanical Ventilation > 24 Hours	1.027	[0.931,1.133]
	Traumatic Brain Injury	0.901	[0.718,1.130]
	Hepatic Failure	3.849***	[2.542,5.828]
	Hydrocortisone ≥ 250 Mg / Day or Equivalent	0.979	[0.849,1.129]
	Transplantation	6.759***	[2.166,21.09]
	Acute Myocardial Infarction	0.577***	[0.467,0.715]
	Sepsis	1.104*	[1.011,1.205]
	Neurological Injuries	0.576***	[0.505,0.656]
	Surgical And Multiple Trauma	0.698***	[0.627,0.776]
	Hypotension	0.996	[0.910,1.091]
	Acute Renal Failure	1.334***	[1.240,1.436]
	Sucralfate	3.042***	[2.220,4.168]
	Antacids	1.028	[0.942,1.121]
	Anticoagulants	0.921	[0.821,1.033]
	Antiplatelets	0.884**	[0.805,0.971]
	Thrombolytics	1.164*	[1.019,1.331]
	NSAIDs	1.034	[0.927,1.154]

Appendix III Table 12, Continued

Characteristics		OR	95%CI
Year of Admission	2008	Reference	
	2009	0.836	[0.635,1.100]
	2010	0.765	[0.578,1.013]
	2011	0.768	[0.578,1.021]
	2012	0.669*	[0.477,0.940]
Physician Specialty	Internal medicine	Reference	
	Pulmonary	0.533***	[0.451,0.630]
	Hospitalist	0.664***	[0.573,0.769]
	Cardiology	0.597***	[0.498,0.717]
	Surgery-general	0.625***	[0.507,0.770]
	Critical care medicine (CCM)	0.540***	[0.389,0.748]
	Family practice	0.716***	[0.610,0.840]
	Surgery-cardiac	0.380***	[0.273,0.530]
	Others	0.513***	[0.447,0.590]
Teaching Hospital		0.567***	[0.472,0.681]
Observations		389782	

* p<0.05, ** p<0.01, *** p<0.001, IV: Instrumental Variable, ICUs: Intensive Care Units, PPIs: Proton Pump Inhibitors, NSAIDs: Non-Steroidal Anti-inflammatory Drugs

The C-statistic which measures the ability of the model to discriminate patients who received PPIs for three days vs. patients who received H2Bs for three days at each time point was 0.801 indicating an acceptable level of discrimination. The residuals calculated from the first stage were Pearson’s residuals adjusted for the number of patients who shares the same covariate pattern²⁰⁸.

The model for the 2nd stage:

$$\text{Log } h(t) = \log \lambda_0(t) + \beta_1 \text{PPISVSH2Bs} + \beta_2 \text{PRESIDUALS} + \beta_3 \text{SURF} + \beta_4 \text{CONDITIONS1} + \beta_5 \text{MEDS} + \beta_6 \text{PHYSICIAN} + \beta_7 \text{ADMISSIONS} + \beta_8 \text{TEACHING} + \beta_9 \text{APACHEIV} + \beta_{10} \text{RACE} + \mu$$

Where:

PPISVSH2Bs: Three days of PPIs therapy vs. Three days of H2Bs therapy.

PRESIDUALS: Pearson's Residuals adjusted for the number of patients sharing the same covariates pattern.

SURF: A vector of dummy variables for stress ulcer risk factors (mechanical ventilation > 24 hrs., major head injuries, major burns, sepsis, corticosteroids therapy > 250 mg of hydrocortisone or equivalent daily, acute renal failure, hepatic failure, transplantation, neurological injuries, hypotension, surgery or trauma, or ICU LOS > 1 week)

CONDITIONS1: A vector of dummy variables for conditions that may influence risk of CDAD (Gastrointestinal diseases, immunosuppression and intubation in the first day)

MEDS: A vector of dummy variables for therapeutic classes that may influence risk of NP (Sucralfate , Antacids, NSAIDs, Aminoglycosides, Cephalosporins, Flouroquinolones, Lincosamide, Linezolid, Macrolides, Metronidazole, Other B-lactams, Penicillins, Tetracyclines, Antibiotics, Others)

ADMISSIONS: A categorical variable for admission source (Direct admission, chest pain center, emergency room, floor, operating room and others (other hospital or ICU, recovery room, step-down unit))

TEACHING: A dummy variable for the teaching status of the admitting hospital.

APACHEIV: A continuous variable for APACHE-IV score

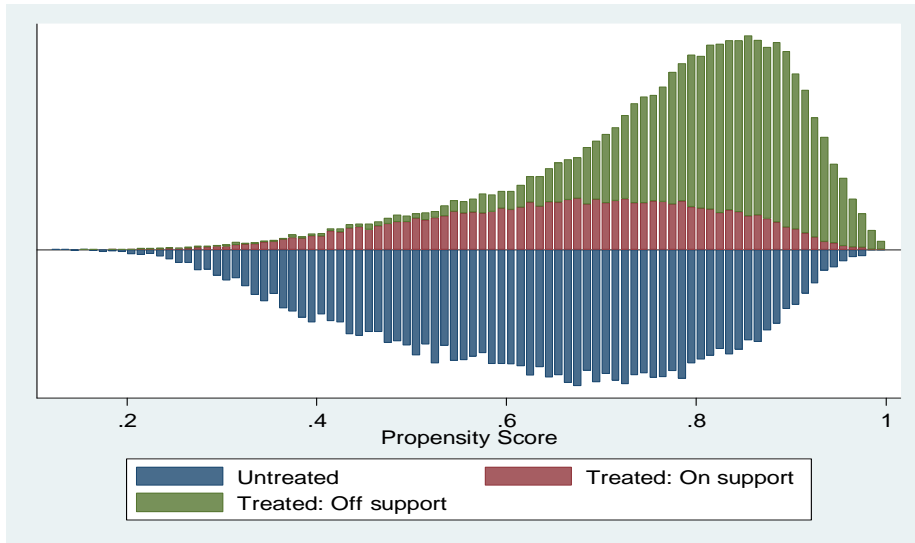
Appendix III Table 13: Cox Proportional Hazard model for the effect of the receipt of Three days PPIs vs. Three days H2Bs on the occurrence of *Clostridium difficile*-associated diseases using the Two Stage Residuals inclusion Method.

Characteristics		HR	95%CI
Exposure	Three-day use of PPIs vs. Three-day use of H2Bs	1.497*	[1.048,2.139]
Residuals	Pearson's Residuals	0.955**	[0.926,0.985]
Race	Caucasian	Reference	
	African American	1.391*	[1.081,1.790]
	Hispanic	2.204**	[1.212,4.009]
	Native American	1.667*	[1.119,2.484]
	Asian	0.891	[0.338,2.344]
	Others	1.883***	[1.357,2.611]
Any Gastrointestinal Diseases		1.021	[0.659,1.584]
Immunosuppression		1.168	[0.778,1.753]
Intubated in the First Day		1.074	[0.864,1.334]
Risk Factors	Mechanical Ventilation > 24 Hours	1.492**	[1.135,1.960]
	Traumatic Brain Injury	0.604	[0.307,1.187]
	Hepatic Failure	0.485	[0.187,1.256]
	Hydrocortisone \geq 250 Mg / Day or Equivalent	0.812	[0.541,1.217]
	Transplantation	2.368	[0.369,15.20]
	Acute Myocardial Infarction	1.032	[0.522,2.042]
	Sepsis	1.005	[0.811,1.244]
	Neurological Injuries	0.679*	[0.475,0.971]
	Surgical And Multiple Trauma	0.899	[0.625,1.292]
	Hypotension	0.998	[0.798,1.248]
	Acute Renal Failure	1.064	[0.878,1.289]
Medication	Sucralfate	0.873	[0.495,1.539]
	Antacids	0.997	[0.806,1.234]
	NSAIDs	1.003	[0.821,1.224]
	Aminoglycosides	1.111	[0.819,1.506]
	Cephalosporins	1.128	[0.928,1.372]
	Flouroquinolones	0.852	[0.707,1.025]
	Lincosamide	1.389*	[1.026,1.882]
	Linezolid	1.923***	[1.501,2.465]
	Macrolides	1.152	[0.886,1.498]
	Metronidazole	2.745***	[2.154,3.497]
	Other B-lactams	1.484***	[1.208,1.823]
	Penicillins	1.386**	[1.118,1.717]
	Tetracyclines	0.603	[0.287,1.267]
	Antibiotics, Others	1.157	[0.803,1.666]
Admission Source	Direct Admission	Reference	
	Emergency Room	0.895	[0.666,1.203]
	Floor	1.21	[0.865,1.693]
	Operating Room	1.147	[0.707,1.860]
	Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	1.069	[0.729,1.568]
Teaching Hospital		0.804	[0.607,1.066]
Continuous Variables	APACHE Score IV	1.004*	[1.000,1.007]
Observations	Observations	389782	

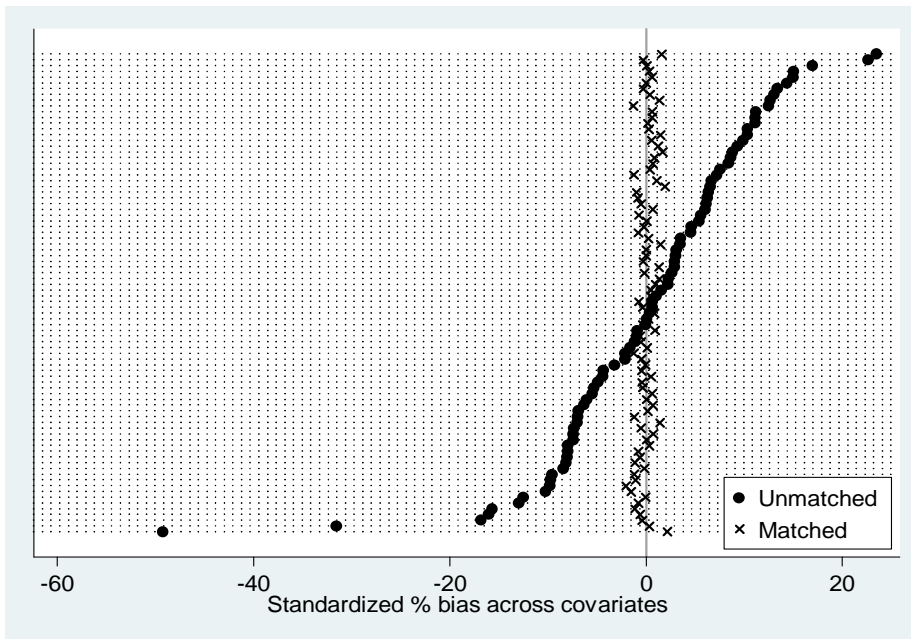
Propensity score matching:

Out of the 84,362 patients, 40,648 patients were one to one matched resulting in 20,249 patients in each group. In more details, out of the 61,254 patients who received PPIs only 20,249 had propensity scores that overlapped with those of the H2Bs group. The C statistic for the propensity score model was 0.73 indicating an acceptable level of predicting the receipt of PPIs compared to the receipt of H2Bs. The model passed the Pearson's X^2 test as the P-value was insignificant (P-value=0.09) but failed the Hosmer-Lemeshow test as the P-value was less than 0.0001. However, with the large number of observations, Hosmer-Lemeshow test becomes very sensitive making the P-value significant most of the times. The groups were matched on all the included covariates in the propensity score model. The maximum absolute percentage of standardized bias was 2.8 with a mean of 0.7 and a median of 0.6. In addition, only being in a teaching hospital had a P-value of t-test below 0.05 indicating very well matched groups (Appendix III, Table 14). However, since the absolute percentage of standardized bias was less than 10%, no further adjustments were needed. The risk of CDAD was higher among patients who received PPIs compared to patients who received H2Bs. (HR: 1.32, 95%CI: 1.034-1.7; P=0.03).

Appendix III Figure 3: Propensity score distribution of patients who received Proton pump inhibitors for three days (labeled Treated) and patients who received Histamine Type-2 receptors Blockers (labeled Untreated)



Appendix III Figure 4: Percentage of Standardized bias across covariates before matching and after matching.



Appendix III Table 14: Covariate Distribution Before and After performing one to one matching with no replacement.

Characteristics			Mean		% bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=	n=				
Male	Unmatched	0.532	0.540	-1.60		-2.10	0.04	
	Matched	0.535	0.537	-0.40	73.30	-0.44	0.66	
Age	18 To 60	Unmatched	0.376	0.415	-8.00		-10.43	0.00
	Matched	0.396	0.396	-0.10	99.00	-0.08	0.94	
61 To 70	Unmatched	0.226	0.221	1.00		1.36	0.18	
	Matched	0.226	0.227	-0.30	67.30	-0.34	0.73	
71 To 80	Unmatched	0.223	0.208	3.60		4.58	0.00	
	Matched	0.218	0.215	0.90	75.10	0.89	0.37	
≥ 81	Unmatched	0.176	0.156	5.40		6.96	0.00	
	Matched	0.160	0.162	-0.50	91.00	-0.50	0.62	
Race	Caucasian	Unmatched	0.773	0.747	6.00		7.88	0.00
	Matched	0.756	0.754	0.60	90.60	0.57	0.57	
African American	Unmatched	0.117	0.097	6.30		7.99	0.00	
	Matched	0.098	0.102	-1.20	80.70	-1.26	0.21	
Hispanic	Unmatched	0.028	0.028	0.30		0.45	0.66	
	Matched	0.029	0.029	0.40	-21.20	0.41	0.68	
Native American	Unmatched	0.008	0.005	3.10		3.82	0.00	
	Matched	0.007	0.006	1.20	60.40	1.26	0.21	
Asian	Unmatched	0.012	0.013	-1.20		-1.54	0.12	
	Matched	0.013	0.012	0.60	50.70	0.58	0.56	
Others	Unmatched	0.063	0.109	-16.80		-23.08	0.00	
	Matched	0.096	0.097	-0.40	97.90	-0.34	0.74	
ICU Type	Mixed	Unmatched	0.426	0.581	-31.50		-40.84	0.00
	Matched	0.545	0.552	-1.40	95.60	-1.39	0.17	
Cardiovascular-Surgical	Unmatched	0.078	0.098	-6.90		-9.14	0.00	
	Matched	0.099	0.097	0.80	87.90	0.80	0.42	
Coronary Care	Unmatched	0.208	0.144	17.00		21.32	0.00	
	Matched	0.159	0.158	0.30	98.50	0.27	0.79	
Trauma	Unmatched	0.003	0.009	-7.40		-10.79	0.00	
	Matched	0.007	0.007	0.20	96.60	0.24	0.81	
Surgical	Unmatched	0.090	0.053	14.40		17.66	0.00	
	Matched	0.060	0.059	0.20	98.50	0.23	0.82	
Medical	Unmatched	0.123	0.059	22.70		27.41	0.00	
	Matched	0.067	0.066	0.50	97.90	0.56	0.58	

Appendix III Table 14, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=20,249	n=20,249				
Neuroscience	Unmatched		0.071	0.056	6.10		7.77	0.00
	Matched		0.063	0.061	0.60	90.80	0.58	0.56
Nutrition	No Feeding	Unmatched	0.383	0.431	-9.80		-12.72	0.00
		Matched	0.414	0.427	-2.60	73.30	-2.61	0.01
	Enteral Nutrition	Unmatched	0.536	0.500	7.20		9.38	0.00
		Matched	0.501	0.507	-1.20	83.90	-1.17	0.24
	Parenteral Nutrition	Unmatched	0.042	0.022	11.20		13.57	0.00
		Matched	0.025	0.024	0.10	99.20	0.10	0.92
Any Gastrointestinal Diseases	Unmatched		0.031	0.018	8.80		10.80	0.00
	Matched		0.019	0.019	-0.10	98.90	-0.11	0.91
Cancer	Unmatched		0.075	0.069	2.20		2.85	0.00
	Matched		0.072	0.071	0.50	76.00	0.54	0.59
HIV	Unmatched		0.002	0.002	0.60		0.81	0.42
	Matched		0.001	0.002	-0.90	-45.10	-0.97	0.33
Cirrhosis	Unmatched		0.018	0.006	11.20		13.07	0.00
	Matched		0.007	0.006	0.80	92.60	1.09	0.28
Neutropenia	Unmatched		0.059	0.075	-6.00		-7.98	0.00
	Matched		0.069	0.069	0.00	99.30	0.04	0.97
Thrombocytopenia	Unmatched		0.175	0.121	15.00		18.80	0.00
	Matched		0.135	0.130	1.30	91.00	1.42	0.16
Immunosuppression	Unmatched		0.035	0.024	6.50		8.12	0.00
	Matched		0.029	0.027	1.30	80.80	1.30	0.19
Intubated in the First Day	Unmatched		0.444	0.495	-10.30		-13.31	0.00
	Matched		0.478	0.484	-1.10	89.00	-1.13	0.26
Risk Factors	Coagulopathy	Unmatched	0.249	0.206	10.30		13.21	0.00
		Matched	0.221	0.215	1.40	86.50	1.43	0.15
	Mechanical Ventilation > 24 Hours	Unmatched	0.516	0.556	-8.00		-10.32	0.00
		Matched	0.543	0.548	-1.00	87.50	-1.01	0.31
	Traumatic Brain Injury	Unmatched	0.035	0.055	-9.80		-13.29	0.00
		Matched	0.044	0.045	-0.20	98.30	-0.17	0.87
	Hepatic Failure	Unmatched	0.011	0.003	8.70		10.12	0.00
		Matched	0.004	0.004	0.60	92.50	0.85	0.39
	Hydrocortisone	Unmatched	0.042	0.043	0.00		-0.05	0.96

Appendix III Table 14, Continued

Characteristics		Mean		%bias	% of Bias Reduction	t-test	
		PPIs	H2Bs			t	p> t
		n=	n=				
≥ 250 Mg / Day or Equivalent							
	Matched	0.041	0.043	-0.80	-1948.90	-0.79	0.43
Transplantation	Unmatched	0.002	0.001	2.30		2.83	0.01
	Matched	0.002	0.001	2.20	5.50	2.12	0.03
Acute Myocardial Infarction	Unmatched	0.025	0.037	-7.40		-10.03	0.00
	Matched	0.036	0.037	-0.90	87.70	-0.85	0.40
Sepsis	Unmatched	0.236	0.191	11.10		14.15	0.00
	Matched	0.201	0.201	-0.20	98.40	-0.19	0.85
Neurological Injuries	Unmatched	0.114	0.168	-15.70		-21.12	0.00
	Matched	0.141	0.143	-0.70	95.30	-0.74	0.46
Surgical And Multiple Trauma	Unmatched	0.180	0.246	-16.00		-21.31	0.00
	Matched	0.235	0.229	1.30	92.20	1.22	0.22
Hypotension	Unmatched	0.241	0.221	4.60		5.92	0.00
	Matched	0.224	0.225	-0.30	93.10	-0.32	0.75
Acute Renal Failure	Unmatched	0.276	0.220	13.10		16.64	0.00
	Matched	0.231	0.233	-0.30	97.80	-0.29	0.77
Medication Sucralfate	Unmatched	0.026	0.012	10.30		12.42	0.00
	Matched	0.017	0.014	2.60	74.60	2.94	0.00
Antacids	Unmatched	0.272	0.297	-5.50		-7.13	0.00
	Matched	0.293	0.292	0.20	96.00	0.22	0.83
Anticoagulants	Unmatched	0.462	0.483	-4.30		-5.60	0.00
	Matched	0.482	0.485	-0.70	82.70	-0.75	0.45
Antiplatelets	Unmatched	0.525	0.564	-8.00		-10.30	0.00
	Matched	0.565	0.565	0.00	99.50	-0.04	0.97
Thrombolytics	Unmatched	0.047	0.067	-8.40		-11.35	0.00
	Matched	0.066	0.065	0.40	94.70	0.42	0.67
NSAIDs	Unmatched	0.446	0.472	-5.30		-6.85	0.00
	Matched	0.462	0.463	-0.30	93.80	-0.33	0.74
Aminoglycosides	Unmatched	0.033	0.030	1.60		2.00	0.05
	Matched	0.031	0.030	0.60	63.70	0.57	0.57
Cephalosporins	Unmatched	0.297	0.335	-8.10		-10.62	0.00
	Matched	0.318	0.321	-0.70	91.30	-0.71	0.48
Flouroquinolones	Unmatched	0.268	0.226	9.90		12.67	0.00
	Matched	0.239	0.239	0.00	99.50	0.05	0.96

Appendix III Table 14, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=20,249	n=20,249				
Lincosamide	Unmatched		0.036	0.038	-1.00		-1.26	0.21
	Matched		0.037	0.037	-0.40	54.00	-0.45	0.66
Linezolid	Unmatched		0.032	0.026	3.50		4.45	0.00
	Matched		0.028	0.028	0.20	93.30	0.24	0.81
Macrolides	Unmatched		0.075	0.073	0.60		0.83	0.40
	Matched		0.071	0.075	-1.30	-103.70	-1.33	0.18
Metronidazole	Unmatched		0.087	0.063	9.30		11.71	0.00
	Matched		0.069	0.068	0.70	92.40	0.75	0.46
Other B-lactams	Unmatched		0.094	0.071	8.40		10.63	0.00
	Matched		0.077	0.076	0.30	96.20	0.34	0.74
Penicillins	Unmatched		0.427	0.354	15.00		19.33	0.00
	Matched		0.376	0.374	0.40	97.20	0.43	0.67
Tetracyclines	Unmatched		0.011	0.009	2.60		3.29	0.00
	Matched		0.009	0.009	-0.50	81.00	-0.53	0.60
Vancomycin	Unmatched		0.338	0.323	3.00		3.92	0.00
	Matched		0.328	0.332	-0.80	73.80	-0.80	0.42
Antibiotics, Others	Unmatched		0.016	0.013	2.90		3.70	0.00
	Matched		0.014	0.014	0.20	93.00	0.21	0.83
Admission Source	Direct Admission	Unmatched	0.084	0.098	-4.90		-6.43	0.00
		Matched	0.095	0.095	0.00	99.30	0.03	0.97
Emergency Room	Unmatched		0.530	0.515	2.90		3.81	0.00
	Matched		0.509	0.513	-0.90	70.90	-0.86	0.39
Floor	Unmatched		0.177	0.132	12.70		15.99	0.00
	Matched		0.142	0.142	0.20	98.30	0.23	0.82
Operating Room	Unmatched		0.130	0.177	-13.00		-17.30	0.00
	Matched		0.172	0.170	0.70	94.90	0.63	0.53
Other (Other Hospital or ICU, Recovery Room, Step-Down Unit)	Unmatched		0.078	0.078	0.10		0.13	0.89
	Matched		0.081	0.080	0.40	-273.10	0.38	0.70
Year of Admission	2008	Unmatched	0.167	0.146	5.60		7.14	0.00
		Matched	0.145	0.148	-0.90	84.50	-0.90	0.37
2009	Unmatched		0.222	0.204	4.50		5.85	0.00
	Matched		0.207	0.206	0.20	96.00	0.18	0.85
2010	Unmatched		0.241	0.255	-3.20		-4.19	0.00
	Matched		0.247	0.253	-1.40	55.10	-1.45	0.15

Appendix III Table 14, Continued

Characteristics			Mean		%bias	% of Bias Reduction	t-test	
			PPIs	H2Bs			t	p> t
			n=20,249	n=20,249				
2011	Unmatched		0.254	0.258	-0.90		-1.18	0.24
	Matched		0.263	0.259	0.90	0.60	0.90	0.37
2012	Unmatched		0.116	0.137	-6.30		-8.32	0.00
	Matched		0.139	0.134	1.40	77.50	1.39	0.17
Physician Specialty	Internal medicine	Unmatched	0.205	0.119	23.50		29.05	0.00
		Matched	0.133	0.133	0.10	99.50	0.12	0.91
Pulmonary	Unmatched		0.167	0.193	-7.00		-9.12	0.00
	Matched		0.194	0.195	-0.40	94.10	-0.40	0.69
Hospitalist	Unmatched		0.112	0.073	13.40		16.68	0.00
	Matched		0.079	0.079	0.00	99.90	0.02	0.99
Cardiology	Unmatched		0.067	0.085	-7.00		-9.30	0.00
	Matched		0.091	0.086	1.60	77.40	1.48	0.14
Surgery-general	Unmatched		0.058	0.069	-4.40		-5.79	0.00
	Matched		0.070	0.066	1.50	66.90	1.42	0.16
Critical care medicine (CCM)	Unmatched		0.065	0.084	-7.30		-9.78	0.00
	Matched		0.079	0.081	-0.80	89.30	-0.77	0.44
Family practice	Unmatched		0.069	0.051	7.60		9.52	0.00
	Matched		0.057	0.057	0.10	98.10	0.15	0.88
Surgery-cardiac	Unmatched		0.035	0.062	-12.50		-17.21	0.00
	Matched		0.055	0.057	-0.90	92.50	-0.89	0.38
Others	Unmatched		0.221	0.262	-9.60		-12.56	0.00
	Matched		0.242	0.245	-0.70	93.00	-0.67	0.50
Teaching Hospital	Unmatched		0.233	0.460	-49.30		-66.31	0.00
	Matched		0.422	0.409	2.80	94.20	2.69	0.01
Continuous Variables	APACHE Score IV	Matched	67.222	63.900	12.50		16.19	0.00
		Unmatched	64.845	64.800	0.20	98.60	0.17	0.86

Appendix IV:



University of Maryland, Baltimore
Institutional Review Board
Phone: (410) 706-5037
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Email: irbo@som.umaryland.edu

NOT HUMAN RESEARCH DETERMINATION

Date: June 28, 2013

To: Ilene Zuckerman
RE: HP-0005985

This letter is to acknowledge that the UMB IRB reviewed the information provided and has determined that the submission does not require IRB review. This determination has been made with the understanding that the proposed project does not involve a systematic investigation designed to develop or contribute to generalizable knowledge **OR** a human participant (see definitions below).

This determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether these activities are human subject research in which the organization is engaged, please submit a new request to the IRB for a determination.

Definitions –

Human Research: Any activity that either:

- Is “Research” as defined by DHHS and involves “Human Subjects” as defined by DHHS (“DHHS Human Research”); or
- Is “Research” as defined by FDA and involves “Human Subjects” as defined by FDA (“FDA Human Research”).

Research as Defined by DHHS: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Research as Defined by FDA: Any experiment that involves a test article and one or more human subjects, and that meets any one of the following:

- Must meet the requirements for prior submission to the Food and Drug Administration under section 505(j) of the Federal Food, Drug, and Cosmetic Act meaning any use of a drug other than the use of an approved drug in the course of medical practice;
- Must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act meaning any activity that evaluates the safety or effectiveness of a device; OR
- Any activity the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

Human Subject as Defined by DHHS: A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through Intervention or Interaction with the

individual, or (2) information that is both Private Information and Identifiable Information. For the purpose of this definition:

- Intervention means physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- Interaction means communication or interpersonal contact between investigator and subject.
- Private Information means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- Identifiable Information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

Human Subject as Defined by FDA: An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. A human subject includes an individual on whose specimen (identified or unidentified) a medical device is used.

Please keep a copy of this letter for future reference. If you have any questions, please do not hesitate to contact the Human Research Protections Office (HRPO) at (410) 706-5037 or HRPO@som.umaryland.edu.

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