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# Health Outcomes of Statin Users Compared to Non-Users with *Clostridium difficile* Infection

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# Health Outcomes of Statin Users Compared to Non-Users with *Clostridium difficile* Infection

**by**

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# Dedication

I dedicate this thesis to my family and friends who have supported me throughout my educational journey.

## Acknowledgements

I would like to thank my supervisor, Dr. Kelly Reveles, for her guidance and support over the past three years. Dr. Reveles inspired me to pursue an academic career and provided me a solid foundation for success. I would not be where I am today without her. I would also like to acknowledge the tremendous efforts of my dissertation committee members, Dr. Grace Lee and Dr. Bryson Duhon. Thank you for your guidance and patience throughout my post-Pharm.D.-graduate program and this thesis project.

# Abstract

## Health Outcomes of Statin Users Compared to Non-Users with *Clostridium difficile* Infection

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**Background:** *Clostridium difficile* infection (CDI) is the most common cause of nosocomial diarrhea, and the primary cause of healthcare-associated infections in the United States. Statins have beneficial effects independent of their lipid-lowering effects; these pleiotropic effects may include anti-inflammatory and immunomodulatory activity. The potential role for statins in CDI is unique in that both the cholesterol-lowering and pleiotropic effects of statins could lead to improvements in clinical response for patients with CDI.

**Rationale:** Limited data currently exist in the literature on the outcomes of statin users who develop CDI compared with non-users. The primary objective of this study was to compare CDI health outcomes in statin users and non-users in a national cohort of patients from a single-payer health system.

**Methods:** This was a longitudinal, retrospective cohort study of all adult CDI patients receiving care from the Veterans Health Administration. Patients were divided into two groups based on statin exposure prior to and during the first CDI encounter. For the

primary analysis, we created a propensity score-matched cohort to account for variables associated with indications for statin use. Once the matched cohort was derived, additional variables known to impact CDI outcomes were entered into a multivariable logistic regression model in order to determine the risk of individual CDI outcomes.

**Results:** CDI outcomes were evaluated for statin users and non-users before and after propensity score-matching. In the unmatched cohort, statin use was significantly associated with reduced risk of 30-day mortality (aOR 0.60, 95% CI 0.36-1.00, p=0.0478). In the matched cohort, statin use remained significantly associated with a reduced risk of 30-day mortality (aOR 0.45, 95% CI 0.23-0.88, p=0.0198). No significant trends were found for inpatient mortality, 60-day recurrence, and severe or complicated CDI.

**Conclusion:** This is the largest study comparing CDI health outcomes among statin users and non-users. Statin users were found to have significantly reduced 30-day mortality in both an unmatched and matched patient cohort compared to non-users. While these data support previous findings reported in the literature, no change in routine care of CDI patients can be recommended at this time.

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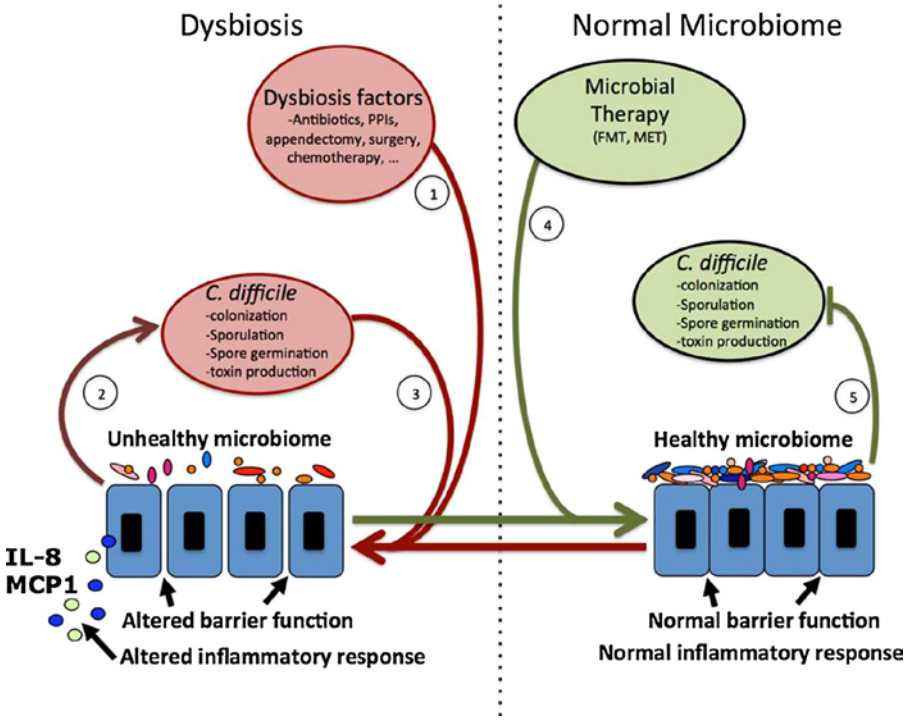
# Chapter One: *Clostridium difficile* Infections

## MICROBIOLOGY AND PATHOGENESIS

*Clostridium difficile* is a Gram-positive, spore-forming, anaerobic bacterium. Its name reflects the difficulty in isolating the organism and its slow growth in culture.[1,2] This species can become a natural colonizer of the human gastrointestinal (GI) tract after exposure to the spores via the fecal-oral route of transmission. *C. difficile* is clinically significant for its association with antibiotic-associated diarrhea.[3,4] Specifically, *C. difficile* infection (CDI) is the most common cause of nosocomial diarrhea, and more recently, became the primary cause of healthcare-associated infections in the United States (US).

*C. difficile* is a non-invasive organism and infections due to this organism are primarily localized to the GI tract.[3] Many people are colonized with non-toxigenic strains of *C. difficile* that are not known to cause disease and may be protective against infection with toxigenic strains.[5,6] Disruption of the gut microflora due to broad-spectrum antibiotic therapy is the most significant risk factor for the development of CDI.[4,7] Following this disruption, exposure to *C. difficile* spores in the environment leads to colonization and proliferation of *C. difficile*.[8] Disease develops when the bacteria produces toxins that elicit an inflammatory response (Figure 1).[9] Symptoms of CDI can include diarrhea, dehydration, fever, leukocytosis, and in severe cases, complications may include prolonged ileus, toxic megacolon, septic shock, intestinal perforation, and death.[8,9]

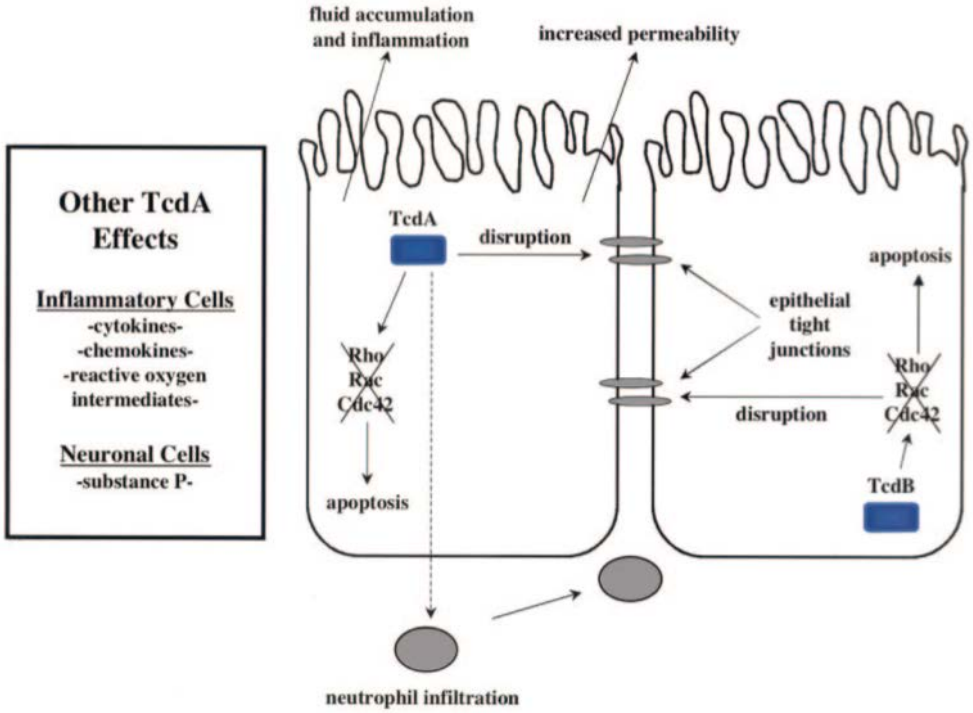
Figure 1. Pathophysiology of CDI[9]




*C. difficile* is known to produce three toxins in the body: Toxin A (tcdA), Toxin B (tcdB), and binary toxin.[5,6] Toxins produced and the amount of toxin produced vary amongst different strains of *C. difficile*. Toxins A and B are known to be the primary virulence factors associated with *C. difficile*.[6] Toxin A acts primarily as an enterotoxin, causing local tissue injury and inflammation. Toxin B acts primarily as a cytotoxin by killing the GI cells. The effects of these toxins are due to their work as glucosyltransferases to inactivate regulatory pathways mediated by the Rho family of guanosine triphosphatases (Rho GTPases).[5,6] These Rho GTPases are proteins involved in cytoskeleton structure and signal transduction, and their inactivation ultimately leads to cell apoptosis, the loss of intestinal barrier integrity, and neutrophilic colitis (Figure 2).[5] Binary toxin is a more recent discovery, and its effect on the pathogenicity of *C. difficile* is not fully understood.[10]

Clinical expression of disease depends on virulence of the infecting strain and the host's immune response.[8] Virulence of an infecting strain is often attributed to increased toxin production as compared to less pathogenic strains. Additionally, there is evidence that asymptomatic *C. difficile* carriers and immune system production of toxin A antibodies are protective against severe CDI.[4,11]

Figure 2. Effects of *C. difficile* Toxins A and B on Intestinal Cells[5]




Unfortunately, the treatment for CDI requires therapy with oral antibiotics, such as metronidazole and vancomycin, which can further disrupt the balance of GI flora.[8] It can take weeks to months for patients to recover from infection and restore normal flora.[12] In that time, patients are susceptible to recurrent CDI, either by reinfection of *C. difficile* through spore exposure or by relapse of the initial infection due to hidden spores

germinating.[13] Other risk factors for CDI include older age (≥65 years), prolonged hospitalization, severe underlying illness, inflammatory bowel disease, and GI surgery or manipulation.[4,7,8,14] In addition to antibiotics, the use of other medications such as immunosuppressants, gastric acid suppressants, antineoplastic agents have been associated with CDI.

## DIAGNOSIS

Diagnosis of CDI relies on a combination of clinical suspicion and laboratory testing (Table 1).[14,15] Healthcare providers should have a strong suspicion of CDI based on patient symptoms or imaging prior to sending stool samples for testing. Laboratory testing can involve multi-step algorithms which incorporate a glutamate dehydrogenase (GDH) antigen testing step to screen patients for CDI followed by a toxin assay or polymerase chain reaction (PCR) test for toxin genes for confirmation of diagnosis.

Table 1. Laboratory Testing for Diagnosis of CDI

| **Test** | **Detects** | **Advantages** | **Disadvantages** |
|---|---|---|---|
| Stool culture | Bacteria | High sensitivity | Slow turnaround |
| Toxin assay | Toxins | Rapid turnaround | Moderate sensitivity |
| GDH testing | Antigen | Rapid turnaround | Screening only |
| PCR | Toxin genes | Rapid turnaround<br>High sensitivity | False positives |

## GUIDELINE RECOMMENDED TREATMENT

In 2010, the Infectious Diseases Society of America (IDSA) published guidelines for the treatment and prevention of CDI.[14] Current IDSA CDI guidelines recommend

treatment based on CDI type and severity (Table 2). Severe CDI is defined as leukocytosis with a white blood cell (WBC) count ≥15,000 cells/μL or an increase in serum creatinine to greater than 1.5 times the baseline level. The guidelines further classify patients as "complicated" if they have hypotension or shock, ileus, or toxic megacolon. Infections complicated by toxic megacolon, intestinal perforation, or necrotizing colitis can require emergency surgical procedures, including a total or partial colectomy.

It is recommended that patients who experience CDI for the first time be treated with metronidazole or oral vancomycin.[14,15] Recent studies have shown that vancomycin is superior to metronidazole in treating severe disease; thus, oral vancomcyin is currently recommended for severe CDI.[8,16] First recurrences are generally treated with the same agent used for the initial episode, but oral vancomycin is preferred for severe recurrences. After receiving approval from the U.S. Food and Drug Administration (FDA) in 2011, fidaxomicin gained notoriety as the first new antibiotic indicated for CDI in 25 years.[8] Data from clinical trials have shown fidaxomicin is non-inferior to vancomycin for mild to moderate CDI and may be more effective than vancomycin at preventing disease recurrence.[17,18]

Table 2: Guideline Recommended CDI Treatment Regimens

| **Clinical definition** | **Recommended treatment** |
|---|---|
| Initial episode: *Mild or moderate* | Metronidazole 500 mg oral q8h x 10-14 days |
| Initial episode: *Severe* | Vancomycin 125 mg oral q6h x 10-14 days |
| Initial episode: *Complicated* | Vancomycin 500 mg oral q6h PLUS<br>Metronidazole 500 mg IV q8h x 10-14 days<br>Optional: vancomycin enema for rectal instillation |
| First recurrence | Same as initial episode, unless severe |
| Second recurrence | Pulsed or tapered vancomycin<br>Fidaxomicin 200 mg oral q12h x 10 days* |
| **Not recommended in 2010 guidelines due to FDA-approved in 2011* | |

## ADDITIONAL TREATMENT OPTIONS

There are non-antibiotic therapies that may be used for the treatment of CDI; however, these have limited effectiveness data. Current research has focused heavily on finding ways to restore the natural balance of the gastrointestinal microbiome, by adjunctive treatment with probiotics and more recently in controlled trials of fecal microbiota transplantation (FMT).[9,19-21] Theoretically, probiotics could improve CDI outcomes by altering the gut flora, providing antimicrobial activity and intestinal barrier protection, and immunomodulation; however, evidence of clinical significance and recommendations for specific probiotic products remains debatable.[14,22] Early trials of FMT have shown high rates of success in recurrent disease when donor feces are administered as a suspension via colonoscope, retention enema, or nasogastric tube to treat CDI recurrence.[19-21]

Immune response to *C. difficile* is a major determinant of health outcomes among patients with CDI; therefore, immunomodulatory therapies, such as intravenous immune globulin (IVIG) and monoclonal antibodies might play a role in the treatment of CDI.[8,14] In 2016, bezlotoxumab (Zinplava®) was approved by the FDA as the first human monoclonal antibody that binds to *C. difficile* Toxin B.[23,24] It must be used in conjunction with antibiotic therapy for CDI and is indicated to reduce recurrence of CDI in patients considered to be at high risk for recurrence.

# Chapter Two: Statin Therapy in CDI

## POTENTIAL ROLE FOR STATINS

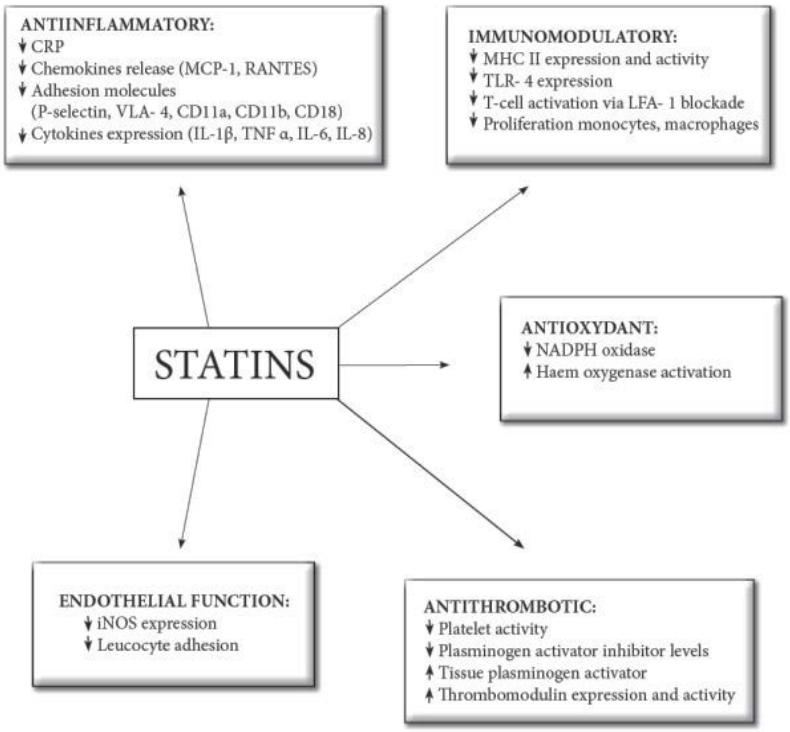
A hypothetical but unique approach to the adjunctive treatment of CDI involves the use of statins for their myriad of effects on inflammatory pathways.[25-27] Statins are reversible, competitive inhibitors of 3-hydroxyl-3-methylgutarul-coenzyme A (HMG-CoA) reductase. Through this mechanism, statins are able to inhibit the rate-limiting step in cholesterol biosynthesis. They are used in the primary and secondary prevention of cardiovascular disease.[28] During its first 15 years on the market (1996-2011), atorvastatin (Lipitor®) became the top selling prescription medication in the world.[29] From 2007 to 2010, data from the National Health and Nutrition Examination Survey showed that, among adults between the ages of 40-64 years, only 19% used a cholesterol-lowering medication while the rate was as high as 39% among adults 65-74 years of age.[30]

The lipid-lowering effects of statins may play a role in CDI for two reasons. First, hyperlipidemia (HLD) is believed to cause a persistent, generalized inflammatory state of the body; one example of this is the elevation of biomarkers such as the C-reactive protein (CRP) seen in patients with atherosclerotic disease.[26-28,31] With regard to CDI patients, those with pre-existing GI inflammation, such as that seen in patients with inflammatory bowel disease (IBD), are associated with poorer clinical outcomes, including recurrence and death.[32-35] Additionally, these patients are also at an increased risk for CDI due to frequent healthcare exposures, gut microbiota dysbioses, and exposure to medications.[32,36,37] Second, cholesterol contributes to the toxin activity of *C. difficile.* Specifically, cholesterol facilitates toxin binding to cells and is required for toxin penetration into the cells.[38,39] In our own preliminary data, dyslipidemia [*International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code 272] was

significantly associated with 60-day recurrence (55% vs. 49%, p<0.0001). Statins may also play a role in CDI therapy beyond the lipid-lowering effects described above.[40]

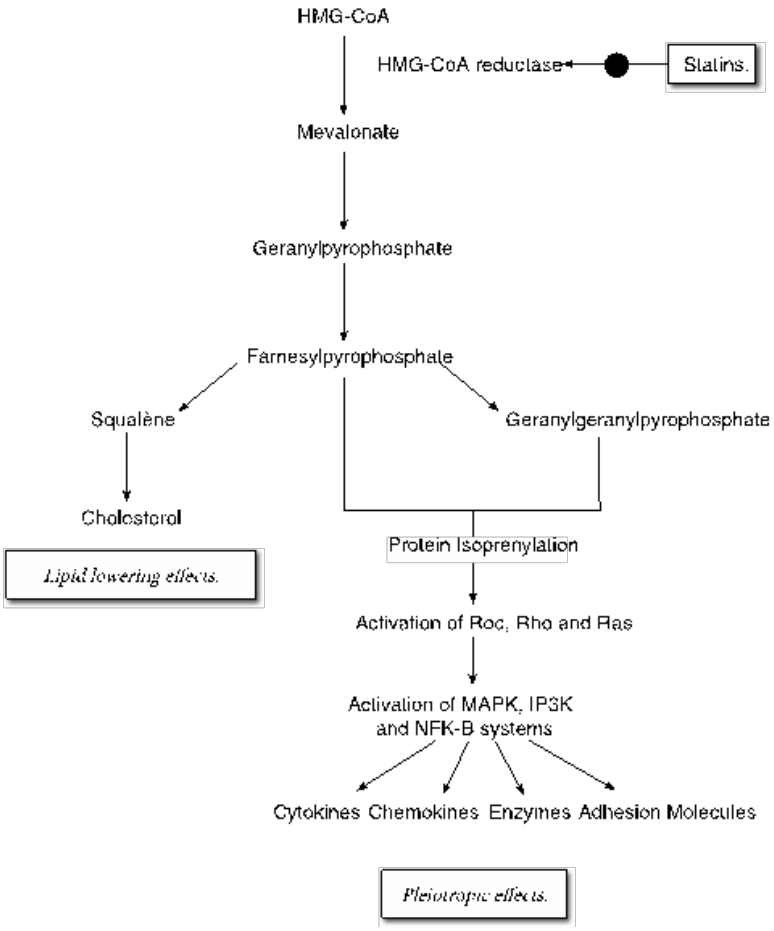
Proposed pleiotropic effects of statins (non-cardiac benefits) date back to a post-hoc analysis of the West of Scotland Prevention Study (1998).[28] Patients taking pravastatin had improved survival despite similar cholesterol levels as compared with patients taking placebo. It was hypothesized that statins have beneficial effects independent of their lipid-lowering effects. These pleiotropic effects of statins may include anti-inflammatory, immunomodulatory, antioxidant, and antithrombotic activity (Figure 3).[41]

Figure 3. Pleiotropic Effects of Statins[41]



The mechanism responsible for these effects is likely related to a reduction in the synthesis of cholesterol intermediary products which leads to decreased activation of Rho GTPases, ultimately reducing the response of inflammatory intracellular signaling pathways (Figure 4).[41] These pathways are of particular importance in patients with CDI due to the activation of these pathways by toxins A and B.[5,6]

Figure 4. Statin Mechanism of Action[41]



The potential benefits associated with statins in observational studies are subject to a type of confounding or bias known as the *healthy user effect.*[42,43] Prior studies have shown that statin users are more likely to live at home, stop smoking, receive better medical care, have health insurance, and be positively engaged in the healthcare system. This leads to controversy regarding any positive associations with statin use and clinical outcomes, in that statin use may not have direct effects on the disease in question and is merely an indicator of low-risk patients.[40] Paradoxically, for a disease like CDI that is known to be associated with frequent healthcare exposure, statin use could potentially indicate patients more likely to be exposed to *C. difficile* spores in a healthcare setting.

Researchers have extensively studied the impact of statin use in other infections, including pneumonia and sepsis, as well as other inflammatory conditions, such as chronic obstructive pulmonary disease (COPD) and multiple sclerosis; however, controversy remains regarding the addition of or the decision to continue statins in many disease specific situations. Estimating the effect of statin therapy on mortality from infection and sepsis is limited by the retrospective design of studies, high heterogeneity, and confounding. In a meta-analysis from 2014, Wan et al. determined that in 27 observational studies, statins were associated with a significant decrease in mortality (aRR 0.65, 95% CI 0.57-0.75), but in five randomized controlled trials statins did not significantly decreased in-hospital mortality (RR 0.98, 95% CI 0.73-1.33) or 28-day mortality (RR 0.93, 95% CI 0.46-1.89).[44] The potential role for statins in CDI is truly unique in that both the cholesterol-lowering and pleiotropic effects of statins could lead to improvements in clinical response for patients with CDI. Prior studies designed to assess the use of statins on CDI outcomes are limited and have been plagued by small sample sizes.[45-47]

## STATINS AND INTESTINAL MICROFLORA

Aside from the hypothetical benefits of statins in CDI due to the cholesterol-lowering and anti-inflammatory effects of these agents, it is unknown if or how statins affect the natural GI flora. Alterations of the natural occurring balance of flora are seen in patients with inflammatory disease processes, obesity, diabetes mellitus, and high-fat diets.[39,48,49] Specifically, decreases in Bacteroidetes and increases in Firmicutes and Proteobacteria have been described. Similar changes to the flora are seen in CDI, leading to the hypothesis that naturally high levels of Bacteroidetes are protective against CDI colonization and overgrowth.[9,50,51] Theoretically, a diet high in cholesterol could increase a patient's risk of CDI while statin therapy could have potentially protective effects on the GI microbiome, further complicating the role of statin therapy in CDI patients.

## STATINS AND CDI RISK

Despite the potential benefits of statins on patients with CDI, few studies describe the effect, if any, of statin use on the risk of developing CDI. In 2011, Naggie et al. found a significantly decreased risk of CDI in statin users (OR 0.35, 95% CI 0.15-0.83) using a small case-control design.[52] Of the 66 CDI cases, 27% were statin users compared to 42% of the 114 controls (p=0.05). Next, in a large retrospective study from 2012, Motzkus-Feagans et al. found a similarly decreased risk of CDI in statin users (aOR 0.78, 95% CI 0.75-0.81).[53] Of the 31,472 CDI cases, 18% were statin users compared to 22% of the 78,096 controls. Finally, in 2013, Nseir et al. found that no statin use was significantly associated with an increased risk of CDI (OR 2.20, 95% CI 1.82-2.73).[54] Of the 197 cases, 33% were statin users compared to 52% of the 169 controls (p=0.02).

## STATINS AND CDI OUTCOMES

To date, three studies on the effect of statin use on CDI outcomes have been published.[45-47] In 2013, Park et al. were the first to publish data depicting an association between statin use and CDI outcomes.[45] Of 949 adult CDI patients, 21% were statin users receiving therapy for over 12 weeks. There was no significant difference in 30-day all-cause mortality (RR 1.23, 95% CI 0.59-2.55) or in the proportion of patients with a severe complication of CDI (RR 0.85, 95% CI 0.55-1.32); however, the risk of 60-day CDI recurrence was significantly lower in statin users (RR 0.39, 95% CI 0.17-0.93). In 2014, Saliba et al. published new data on the risk of 30-day all-cause mortality in CDI associated with statin use.[46] Of the 1,888 adult CDI patients included in the study, 35% were considered current statin users who had filled at least one prescription for a statin in the 90 days prior. This study found statin use was significantly associated with decreased mortality (aOR 0.57, 95% CI 0.42-0.79). In the smallest but most recent study, from 2016, assessing the impact of statin use on CDI outcomes, Atamna et al. found that 36% of their cohort of 499 adult CDI patients had been on statin therapy within the 3 months prior to diagnosis.[47] In multivariate analysis, statin use was not significantly associated with 30-day mortality (OR 1.54, 95% CI 0.85-2.79).

# Chapter Three: Objectives and Hypotheses

## KNOWLEDGE GAP

Limited data currently exist in the literature on the outcomes of statin users who develop CDI compared with non-users. Of the three studies previously described, only one study assessed both 60-day recurrence and 30-day mortality. A study with a larger sample size and more robust methodology is needed to evaluate the association between statin use and CDI outcomes (mortality, recurrence, and severity).

## OBJECTIVE 1

The primary objective of this study was to compare CDI health outcomes in statin users and non-users in a national cohort of patients from a single-payer health system.

### Hypothesis 1a

Statin use is associated with improved CDI outcomes (inpatient mortality, 30-day mortality, 60-day recurrence, and severe or complicated CDI) when compared to unmatched non-users.

### Hypothesis 1b

Statin use is associated with improved CDI outcomes (inpatient mortality, 30-day mortality, 60-day recurrence, and severe or complicated CDI) when compared to propensity-score matched non-users.

## OBJECTIVE 2

In a subgroup analysis, evaluate only prior statin users with adherence >60% in the past year for CDI outcomes to better explore the impact of long-term (chronic) statin use. Evaluate chronic statin users for a dose-response relationship between the degree of LDL lowering or the intensity of statin therapy and CDI outcomes.

### Hypothesis 2a

Chronic statin use with an LDL ≥100 mg/dL is associated with poorer CDI outcomes (30-day mortality, 60-day recurrence, and severe or complicated CDI) when compared to patients with an LDL <100 mg/dL.

### Hypothesis 2b

High intensity chronic statin therapy is associated with improved CDI outcomes (30-day mortality, 60-day recurrence, and severe or complicated CDI) when compared to low-moderate intensity chronic statin therapy.

# Chapter Four: Methods

## STUDY DESIGN

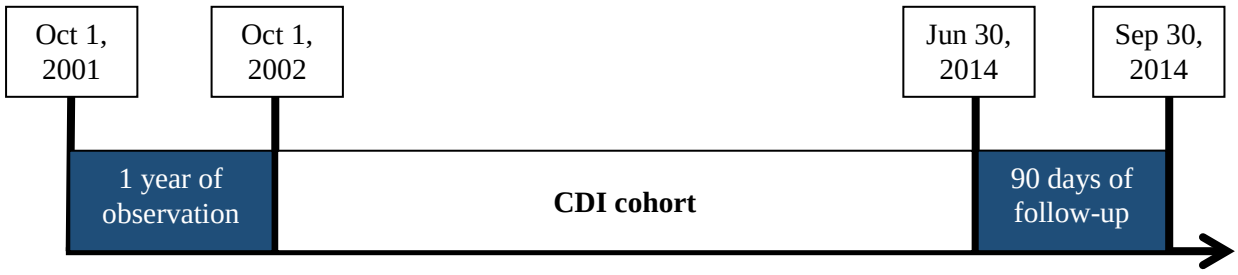
This was a longitudinal, retrospective cohort study of all CDI patients receiving care at any of the approximately 150 Veterans Health Administration (VHA) hospitals and 820 VHA clinics in the U.S. Data for this study were obtained from the Veterans Affairs Informatics and Computing Infrastructure (VINCI), which includes administrative, clinical, laboratory, and pharmacy data repositories which are linked using unique patient identifiers. All data collection and analyses were performed at the South Texas Veterans Health Care System, Audie L. Murphy Veterans Affairs (VA) Hospital, San Antonio, TX. This study was approved by the Institutional Review Boards at the University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System Research and Development Committee.

## STUDY POPULATION

The initial cohort was created by identifying all adult patients (age 18 to 89 years) who had any inpatient or outpatient ICD-9-CM code for CDI (008.45) plus any positive laboratory value for CDI (Table 1) during the visit or within 7 days of the visit from October 1, 2002 through September 30, 2014 (Figure 5). We also included a one-year observation window (October 1, 2001 through October 1, 2002) to assess prior comorbidities and medication use. For health outcomes, we limited the cohort to those patients with CDI between October 1, 2002 through June 30, 2014 to allow for a 90-day follow-up window (July 1, 2014 through September 30, 2014). The cohort was limited to first episode CDI patients and excluded patients without active CDI treatment. This was accomplished by excluding those patients with an ICD-9-CM code for CDI (008.45) in the

year prior to study inclusion (observation window). For analyses of the risk of 60-day recurrence, we also excluded those who died within 60 days of the end of treatment discontinuation for the initial episode to capture only those patients at risk for 60-day recurrence. The CDI encounter date, meaning the initial date of inpatient hospitalization or outpatient clinic visit during which CDI was diagnosed, was used as the index date for all variables unless otherwise noted.

Figure 5. Overview of Study Timeline




**STUDY DEFINITIONS**

Patients were divided into two groups, statin users and non-users, based on statin exposure prior to and during the CDI encounter. Statin use was a composite variable, defined as patients meeting criteria for both prior and concomitant statin use (Table 3). Prior statin users were defined as patients who filled at least one prescription for a statin medication in the 90 days prior to initial CDI encounter. Concomitant statin use represents documented statin use during a CDI episode. Non-users were defined as patients who had no prescription history of statins in the 90 days prior to initial CDI encounter or within 14 days of the CDI treatment start date. These two groups were used for analysis of the primary objective. All statin products available in the United States were evaluated for

prescription use (Table 4), and high-intensity statin therapy was defined as atorvastatin (Lipitor®) 40-80 mg daily or rosuvastatin (Crestor®) 20-40 mg daily according to recommendations published in 2015 by the National Lipid Association.

Table 3. Definitions of Statin Variables

| **Variable name** | **Definition** | **Objective accomplished** |
|---|---|---|
| Prior statin user | Statin prescribed ≥48 hours in the 90 days prior to initial CDI encounter | Used to create the statin user composite variable |
| Concomitant statin user | Statin prescribed ≥48 hours within 14 days of CDI treatment start date | Used to create the statin user composite variable |
| Statin user | Meets criteria for both prior statin user and concomitant statin user | Objective 1 |
| Non-user | No prior statin use and no concomitant statin use | Objective 1 |
| Long-term/chronic user | Statin adherence >60% in the 360 days preceding first CDI encounter | Objective 2 |

Table 4. Statins Currently Available in the United States

| **Generic name** | **Trade name** | **Recommended daily dose** |
|---|---|---|
| Atorvastatin | Lipitor® | 10-80 mg |
| Fluvastatin | Lescol® | 20-80 mg |
| Lovastatin | Mevacor® | 10-80 mg |
| Pitavastatin | Livalo® | 1-4 mg |
| Pravastatin | Pravachol® | 10-80 mg |
| Rosuvastatin | Crestor® | 5-40 mg |
| Simvastatin | Zocor® | 5-80 mg |

In subgroup analyses of the statin-user cohort, statin use was further categorized as long-term or chronic statin users if patients had greater than 60% adherence in the year

prior to CDI encounter (Table 3). Adherence was defined as the proportion of days covered (PDC) in the 360 days preceding the initial CDI encounter and limited to patients with over 60% adherence based on nationally representative findings from Yeaw et al. showing the mean 12-month adherence rate for statins was 61% based on PDC calculations.[55] These users were then assessed for a dose-response relationship between the degree of cholesterol lowering or the intensity of statin therapy and CDI outcomes.

To better differentiate the effect of statins beyond cholesterol control, we collected the patient's most recent serum low-density lipoprotein (LDL) cholesterol level drawn in the year prior to first CDI encounter. The National Lipid Association's recommendations from 2015 for the management of dyslipidemia include a goal LDL level <100 mg/dL as desirable for most patients.[56] Chronic statin users were stratified based on this threshold to assess CDI outcomes in the subgroup analysis.

Patient demographics included patient age during the initial CDI episode, sex, race, and ethnicity. Sex, race, and Hispanic ethnicity were defined as the most common reporting of each characteristic over the study period. Tobacco use was defined as ICD-9-CM code 305.1 or V15.82 or CPT-4 code 99406 or 99407 in year prior to first CDI encounter. Principal CDI was defined as ICD-9-CM code 008.45 in the first position. This often indicates that CDI was the primary contributor to hospitalization. Secondary CDI was defined as ICD-9-CM code 008.45 in any position except first. CDI was also characterized by type. Community-associated CDI (CA-CDI) was defined as CDI therapy initiated in the outpatient setting or on days 1 or 2 of hospitalization. Community-onset, healthcare facility-associated CDI (CO-HCFA-CDI) was defined the same way, with the addition of a hospitalization in the prior 90 days. Lastly, healthcare facility-onset CDI (HCFO-CDI) was defined as CDI therapy beginning on day 3 or later of hospitalization.

We collected Charlson comorbidities and other relevant diagnoses, as defined by ICD-9-CM codes, in the year prior to the first CDI episode (Appendix). We also calculated the Charlson comorbidity score as described by Deyo et al.[57] In addition, we collected other infections that occurred during a CDI episode (between CDI episode start date and end of CDI therapy), including: bacteremia, pneumonia, skin infection, intra-abdominal infection, urinary tract infection, device-related infection, endocarditis, and acute respiratory infection (Appendix). Markers of CDI severity that occurred during a CDI encounter were also captured, including ICU admission, sepsis/septicemia, shock, acute renal failure, megacolon, prolonged ileus, perforated intestine, colectomy, white blood cell count (WBC) ≥15,000 cells/μL, C-reactive protein (CRP) ≥160 mg/L, serum creatinine (SCr) >1.5 mg/dL, and albumin <2.5 g/dL.

CDI-related medication therapy, administered during a CDI episode, could include: metronidzazole (oral or intravenous), vancomycin (oral or rectal), fidaxomicin, rifaximin, nitazoxanide, IVIG, probiotics, and FMT. Prior and concomitant non-CDI antibiotics (excludes oral vancomycin, metronidazole, fidaxomicin, rifaximin, and nitazoxanide), non-CDI high-risk antibiotics (third and fourth generation cephalosporins, fluoroquinolones, and clindamycin), gastric acid-suppressing (GAS) drugs (antacids, $H_2$-receptor blockers, proton pump inhibitors), anti-diarrhea medications, narcotics, and bowel prep medications were collected. Prior use was defined as any use in the 90 days prior to a CDI encounter. Concomitant use was defined as any use during or within 60 days following a CDI encounter.

To minimize potential confounding from a healthy user effect, variables accounting for healthcare utilization were collected. These include: 1) ≥1 outpatient visit in the 90-days prior to initial CDI diagnosis, 2) hospitalization or surgery within the 90-days prior to initial CDI diagnosis, 3) receiving chronic dialysis therapy, and 4) residence in a long-term

care facility (LTCF). These variables will account for a wider variety of patients at risk of exposure to *C. difficile* spores than is included in the surveillance definition for CO-HCFA-CDI. History of aspirin and non-statin antilipemic agents (bile acid sequestrants, ezetimibe, fibric acids, and niacin) used in the 90 days prior to the initial CDI encounter was also collected.

Mortality was defined as death from any cause during inpatient hospitalization or within 30 days following CDI treatment discontinuation. Severe or complicated CDI was defined as the presence of at least one CDI severity indicator as described above. A recurrence was defined as a second outpatient or inpatient visit during which a patient received an ICD-9-CM code for CDI with a minimum 3-day gap between the visit and the end of active CDI therapy for the initial episode. As in previous studies, 60-day recurrence was used as a specific endpoint.

### DATA AND STATISTICAL ANALYSES

Data extraction and variable creation were conducted using SAS Version 9.4® (SAS Institute, Cary, NC, USA). Propensity score matching was performed using STATA 14® (StataCorp, College Station, TX, USA). All other data and statistical analyses were conducted using JMP 13® (SAS Institute, Cary, NC, USA).

All independent and dependent variables were first presented descriptively. Variables that were absent from the medical chart (e.g., comorbidities) were assumed to have not occurred. Patient demographics and medication use were characterized during the baseline period. Categorical variables were described as number (percentage) and continuous variable were described as median (interquartile range, IQR).

**Objective 1: Hypothesis 1a**

For the primary analysis of the unmatched cohort, we entered baseline characteristics known to impact statin use, also included in the propensity score (Table 5), and variables known to affect CDI outcomes (Table 6) into a multivariable logistic regression model in order to determine the risk of individual CDI outcomes. Variables with less than 5% of the cohort were not entered into the model to improve model stability. The dependent variables collectively referred to as CDI outcomes included inpatient mortality, 30-day mortality, 60-day recurrence, and severe or complicated CDI. An adjusted odds ratios (aOR) and 95% confidence interval (95% CI) was calculated using logistic regression for each CDI outcome.

**Objective 1: Hypothesis 1b**

For the primary analysis of the matched cohort, we created a propensity score-matched cohort to account for the variables associated with indications for statin use. Propensity scores were created using a multivariable logistic regression model. We then performed nearest neighbor matching (1:1) with a caliper of 0.2. Over 40 variables were considered for the derivation of the propensity scores (Table 5); these variables were included because they could affect the likelihood of a patient receiving a statin or affect the patient's statin use. Once the matched cohort was derived, variables known to impact CDI outcomes (Table 6) were entered into a multivariable logistic regression model in order to determine the risk of individual CDI outcomes. Variables with less than 5% of the cohort were not entered into the propensity score model or CDI outcomes models in order to improve model stability. Finally, an aOR and 95% CI was calculated using logistic regression for each CDI outcome.

Table 5. Variables Included in the Propensity Score

| **Baseline characteristic** |
|---|
| Age (continuous) |
| Gender |
| Race |
| Ethnicity |
| Fiscal year of initial CDI encounter |
| VHA priority group |
| Tobacco use |
| LDL (continuous) |
| Comorbidities, present in at least 5% of cohort (21 possible) |
| Aspirin therapy |
| Non-statin antilipemic therapy |
| Healthcare utilization (4) |

Table 6. Variables Associated with CDI Outcomes

| **Patient characteristic** |
|---|
| Principal CDI |
| CDI surveillance type |
| Concomitant infections, present in at least 5% of cohort (8 possible) |
| CDI severity indicators, present in at least 5% of cohort (12 possible) |
| Prior medication (antibiotics, GAS) |
| Concomitant medication (narcotics, anti-diarrheals, bowel prep) |
| CDI-related medication (metronidazole, vancomycin, probiotics) |

**Objective 2: Hypothesis 2a**

Subgroup analyses were conducted using a cohort of long-term (chronic) statin users defined as prior statin users with at least 60% adherence in the year prior to the CDI encounter. These users were stratified by the patient's LDL value (<100 mg/dL or ≥100 mg/dL) to assess for a dose-response relationship between the degree of cholesterol lowering and CDI outcomes. Risk was calculated using multivariable logistic regression

(Table 7) in which LDL <100 mg/dL was used as the reference. Variables with less than 5% of the cohort were not entered into the model to improve model stability.

**Objective 2: Hypothesis 2b**

Chronic users were also stratified by the intensity of the statin regimen to assess for a dose-response relationship between the intensity of the statin and CDI outcomes. Risk was calculated using multivariable logistic regression (Table 7) in which low-moderate intensity statin therapy was used as the reference. Variables with less than 5% of the cohort were not entered into the model to improve model stability.

Table 7. Variables Included in the Chronic User Models

| **Patient characteristic** |
|---|
| Age (continuous) |
| Gender |
| Race |
| Ethnicity |
| Fiscal year of initial CDI encounter |
| VHA priority group |
| Tobacco use |
| Comorbidities, present in at least 5% of cohort (21 possible) |
| Aspirin therapy |
| Non-statin antilipemic therapy |
| Healthcare utilization (4) |
| Principal CDI |
| CDI surveillance type |
| Concomitant infections, present in at least 5% of cohort (8 possible) |
| CDI severity indicators, present in at least 5% of cohort (12 possible) |
| Prior medication (antibiotics, GAS) |
| Concomitant medication (narcotics, anti-diarrheals, bowel prep) |
| CDI-related medication (metronidazole, vancomycin, probiotics) |

# Chapter Five: Results

## COHORT DESCRIPTION

The overall cohort meeting study inclusion criteria contained 24,813 VHA enrollees diagnosed and treated for CDI. Of these patients, only 2.8% met criteria as a statin user. Due to VHA formulary restrictions, the statins prescribed were limited to pravastatin and rosuvastatin. Overall, the population was predominately elderly, non-Hispanic, white males (Table 8). Patients were primarily categorized with HCFO-CDI, and the most common concomitant infections were pneumonia and skin infection. Notably, complications of CDI (megacolon, ileus, perforated intestine, and colectomy) were rare events, occurring in less than 5% of the patient population.

Characteristics of statin users and non-users were recorded before and after propensity-score matching was performed (Table 8). In both the statin user and non-user groups, the majority of patients had an LDL level in a desirable range. The final propensity score included 26 variables (Table 8). Comorbidities were included if present in at least 5% of the unmatched population. These included: hypertension, dyslipidemia, obesity, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, diabetes, renal disease, neoplastic disease, and GERD. Approximately 26% of all statin users were retained after propensity score matching was performed (Table 8). In the matched cohort, over 90% of patients had a diagnosis of dyslipidemia in each group and 10% had a prior prescription for a non-statin antilipemic agent.

Table 8. Characteristics of Unmatched and Matched Cohorts

| | **Unmatched Cohort** | | **Matched Cohort** | |
|---|---|---|---|---|
| **Characteristic** | **Statin users n=699** | **Non-users n=24,114** | **Statin users n=181** | **Non-users n=181** |
| Age (years), median (IQR)* | 68 (63-77) | 68 (60-79) | 66 (63-75) | 68 (63-77) |
| Male sex, n (%)* | 679 (97.1) | 23,115 (95.9) | 177 (97.8) | 179 (98.9) |
| White, n (%)* | 500 (71.5) | 17,286 (71.7) | 133 (73.5) | 130 (71.8) |
| Black, n (%)* | 158 (22.6) | 4,993 (20.7) | 39 (21.5) | 46 (25.4) |
| Hispanic, n (%)* | 31 (4.4) | 1,295 (5.4) | 9 (5.0) | 9 (5.0) |
| Priority group, median (IQR)* | 5 (2-5) | 5 (3-5) | 5 (2-5) | 5 (2-5) |
| LDL (mg/dL), median (IQR)* | 79 (63-104) | 85 (66-108) | 83 (65-107) | 76 (60-97) |
| Smoker, n (%)* | 219 (31.3) | 5,743 (23.8) | 63 (34.8) | 48 (26.5) |
| Principal CDI, n (%) | 226 (32.3) | 7,383 (30.6) | 57 (31.5) | 52 (28.7) |
| CDI type, n (%) | | | | |
| CA-CDI | 115 (16.5) | 4,968 (20.6) | 26 (14.4) | 30 (16.6) |
| CO-HCFA-CDI | 143 (20.5) | 5,530 (22.9) | 40 (22.1) | 53 (29.3) |
| HCFO-CDI | 441 (63.0) | 13,616 56.5) | 115 (63.5) | 98 (54.1) |
| Comorbidities, n (%) | | | | |
| Hypertension* | 639 (91.4) | 18,428 (76.4) | 161 (90.0) | 163 (90.0) |
| Dyslipidemia* | 618 (88.4) | 12,524 (51.9) | 164 (90.1) | 170 (93.9) |
| Obesity* | 179 (25.6) | 3,801 (15.8) | 55 (30.4) | 57 (31.5) |
| Myocardial infarction* | 128 (18.3) | 2,539 (10.5) | 31 (17.1) | 28 (15.5) |
| Congestive heart failure* | 271 (38.8) | 6,100 (25.3) | 58 (32.0) | 64 (35.4) |
| Peripheral vascular disease* | 209 (29.9) | 4,364 (18.1) | 48 (26.5) | 51 (28.2) |
| Cerebrovascular disease* | 208 (29.8) | 4,469 (18.5) | 52 (28.7) | 39 (21.5) |
| Dementia | 24 (3.4) | 930 (3.9) | 3 (1.7) | 6 (3.3) |
| COPD* | 276 (39.5) | 9,029 (37.4) | 56 (30.9) | 60 (33.1) |
| Rheumatologic disease | 21 (3.0) | 656 (2.7) | 4 (2.2) | 2 (1.1) |
| Peptic ulcer disease | 25 (3.6) | 1,143 (4.7) | 3 (1.7) | 7 (3.9) |
| Liver disease | 20 (2.9) | 1,773 (7.4) | 5 (2.8) | 8 (4.4) |
| Diabetes* | 437 (62.5) | 9,358 (38.8) | 109 (60.2) | 113 (62.4) |
| Hemi-/paraplegia | 33 (4.7) | 928 (3.8) | 11 (6.1) | 8 (4.4) |
| Renal disease* | 282 (40.3) | 6,459 (26.8) | 65 (35.9) | 62 (34.3) |
| Neoplastic disease* | 195 (27.9) | 6,982 (29.0) | 53 (29.3) | 50 (27.6) |
| HIV/AIDS | 16 (2.3) | 422 (1.8) | 4 (2.2) | 2 (1.1) |
| GERD* | 218 (31.2) | 6,288 (26.1) | 58 (32.0) | 62 (34.3) |
| Transplant | 27 (3.9) | 429 (1.8) | 6 (3.3) | 6 (3.3) |
| Inflammatory bowel disease | 10 (1.4) | 546 (2.3) | 4 (2.2) | 5 (2.8) |
| Irritable bowel syndrome | 8 (1.1) | 260 (1.1) | 2 (1.1) | 2 (1.1) |

Table 8. Characteristics of Unmatched and Matched Cohorts, cont.

| | | | | |
|---|---|---|---|---|
| Charlson score, median (IQR) | 4 (3-7) | 3 (2-6) | 4 (2-6) | 4 (3-6) |
| Concomitant infections, n (%) | | | | |
| Bacteremia | 62 (8.9) | 1,765 (7.3) | 16 (8.8) | 13 (7.2) |
| Pneumonia | 165 (23.6) | 5,782 (24.0) | 32 (17.7) | 39 (21.5) |
| Skin infection | 101 (14.4) | 2,787 (11.6) | 20 (11.1) | 24 (13.3) |
| Intra-abdominal infection | 52 (7.4) | 1,489 (6.2) | 13 (7.2) | 14 (7.7) |
| Device-related infection | 27 (3.9) | 838 (3.5) | 5 (2.8) | 2 (1.1) |
| Acute respiratory infection | 33 (4.7) | 936 (3.9) | 8 (4.4) | 2 (1.1) |
| Endocarditis | 15 (2.1) | 259 (1.1) | 2 (1.1) | 2 (1.1) |
| Urinary tract infection | 19 (2.7) | 456 (1.9) | 6 (3.3) | 4 (2.2) |
| CDI severity indicators, n (%) | | | | |
| ICU admission | 12 (1.7) | 899 (3.7) | 2 (1.1) | 4 (2.2) |
| Sepsis/septicemia | 160 (22.9) | 4,347 (18.0) | 41 (22.7) | 39 (21.5) |
| Shock | 52 (7.4) | 1,252 (5.2) | 14 (7.7) | 7 (3.9) |
| Acute renal failure | 311 (44.5) | 7,554 (31.3) | 80 (44.2) | 58 (32.0) |
| Megacolon | 2 (0.3) | 82 (0.3) | 0 | 0 |
| Ileus | 29 (4.1) | 1,016 (4.2) | 7 (3.9) | 6 (3.3) |
| Perforated intestine | 6 (0.9) | 123 (0.5) | 3 (1.7) | 2 (1.1) |
| Colectomy | 0 | 37 (0.2) | 0 | 1 (0.6) |
| WBC ≥15,000 cells/μL | 343 (49.1) | 10,347 (42.9) | 84 (46.4) | 87 (48.1) |
| CRP ≥160 mg/L | 17 (2.4) | 426 (1.8) | 4 (2.2) | 3 (1.7) |
| Albumin <2.5 g/dL | 286 (40.9) | 8,834 (36.6) | 69 (38.1) | 79 (43.6) |
| SCr >1.5 mg/dL | 224 (32.0) | 5,746 (23.8) | 44 (24.3) | 46 (25.4) |
| Prior medications, n (%) | | | | |
| Antibiotics | 413 (59.1) | 13,312 (55.2) | 99 (54.7) | 107 (61.9) |
| High-risk antibiotics | 272 (38.9) | 8,990 (37.3) | 68 (37.6) | 74 (40.9) |
| GAS drugs | 476 (68.1) | 13,256 (55.0) | 121 (66.9) | 110 (60.8) |
| Narcotics | 312 (44.6) | 9,035 (37.5) | 82 (45.3) | 93 (51.4) |
| Anti-diarrheals | 46 (6.6) | 1,747 (7.2) | 8 (4.4) | 12 (6.6) |
| Bowel prep | 150 (21.5) | 3,537 (14.7) | 38 (21.0) | 48 (26.5) |
| Aspirin use* | 332 (47.5) | 6,533 (27.1) | 82 (45.3) | 78 (43.1) |
| Non-statin antilipemic* | 50 (7.2) | 757 (3.1) | 18 (9.9) | 18 (9.9) |
| Conc. medications, n (%) | | | | |
| Antibiotics | 535 (76.5) | 18,150 (75.3) | 132 (72.9) | 139 (77.0) |
| High-risk antibiotics | 378 (54.1) | 12,767 (52.9) | 95 (52.5) | 97 (53.6) |
| GAS drugs | 585 (83.7) | 19,102 (79.2) | 150 (82.9) | 143 (79.0) |
| Narcotics | 400 (57.2) | 12,174 (50.1) | 110 (60.8) | 106 (58.6) |
| Anti-diarrheals | 67 (9.6) | 2,773 (11.5) | 18 (9.9) | 17 (9.4) |
| Bowel prep | 169 (24.2) | 4,597 (19.1) | 51 (28.2) | 46 (25.4) |

Table 8. Characteristics of Unmatched and Matched Cohorts, cont.

| | | | | |
|---|---|---|---|---|
| CDI-related medications, n (%) | | | | |
| Metronidazole | 631 (90.3) | 20,822 (86.3) | 162 (89.5) | 143 (79.0) |
| Oral vancomycin | 359 (51.4) | 10,454 (43.4) | 86 (47.5) | 91 (50.3) |
| Fidaxomicin | 10 (1.4) | 144 (6.0) | 3 (1.7) | 3 (1.7) |
| Probiotics | 226 (32.3) | 6,726 (27.9) | 54 (29.8) | 55 (30.4) |
| Healthcare utilization, n (%)* | | | | |
| Prior outpatient visit | 687 (98.3) | 22,386 (92.8) | 178 (98.3) | 179 (98.9) |
| Prior hospitalization or surgery | 531 (76.0) | 15,733 (65.2) | 140 (77.3) | 142 (78.5) |
| Chronic dialysis therapy | 36 (5.1) | 676 (2.8) | 8 (4.4) | 3 (1.7) |
| Residence in LTCF | 109 (15.6) | 3,005 (12.5) | 24 (13.3) | 29 (16.0) |
| **Denotes variables included in propensity score* | | | | |

**OBJECTIVE 1: CDI OUTCOMES**

CDI outcomes were evaluated for statin users and non-users before and after propensity score-matching (Table 9). The logistic regression model for the unmatched cohort included all factors used in the derivation of the propensity scores in addition to all the factors used in the matched cohort regression model. In the unmatched cohort, statin use was significantly associated with a reduced risk of 30-day mortality (aOR 0.60, 95% CI 0.36-1.00, p=0.0478). No significant associations were noted for inpatient mortality, 60-day recurrence, and severe or complicated CDI in the unmatched cohort.

In the matched cohort, statin use remained significantly associated with a reduced risk of 30-day mortality (aOR 0.45, 95% CI 0.23-0.88, p=0.0198). No significant trends were found for inpatient mortality, 60-day recurrence, and severe or complicated CDI in the matched cohort. In both the unmatched and matched cohorts, a non-significant association exists for a decreased risk of 60-day recurrence in statin users.

Table 9. CDI Outcomes among Statin Users and Non-users

| | **Statin users** | **Non-users (reference)** | **aOR (95% CI)** | **p-value** |
|---|---|---|---|---|
| **Unmatched cohort** (statin users, n=699; non-users, n=24,114) | | | | |
| Inpatient mortality | 68 (9.7) | 2,291 (9.5) | 1.18 (0.66-2.13) | 0.5783 |
| 30-day mortality | 147 (21.0) | 5,483 (22.7) | ***0.60 (0.36-1.00)*** | ***0.0478*** |
| 60-day recurrence[a] | 45 (8.6) n=525 | 2,341 (13.3) n=17,645 | 0.71 (0.39-1.28) | 0.2577 |
| Severe or complicated | 558 (79.8) | 17,028 (70.6) | 1.01 (0.67-1.51) | 0.9708 |
| **Propensity score-matched cohort** (statin users, n=181; non-users, n=181) | | | | |
| Inpatient mortality | 16 (8.8) | 14 (7.7) | 1.11 (0.44-2.76) | 0.8267 |
| 30-day mortality | 23 (12.7) | 41 (22.7) | ***0.45 (0.23-0.88)*** | ***0.0198*** |
| 60-day recurrence[a,b] | 14 (9.3) n=151 | 19 (14.4) n=132 | 0.84 (0.35-2.00) | 0.6941 |
| Severe or complicated | 138 (76.2) | 139 (76.8) | 0.95 (0.53-1.70) | 0.8680 |

[a]Excludes patients with 60-day mortality
[b]Not adjusted for shock due to model instability

### OBJECTIVE 2: CHRONIC USERS AND CHOLESTEROL LEVEL

Prior statin users with at least 60% adherence in the year prior to the CDI encounter were assessed for a dose-response relationship between the degree of cholesterol-lowering and CDI outcomes (Table 10). Of the chronic statin users (n=1,104), approximately 21% had an undesirable or elevated LDL. In multivariate analysis, no significant association was found between LDL ≥100 mg/dL and the CDI outcomes assessed.

### OBJECTIVE 2: CHRONIC USERS AND STATIN INTENSITY

Patients meeting criteria for chronic statin use (n=1,221) were stratified by intensity of the statin therapy. Approximately 30% of chronic users were on high intensity therapy and were assessed for a dose-response relationship between the degree of statin intensity

and CDI outcomes (Table 10). In multivariate analysis, no significant association was found for high intensity therapy and each CDI outcome evaluated.

Table 10. CDI Outcomes for Chronic Statin Users

| **Outcome** | **30-day mortality** | | **60-day recurrence[a]** | | **Severe or complicated** | |
|---|---|---|---|---|---|---|
| | **n (%)** | **aOR[b] (95% CI)** | **n (%)** | **aOR (95% CI)** | **n (%)** | **aOR (95% CI)** |
| LDL (mg/dl), n=1,104 | | | | | | |
| <100 (n=871) | 154/871 (17.7) | Reference 1.00 | 129/691 (18.7) | Reference 1.00 | 621/871 (71.3) | Reference 1.00 |
| ≥100 (n=233) | 32/233 (13.7) | 0.43 (0.10-1.75) | 40/194 (20.6) | 1.09 (0.44-2.67) | 160/233 (68.7) | 0.74 (0.34-1.61) |
| Statin intensity, n=1,221 | | | | | | |
| Low-mod. (n=855) | 149/855 (17.4) | Reference 1.00 | 125/673 (18.6) | Reference 1.00 | 604/855 (70.6) | Reference 1.00 |
| High (n=366) | 58/366 (15.9) | 0.71 (0.25-2.02) | 61/300 (20.3) | 1.12 (0.50-2.50) | 262/366 (71.6) | 1.03 (0.53-2.01) |

[a]Excludes patients with 60-day mortality
[b]Not adjusted for gender, ethnicity, and prior outpatient visit due to model instability

# Chapter Six: Discussion

## OBJECTIVE 1

From 2000 to 2014, a total of 24,813 VHA enrollees were diagnosed and treated for CDI. Of these patients, 699 VHA enrollees had a history of prior statin use and continued concomitant statin use during CDI infection while 24,114 VHA enrollees were considered statin non-users. After propensity score matching, the cohort was limited to 181 statin users and 181 non-users. In both the unmatched and matched cohorts, statin use was significantly associated with a reduced risk of 30-day mortality. Additionally, no significant associations were found for inpatient mortality, 60-day recurrence, and severe or complicated CDI. In both the unmatched and matched cohorts, a non-significant association exists for a decreased risk of 60-day recurrence in statin users. In subgroup analyses of chronic statin users, LDL level and intensity of statin therapy were not significantly associated with mortality, recurrence, and severe or complicated CDI.

Compared to prior literature on this topic, our study has the largest overall patient cohort reported spanning the longest period of time. Due to strict criteria in the definition of statin users and the use of propensity score matching with replacement, the final matched cohort was limited to only 1.4% of our CDI cohort for the matched analyses. Despite the reduced population size, the risk of 30-day mortality was found to be significantly reduced in the statin user population compared to non-users. Additionally, statin use appears to be associated with a non-significant reduction in risk of 60-day recurrence.

Overall, the inpatient mortality rate in our study of 10% and the 30-day mortality rate of approximately 20% are in line with contemporary epidemiological data for CDI. In a 2012 literature review of all-cause mortality in hospitalized patients with CDI in the northern hemisphere, researchers found 30-day mortality varied from 9% to 38% and in-hospital mortality ranged from 8% to 37%.[58] Our 30-day mortality rates for the matched

statin users and non-users (13% vs. 23%) are very similar to those reported by Saliba et al. (13% vs. 21%, p<0.001), making our study the second to report finding a significant reduction in risk of 30-day mortality associated with statin use.[46]

In the two other studies published on this topic, Atamna et al. and Park et al. both found statins were not significantly associated with 30-day mortality or severity using multivariate logistic regression.[45,47] Additionally, these two studies are limited in that they both only utilized unmatched data from a single hospital and did not collect data regarding statin regimens. The study by Park et al. was the only prior study to look at 60-day recurrence rates.[45] Although they found a significantly reduced rate of recurrence associated with statin use compared to non-users (3% vs. 7%, p=0.033), the association was not seen in our study (9% vs. 14%, p=0.6941). The reasons for this are unclear, but are likely related to differences in study design as opposed to any clinical mechanism underlying this hypothetical effect.

**OBJECTIVE 2**

Unlike the findings from Saliba et al., our study did not find a dose-response effect when assessing the impact of long-term or chronic statin use on mortality.[46] One explanation for this, is that our study used a more rigorous definition of long-term users by assessing adherence to statin therapy in the year prior to the first CDI episode whereas Saliba et al. only looked at number of prescriptions filled.

In our secondary analysis of chronic users, neither statin intensity nor LDL level appeared to be significantly with any CDI outcomes. This analysis, though limited by our small sample size, did find a non-significant reduction in 30-day mortality associated high-intensity chronic statin use. Given the lack of findings regarding a dose-response

relationship between chronic statin therapy and CDI outcomes, the mechanism for statins' protective effects is likely unrelated to the cholesterol-lowering effects and the cholesterol-lowering potency of the statin therapy.

Contrary to our hypothesis, chronic statin users with elevated cholesterol or undesirable LDL levels (≥100 mg/dL) appeared to have no increased risk associated with CDI outcomes. In addition to the small sample size, it is possible that if an effect exists it can only be seen at much greater extremes of cholesterol levels.

### STRENGTHS

This study has multiple strengths. First, we collected data on all patients with CDI managed at any VHA facility over a 12-year period. The VHA is a closed healthcare system with pharmacy data available for all prescriptions filled within the system. Our definition for prior statin use was similar to that used in previous studies; however, statin users in our study were ultimately limited to those with continued use during a CDI encounter to ensure chronic and recent receipt of statin therapy relative to the acquisition of CDI. This ensured no significant lapse in statin therapy prior to the CDI encounter. Additionally, propensity-score matching was used to minimize confounding, including the potential for a healthy user effect. Ours is the only study on this topic to utilize a matched design to compare statin users and non-users with CDI.

Second, the VHA maintains a comprehensive computerized system, which allowed for the collection of data on inpatient and outpatient CDI diagnoses and outcomes. By reviewing patient history for a year prior to CDI diagnosis and for 90 days after, we were able to distinguish first episodes from recurrences. Furthermore, the inclusion of only patients with an ICD-9 code for CDI who received CDI therapy and had a positive CDI

laboratory test result minimized the possibility of misclassification seen with administrative coding alone.

## LIMITATIONS

This study is limited by the use of extracted medical data, and a retrospective cohort study design. All data collection relied on electronic medical records, and no individual chart reviews were performed. Cohort studies might be subject to misclassification bias and confounding by unmeasured variables. Similarly, comorbidities might not be fully captured using administrative codes and cannot be considered equivalent to medical chart reviews. Additionally, electronic medical data are created for the purpose of patient care, not for research, and might contain errors.

Although several CDI morbidity and mortality risk factors were included in the logistic regression models, additional factors exist that are not included in the analysis. For example, specific *C. difficile* ribotypes are associated with increased virulence.[8] Additionally, we were unable to assess all medications a patient was prescribed. Patients could have been on additional agents not accounted for that could modify a patient's risk for development of CDI as well as a patient's CDI outcomes. Physician attitudes and prescribing preferences could also impact a patient's risk for development CDI, promptness of treatment, and risk for recurrent episodes. Furthermore, the predominately elderly, male, veteran CDI population might not be representative of all CDI populations, limiting the generalizability of our findings.

## CONCLUSIONS

The results of our study are unable to yield recommendations for changes directly impacting routine care of CDI patients. The clinical significance of our findings is unknown due to many factors. First, the mechanisms underlying these results are theoretical. Second, these results can only be generalized to patients meeting our study criteria with a history of statin use prior to CDI and continued use during infection. It is unknown what effect, if any, initiating statin therapy during CDI could have on CDI outcomes. Third, the effect of chronic statin therapy on CDI outcomes appears unrelated to the cholesterol-lowering effects and the cholesterol-lowering potency of the statin therapy.

To date, this is the largest study comparing CDI health outcomes among statin users and non-users. Statin users were found to have significantly reduced 30-day mortality in both an unmatched and matched patient cohort compared to non-users. While these data support previous findings reported in the literature, no change in routine care of CDI patients can be recommended at this time.

## FUTURE RESEARCH

Additional studies on the effects of statins on CDI outcomes may be warranted, but will likely elucidate no new information without a randomized controlled trial. Instead, future studies evaluating the impact of statin therapy on other non-cardiac conditions are recommended to further explore the potential benefits of the pleiotropic effects seen with this class of medication.

# Appendix

| Patient variable | ICD-9-CM code(s) |
|---|---|
| Comorbidities in year prior to CDI episode | |
| Hypertension | 401-405 |
| Dyslipidemia | 272 |
| Obesity | 278 |
| Myocardial infarction | 410, 412 |
| Congestive heart failure | 428 |
| Peripheral vascular disease | 441, 443.9, 785.4, V43.4 |
| Cerebrovascular disease | 430-438 |
| Dementia | 290 |
| COPD | 490-496, 500-505, 506.4 |
| Rheumatologic disease | 710.0-710.1, 710.4, 714.0-714.2, 714.81, 725 |
| Peptic ulcer disease | 531.0-531.9, 532.0-532.9, 533.0-533.9, 534.0-534.9 |
| Liver disease | 571.2, 571.4, 571.5, 571.6, 572.2-572.8, 456.0-456.21 |
| Diabetes | 250.0-250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9 |
| Hemiplegia or paraplegia | 342, 344.1 |
| Renal disease | 582, 583, 585, 586, 588 |
| Neoplastic disease | 140-172, 174-208 |
| HIV/AIDS | 42-44, V08 |
| GERD | 530.11, 530.81 |
| Transplant | V42, E878.0 |
| Inflammatory bowel disease | 555, 556 |
| Irritable bowel syndrome | 564.1 |
| Concomitant infections | |
| Bacteremia | 790.7 |
| Pneumonia | 480.0-483.99, 485–487 |
| Skin infection | 680-686 |
| Intra-abdominal infection | 540–543, 562, 567, 569, 574–577 |
| Urinary tract infection | 590-599 |
| Device-related infection | 996.31, 996.62, 996.64, 999.31 |
| Acute respiratory infection | 460-466 |
| Endocarditis | 421.0, 421.1, 421.9, 424.9 |
| CDI severity indicators | |
| Shock | 639.5, 785.52, 785.59 |
| Sepsis/septicemia | 020.2, 038.0-038.9, 995.91, 995.92 |
| Perforation of intestine | 569.83 |
| Prolonged ileus | 560.1 |
| Megacolon | 558.2, 564.7 |
| Acute renal failure | 584, 586 |
| Colectomy | 45.73, 45.81-83 (procedure codes) |

# Glossary

| Acronym | Definition |
|---|---|
| CDI | *Clostridium difficile* Infection |
| CO-CDI | Community-Onset CDI |
| CO-HCFA-CDI | Community-Onset, Healthcare Facility-Onset CDI |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRP | C-Reactive Protein |
| FDA | United States Food and Drug Administration |
| FMT | Fecal Microbiota Transplantation |
| GAS | Gastric Acid-Suppressing |
| GDH | Glutamate Dehydrogenase |
| GERD | Gastroesophageal Reflux Disease |
| GI | Gastrointestinal |
| HCFO-CDI | Healthcare Facility-Onset CDI |
| HIV/AIDS | Human Immunodeficiency Syndrome/Acquired Immune Deficiency Syndrome |
| HLD | hyperlipidemia |
| HMG-CoA | 3-hydroxyl-3-methylgutarul-coenzyme A |
| ICD-9-CM | International Classification of Diseases, 9th Revision, Clinical Modification |
| IBD | Inflammatory Bowel Disease |
| ICU | Intensive Care Unit |
| IDSA | Infectious Diseases Society of America |
| IQR | Interquartile Range |
| IVIG | Intravenous Immunoglobulin |
| LDL | Serum Low-Density Lipoprotein Cholesterol |
| LOS | Length Of Stay |
| LTCF | Long-Term Care Facility |
| NCEP | National Cholesterol Education Program |
| NIH | National Institutes of Health |
| OR | Odds Ratio |
| PCR | Polymerase Chain Reaction |
| PDC | Proportion of Days Covered |
| SCr | Serum Creatinine |
| US | United States |
| VA | Veterans Affairs |
| VHA | Veterans Health Administration |
| VINCI | VA Informatics and Computing Infrastructure |
| WBC | White Blood Cells |
| 95% CI | 95% Confidence Interval |

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