Meta-analysis comparing the effects of statins on the risk of *Clostridium difficile* diarrhea

Sakolwan Suchartlikitwong, MD^a , Passisd Laoveeravat, MD^a, Jirapat Teerakanok, MD^a ,
Thammasak Mingbunjerdasuk, MD^a , Subhanudh Thavaraputta, MD^a , Wasawat Vutthikraivit, MD^a ,
Charat Thongprayoon, MD^b , Kenneth Nugent, MD^a , and Wisit Cheungpasitporn, MD^{c,d}

^aDepartment of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas; ^bDepartment of Internal Medicine, Bassett Medical Center, Cooperstown, New York; ^cDivision of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, Minnesota; ^dDivision of Nephrology, Department of Internal Medicine, University of Mississippi Medical Center, Jackson, Mississippi

ABSTRACT

A literature search was performed through May 2017. Studies that compared the risk of developing *Clostridium difficile* infection (CDI) and/or the clinical outcomes of CDI in patients who received statin treatment versus those who did not receive statins were included. Ten observational studies with 37,109 patients were included. Compared to no treatment, statins reduced the risk of CDI development (odds ratio [OR] = 0.66, 95% confidence interval [CI], 0.44–0.99). However, among patients who developed CDI, the use of statins did not significantly reduce recurrent CDI risk (OR = 0.69, 95% CI, 0.28–1.71) or 30-day mortality (OR = 0.77, 95% CI, 0.51–1.14). In conclusion, our study demonstrates a significant association between statin use and a reduced risk of CDI development. However, the findings of our study suggest no significant associations between statin use and improvement in clinical outcomes of CDI. These findings might impact the clinical management and primary prevention of CDI.

KEYWORDS *Clostridium difficile* diarrhea; *Clostridium*; infectious diarrhea; meta-analysis; nosocomial diarrhea; statins

Clostridium difficile is one of the most common pathogens in infectious nosocomial diarrhea.¹ Many studies in the last decade have reported an increasing number of *C. difficile* infections (CDIs).^{2,3} The reported case fatality rates of CDIs are 6% to 30% and have been rising recently.^{4,5} The infection increases not only patient mortality but also health care expenditures and length of hospital stay.^{2,6–8} Some drugs, such as antibiotics or proton pump inhibitors, can increase the risk for these infections.⁹ Recent observational studies also suggest an effect of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) on the risk of CDI development. To investigate this association further, we performed a meta-analysis to determine the risk and clinical outcomes of CDI in patients who receive statin therapy and in patients not on statin therapy.

METHODS

A systematic search was developed using the keywords “statins,” “hydroxymethylglutaryl-coenzyme A reductase

inhibitors,” “*Clostridium difficile*,” and “*Clostridium*” (*Supplement 1*). MEDLINE and EMBASE were searched independently by two authors (S.S. and P.L.) from inception through May 2017 using the same keywords. Thirty-five studies in MEDLINE and 74 studies in EMBASE were found. The study was registered in PROSPERO, number CRD42017072810.

The study had three inclusion criteria: (1) the study had to be a randomized controlled trial, cohort study, case-control study, or abstract presented at a national meeting; (2) study outcomes included CDI and clinical outcomes of CDI, such as 30-day mortality, recurrent infection after treatment completion, and the severity of CDI; and (3) the study reported odds ratios (ORs) or relative risks of developing CDI and/or the clinical outcomes of CDI among statin users and nonusers. Articles were excluded if they (1) were not written in English or (2) were review articles, case reports, case series, or editorials.

Two authors (S.S. and P.L.) independently searched the literature using the same search terms. Any discrepancy of

Corresponding author: Sakolwan Suchartlikitwong, MD, Department of Internal Medicine, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9410, Lubbock, TX 79415 (e-mail: sakolwan.suchartlikitwong@ttuhsc.edu)
Received February 23, 2018; Revised April 29, 2018; Accepted April 30, 2018.

eligible articles was discussed in detail and resolved by consensus from both authors. The references in the identified papers were searched, but no additional articles were eligible for inclusion. Data were extracted from original papers by incorporating the crude data reported in each study. Data included number of enrolled patients, number of cases and controls who were statin users and nonusers, ORs and adjusted ORs, relative risks and adjusted relative risks, and 95% confidence intervals (CIs).

Pooled ORs and 95% CIs were calculated based on the number of patients using a random-effect model. Cochran's Q test and I^2 statistics were used to assess heterogeneity among studies, with I^2 of 0% to 25% indicating insignificant heterogeneity, 26% to 50% indicating low heterogeneity, 51% to 75% indicating moderate heterogeneity, and >75% indicating high heterogeneity.¹⁰ Publication bias was demonstrated by funnel plots and the Egger regression asymmetry test. Data analysis was performed using the Comprehensive Meta-Analysis software (Version 2.2.064; Biostat Inc.).

The quality of included studies was assessed by the Newcastle-Ottawa Scale. Individual studies were appraised by rating scores of the following categories: (1) selection of cases and controls, (2) comparability between two groups, and (3) exposure of statins comparable between cases and controls.

RESULTS

Of the 109 articles identified by database searches, nine studies were excluded due to duplication (*Figure 1*). Titles and abstracts of 100 studies were reviewed; 88 studies were excluded because they were case reports, letters to the editor, or review articles or reported no CDIs or CDI outcomes.

Figure 1. Flow diagram of search results and screening process.

Twelve studies were eligible for full-text article assessment. Two studies were excluded because one study did not provide more detailed data (the corresponding authors were contacted, but we did not receive a response) and the other one included participants who took proton pump inhibitors. Ten relevant studies were included in the meta-analysis—one cohort study¹¹ and nine case-control studies^{12–20} (*Table 1*). Seven studies were published in full text; the other three studies^{18–20} were in abstract format with no available full text.

There were 37,109 CDI patients; 7382 used statins, and 29,727 did not use statins. CDI was diagnosed with positive stool toxin assay, positive endoscopic finding of pseudomembranous colitis, or positive polymerase chain reaction for *C. difficile* in seven studies. Three studies did not report the diagnostic methods. Eight studies were classified as good quality based on a Newcastle-Ottawa Quality Assessment Scale score of ≥ 5 out of 9. Two studies were considered fair quality with a score <5.

Of the 10 included studies, 6 studies had available data to calculate pooled OR for risk of CDI development. Five studies found statistically significant reductions in CDI risk in statin users; one study found an increased risk of CDI with statins. Four studies reported adjusted ORs and the other two studies used unadjusted ORs. ORs were adjusted for sex, age, comorbidities, proton pump inhibitor use, and antibiotic use. Compared to patients who did not receive statins, the pooled OR of developing CDI in statin users was 0.66 (95% CI, 0.44 to 0.99, $I^2 = 78\%$) (*Figure 2*).

Based on a prespecified subgroup analysis of patients who developed CDI, statin use did not statistically reduce the risk of recurrent CDI or 30-day mortality. Pooled ORs were 0.69 (two studies; 95% CI, 0.28 to 1.71, $I^2 = 77\%$) and 0.77 (three studies; 95% CI, 0.51 to 1.14, $I^2 = 57\%$), respectively (*Figure 3*). Data on the severity of CDI in patients who used statins were limited. One study demonstrated a nonsignificant association between statin use and reduced severity of CDI, with an OR of 0.85 (95% CI, 0.55 to 1.32) when compared with no statin use.

A funnel plot was performed as planned per protocol to assess potential publication bias for association between statin use and CDI (*Supplementary Figure 1*). However, due to the limited number of studies, as a rule of thumb, the power of the test was too low to distinguish chance from real asymmetry.²¹ The Egger regression asymmetry test was performed and showed no publication bias with a $P = 0.66$.

DISCUSSION

There are observational studies suggesting a protective effect of statins against CDI.^{13,15} This is the first meta-analysis of case-control and cohort studies demonstrating risk reduction of CDI infection in statin users compared to nonusers.

Six studies provided data to calculate pooled ORs for risk of CDI development. Only one study¹¹ showed an increased risk of CDI, with a high OR of 4.321 ($P = 0.0036$).

Table 1. Study characteristics

Variable	First author, publication year									
	McGuire, 2009	Zachow, 2010 ^a	Naggie, 2011	Kumarappa, 2012 ^a	Motzkus, 2012	Nseir, 2013	Park, 2013	Abdelfatah, 2014 ^a	Saliba, 2014	Atamna, 2016
Study country	USA	Germany	USA	NA	USA	Israel	Korea	NA	Israel	Israel
Study design	Cohort	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control
Study period	NA	1998–2008	2006–2007	NA	2002–2009	2011	2005–2012	NA	2011–2012	2009–2014
Patients (<i>n</i>)	564	3672	180	564	109,568	366	1725	2019	1888	6719
Type of population	Intensive care unit	Inpatient	Community	Inpatient and community	Inpatient	Inpatient	Inpatient and community	Inpatient	Inpatient and community	Inpatient
Age (years) of statin users, nonusers	Mean (SD) 68.7 (12.6), 65.4 (13.3)	NA	Median (IQR) 64 (50–73), 63 (52–74) ^b	NA	Range (%) 35–64 (51.3%), 35–64 (50.5%) ^b	Mean (SD) 65 (17), 62.5 (17) ^b	Mean (SD) 65.9 (14.2), 62.5 (16)	Mean (SD) 73 (18.3), 67 (18.3)	Mean (SD) 76.6 (10.3), 75.2 (13.7)	Mean (SD) 75.8 (10.5), 70.58 (19)
Type of statins (-vastatin)	Unspecified	Unspecified	Unspecified	Unspecified	Sim-, lo-, ator-, pra-	Unspecified	Sim-, ator-, rosu-, pita-, pra-	Sim-, ator-, pra-, lo-, flu-, rosu-	Sim-, ator-, pra-, rosu-	Unspecified
Definition of <i>C. difficile</i> infection	NA	NA	Stool frequency and stool toxin	NA	ICD-9 code 008.45	Stool frequency and endoscopy/stool toxin	Stool toxin or endoscopy	Stool frequency and stool toxin	Stool toxin	Stool toxin and stool antigen
Definition of recurrent <i>C. difficile</i> infection	NA	NA	NA	NA	NA	NA	New diarrhea 10–60 days after completion of antibiotics	New diarrhea 15–90 days after completion of antibiotics	NA	NA
OR (95% CI) for CDI	4.321*	0.34 (0.1–1)*	0.52 (0.3–1)*, 0.31 (0.1–0.8)**	0.62 (0.4–0.9)*	0.78 (0.8–0.8)**	0.45*, 0.45 (0.3–0.7)**	NA	NA	NA	NA
OR (95% CI) for recurrence	NA	NA	NA	NA	NA	NA	0.39 (0.167–0.926)**	0.891*	NA	NA
OR (95% CI) for 30-day mortality	NA	NA	NA	NA	NA	NA	1.23 (0.6–2.5)**	NA	0.59 (0.5–0.8)*, 0.57 (0.4–0.8)**	0.84 (0.6–1.3)*, 1.54 (0.8–2.8)**
	NA	NA	NA	NA	NA	NA		NA	NA	NA
<i>(continued)</i>										

(continued)

Table 1. Continued

Variable	First author, publication year									
	McGuire, 2009	Zachow, 2010 ^a	Naggie, 2011	Kumarappa, 2012 ^a	Motzkus, 2012	Nseir, 2013	Park, 2013	Abdelfatah, 2014 ^a	Saliba, 2014	Atamna, 2016
OR (95% CI) for severe infection							0.85 (0.6–1.3)**			
Confounders adjusted	NA	NA	Age, comorbidities, outpatient visits, antibiotic	PPI, H2-RA, antibiotic, CKD	Antibiotic, PPI, comorbidities, sex, race, ethnicity	Sex, inpatient, antibiotic	NA	Age, albumin, comorbidities, PPI, antibiotic	Sex, age, comorbidities, aspirin, antibiotic, PPI	NA
Quality assessment total score of 9	5	2	6	3	7	7	8	7	9	6

^aOnly abstract is available.^bAge of patients with CDI vs without CDI.CDI indicates *C. difficile* infection; CKD, chronic kidney disease; CI, confidence interval; H2-RA, histamine H2-receptor antagonists; ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; OR, odds ratio (*unadjusted, **adjusted); PPI, proton pump inhibitors; NA, no available data provided; SD, standard deviation. Figure 2. Pooled odds ratio for the association between statin use and risk of *C. difficile* infection. Figure 3. Pooled odds ratios for the association between statin use and (a) recurrent *C. difficile* infection and (b) 30-day mortality.

McGuire et al's study was conducted in patients who were admitted to the intensive care unit due to severe sepsis.¹¹ Half of the patients were on corticosteroids, and two-thirds of them received quinolones, which are known to increase CDI. Exposure to corticosteroids and antibiotics in enrolled subjects might confound the results in the study. In a subgroup analysis excluding McGuire et al's study, the pooled OR of CDI risk was 0.56, which still favored a protective effect of statins against CDI.

The possible mechanism of the protective effect of statins against *C. difficile* is unclear. It may be related to changes in the gut microflora by statins. An experimental animal study in *Toxoplasma gondii*-induced ileitis in mice reported that statins improved the enteric dysbiosis during the infection. The numbers of anti-inflammatory bacteria, such as *Lactobacillus* and *Bifidobacterium*, increased, whereas the numbers of pro-inflammatory bacteria declined.²²

Similar clinical effects of statins have been reported in noninfectious colitis, such as inflammatory bowel disease, as well. A large observational study by Ungaro et al²³ demonstrated a protective effect of statins against new-onset inflammatory bowel disease. The effect did not change with type or

dose of statins. A similar retrospective cohort study by Crockett et al²⁴ showed that in those with ulcerative colitis, statins were associated with reduced use of oral corticosteroids and reduction of corticosteroid initiation. This might be explained by an immunomodulatory effect of statins via T-cell activation in T-cell-mediated diseases.²⁵

Our meta-analysis did not show an association between statins and outcomes of CDI. In subgroup analysis, statins did not statistically reduce the risk of recurrent CDI. A total of 128 subjects from two studies were statin users and had recurrent CDI. The nonsignificant association could result from the limited number of patients. Nonetheless, three studies^{12,16,17} reported 30-day mortality. Two out of three studies included patients from both inpatient and outpatient settings. This could have an influence on 30-day mortality outcome, because patients in an outpatient setting were not as ill and might have a better prognosis. More studies focusing on statin use and the risk of recurrent CDI and 30-day mortality are needed to determine statins' effects on these outcomes.

There were heterogeneities among studies in our meta-analysis. In an analysis between statin use and CDI, the I^2 was 78%, indicating significant heterogeneity. That could be caused by different CDI definitions used among studies, the variety of inpatient and outpatient settings, and the different types of statins.

There were some limitations in our study. First, including patients from both outpatient and inpatient settings increased the heterogeneity of analysis. Subgroup analysis could not be performed because studies did not report inpatient and outpatient data separately. Second, in a few studies, full-text articles were not available, so some information regarding the crude number of patients was missing and we had to use the ORs provided in the article. Third, most studies did not report exposure time with statins, which could affect CDI in those studies. Although our analysis using adjusted ORs demonstrated a significant reduced risk of CDI development with the use of statins, future studies are required to assess the effect of statin type on the severity of CDI. Lastly, this is a meta-analysis of observational studies. Therefore, it can at best confirm only an association between statin use and a reduced CDI risk.

In conclusion, this meta-analysis demonstrates a significant association between statin use and a reduced risk of CDI development. However, the findings of our study suggest no significant associations between statin use and improvement in clinical outcomes of CDI, including recurrent CDI or 30-day mortality. These results form the basis for prospective clinical studies on the management and primary prevention of CDI.

ACKNOWLEDGMENTS

We are grateful to Texas Tech University Health Sciences Center librarians for assistance with literature searches and resources.

ORCID

Sakolwan Suchartlikitwong <http://orcid.org/0000-0001-7328-8445>
 Jirapat Teerakanok <https://orcid.org/0000-0001-6129-7010>
 Thammasak Mingbunjerdasuk <http://orcid.org/0000-0003-2525-8473>
 Subhanudh Thavaraputta <https://orcid.org/0000-0001-7085-1167>
 Wasawat Vutthikraivit <https://orcid.org/0000-0003-1701-9800>
 Charat Thongprayoon <http://orcid.org/0000-0002-8313-3604>
 Kenneth Nugent <https://orcid.org/0000-0003-2781-4816>
 Wisit Cheungpasitporn <http://orcid.org/0000-0001-9954-9711>

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Avocations

A gorilla in the Fort Worth Zoo. Photo by Jay Hoppenstein, MD. Dr. Hoppenstein (e-mail: navigato@aol.com) is a surgeon who was on the medical staff at Baylor University Medical Center at Dallas from 1971 until his retirement in 2005. He also served as chairman of the Department of Surgery at Presbyterian Hospital of Dallas.