Systematic Review

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Statins & risk of *Clostridium difficile* infection: A meta-analysis

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***Background & objectives*: *Clostridium difficile* infection is one of the most common healthcare-associated infections worldwide. Recent epidemiologic studies have suggested that statin users may have a lower risk of *C. difficile* infection, although the results are inconsistent. This meta-analysis was conducted with the aim of summarizing all available data to assess the risk of *C. difficile* infection among statin users versus non-users.**

***Methods*: A literature review was performed using the MEDLINE and EMBASE databases from inception to October 2017. Cohort, case-control and cross-sectional studies that compared the risk of *C. difficile* infection among statin users versus non-users were included. Pooled odds ratio (OR) and 95 per cent confidence interval (CI) were calculated using a random-effect, generic inverse variance method.**

***Results*: Six case-control studies and two cross-sectional studies met the eligibility criteria and were included in this meta-analysis. The risk of *C. difficile* infection among statin users was significantly lower than non-users with the pooled OR of 0.74 (95% CI, 0.61-0.89). The statistical heterogeneity of this study was high (I^2=90%).**

***Interpretation & conclusions*: This meta-analysis demonstrated a decreased risk of *C. difficile* infection among statin users versus non-users. Further studies are required to clarify the role of statins for prevention of *C. difficile* infection in clinical practice.**

Key words *Clostridium difficile* - HMG-CoA reductase inhibitors - meta-analysis - statins

Clostridium difficile is a spore-forming, toxin-producing Gram-positive bacterium that is the causative agent of antibiotic-associated colitis. *C. difficile* infection is one of the most common healthcare-associated infections that caused approximately 29,000 deaths in the United States in 2011[1]. The healthcare cost of *C. difficile* infection is substantial with an estimated direct and indirect cost of up to five billion dollars in the US[2]. It is also a significant problem in India with the prevalence of as high as four per cent among hospitalized patients in a study from a tertiary care teaching hospital[3]. Antibiotic use is the most important risk factor for *C. difficile* infection, although studies have demonstrated that several other factors such as advanced age, gastric acid suppression therapy, enteral feeding, obesity and

inflammatory bowel disease are also associated with an increased risk of this infection[4].

Statins or hydroxymethylglutaryl (HMG)-CoA reductase inhibitors are one of the most commonly used medications worldwide as a result of the global epidemic of obesity, metabolic syndrome and cardiovascular diseases[5]. Over the past decades, it has been recognized that the benefits of statins go beyond the conventional cholesterol-lowering effect, as they also have an anti-inflammatory and immunomodulatory property[6]. It has also been shown that statins may be used as an adjunctive therapy for several chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis[7,8].

Use of statins may also decrease the risk of *C. difficile* infection as suggested by several epidemiologic studies[9-13], although the observations are inconsistent[14-16]. This systematic review and meta-analysis was conducted to summarize all available evidence to assess the risk of *C. difficile* infection among statin users versus non-users.

Material & Methods

Search strategy: Two investigators independently searched for published studies indexed in the MEDLINE and EMBASE databases from inception to October 2017 using a search strategy that included the terms for '*C. difficile*', 'HMG-CoA Reductase Inhibitors' and 'Statins.' A manual search for additional studies using references of selected retrieved articles was also performed. No language limitation was applied in this study. This study was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. EndNote X7 (Clarivate Analytics, Pennsylvania, USA) was used for study retrieval.

Inclusion criteria: The inclusion criteria were as follows: (*i*) case-control, cross-sectional or cohort studies published as original articles to determine the risk of *C. difficile* infection among individuals who use statins compared with individuals who do not use statins, and (*ii*) odds ratios (OR), relative risks (RR), hazard ratios or standardized incidence ratios with 95 per cent confidence intervals (CI) or sufficient raw data to calculate these ratios were provided.

Study eligibility was independently determined by three investigators. Differences in the determination of study eligibility were resolved by mutual consensus. The quality of each study was also independently evaluated by each investigator using the validated Newcastle–Ottawa quality assessment scale[17]. This scale evaluates each study in three domains including the selection of the participants, the comparability between the groups as well as the ascertainment of the exposure of interest for case-control study and the outcome of interest for cohort study. The modified Newcastle–Ottawa scale as described by Herzog *et al*[18] was used for the cross-sectional study. Kappa statistics were used for evaluation of inter-rater agreement on the Newcastle–Ottawa scale.

Data extraction: A standardized data collection form was used to extract the following data from each study: title of the study, name of the first author, year when the study was conducted, year when the study was published, country where the study was conducted, number of individuals, demographic data, method used to identify and verify *C. difficile* infection as well as statin use, adjusted effect estimates with 95 per cent CIs and covariates that were adjusted in the multivariate analysis.

To ensure the accuracy of data extraction, this process was independently conducted by three investigators. Case record forms were cross-checked, and any data discrepancy was also resolved by referring back to the original articles.

Statistical analysis: Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Adjusted point estimates from each study were combined using the generic inverse variance method of DerSimonian and Laird[19], which assigned the weight of each study in reverse to its variance. As the outcome of interest was relatively uncommon, it was planned to use RR of the cohort studies as an estimate for OR to combine with the OR from cross-sectional and case-control studies. In light of the possibility of high between-study variance due to different study designs and populations, a random-effect model was used rather than a fixed-effect model. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. This I^2 statistic quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0-25 per cent represents insignificant heterogeneity, >25 per cent but ≤50 per cent represents low heterogeneity, >50 per cent but ≤75 per cent represents moderate heterogeneity and >75 per cent represents high heterogeneity[20]. Funnel

plot was used to assess the presence of publication bias.

Results

Our search strategy yielded 218 potentially relevant articles (79 articles from MEDLINE and 139 articles from EMBASE). After the exclusion of 78 duplicate articles, 140 of them underwent title and abstract review. One hundred and sixteen articles were excluded at this stage since those were case reports, letters to the editor, review articles, basic science studies, animal studies or interventional studies, leaving 24 articles for a full-length article review. Thirteen of these were excluded since they did not report the outcome of interest whereas three articles were excluded due to duplication. Finally, eight studies (6 case-control studies and 2 cross-sectional studies) were included in the data analysis[9-16]. The literature review and study selection process are demonstrated in Figure 1. It should be noted that the inter-rater agreement for the quality assessment using the Newcastle–Ottawa scale was high with a kappa statistics of 0.81.

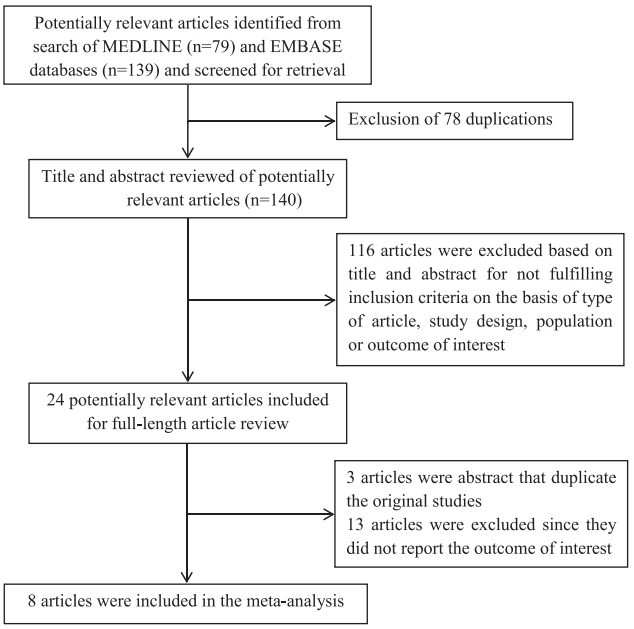

Fig. 1. Literature review process of systematic review and meta-analysis.

In this meta-analysis, the risk of *C. difficile* infection was significantly lower among patients who used statins compared with those who did not, with a pooled OR of 0.74 (95% CI, 0.61-0.89). The heterogeneity in this study was high (I^2=90%). The forest plot of this meta-analysis is shown in Fig. 2.

Evaluation for publication bias: The X-axis of the funnel plot (Fig. 3) represents the effect estimate, whereas the Y-axis represents the accuracy of the study. The eight included studies had a symmetric distribution around the pooled effect estimate (dotted line), with more variation among studies with lower accuracy and less variation among studies with higher accuracy. Therefore, this funnel plot did not suggest the presence of publication bias in favour of positive studies.

Sensitivity analysis: Three sensitivity analyses were conducted to explore the high heterogeneity observed in this meta-analysis. First, the study by Nseir *et al*[12] was excluded from the meta-analysis, as it was the only study not conducted in the US (therefore, only 7 studies were included in this sensitivity analysis)[9-11,13-16]. Exclusion of this study reduced the I^2 to 84 per cent and did not significantly alter the pooled effect estimate (pooled OR 0.83; 95% CI, 0.71-0.98). Second, the studies by Tartof *et al*[13] and Dobesh *et al*[14] were excluded from the meta-analysis as these were the only two studies with a cross-sectional

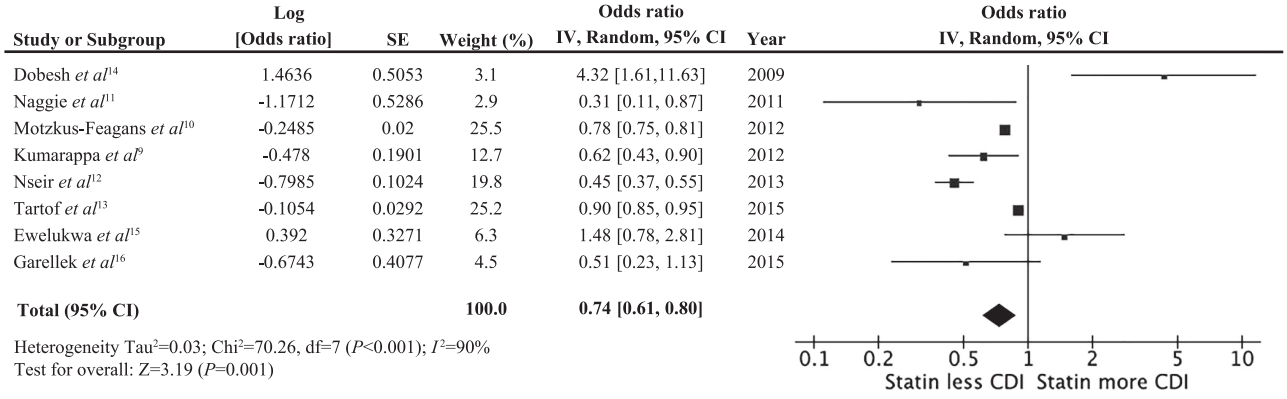

Fig. 2. Forest plot demonstrated the association between statin and risk of *Clostridium difficile* infection (CDI).

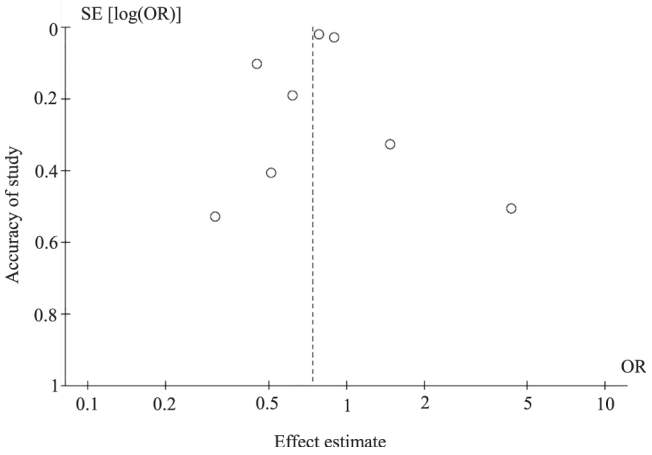

Fig. 3. Funnel plot assesses for publication bias. Dotted line indicates a symmetric distribution around the pooled effect estimate.

design (therefore, only 6 studies were included in this sensitivity analysis)[9-12,15,16]. Exclusion of these studies reduced the I^2 to 86 per cent and also did not significantly alter the pooled effect estimate (pooled OR 0.64; 95% CI, 0.45-0.89). Third, the studies by Dobesh *et al*[14], Kumarappa *et al*[9] and Garellek *et al*[16] were excluded from the meta-analysis as these studies did not adjust their effect estimates for other known risk factors of *C. difficile* infection such as antibiotic use (therefore, only 5 studies were included in this sensitivity analysis)[10-13,15]. Exclusion of these studies did not significantly alter the pooled effect estimate (pooled OR 0.73; 95% CI, 0.60-0.88). However, the I^2 increased to 93 per cent.

Discussion

This systematic review and meta-analysis demonstrated the protective effect of statins against *C. difficile* infection. The risk of developing *C. difficile* infection was significantly lower among statin users compared with non-users with an approximately 25 per cent decrease in risk. There is a previously published meta-analysis on this issue, but its literature review was completed in 2016[21]. Thus, the current work included more updated data. It should also be noted that across the included studies, two studies[14,15] did demonstrate that use of statins increased the risk of *C. difficile* infection. The most likely explanation is that these studies had a relatively small sample size and, therefore, more variability and less accuracy.

There were two studies investigating the influence of the use of statins to the outcome of *C. difficile* infection. The result of the first study[22] was in line with the current systematic review and meta-analysis, as use of statins in that study was associated with a better outcome among hospitalized patients who had *C. difficile* infection. However, the other study[23] failed to show such benefit and, thus, more studies are required.

The exact mechanisms of the decrease in risk of *C. difficile* infection in statin users are not known, but there are some plausible explanations. First, *in vitro* studies have demonstrated that statins can promote neutrophil function and increase the capacity of phagocytes to create extracellular traps[24], and this immunomodulatory property of statins may partly explain the lower risk of *C. difficile* infection. In fact, use of statins has been shown to decrease the risk of other types of infection as well[25]. Second, statins may have direct antimicrobial effects as shown by *in vitro* studies[26,27], although there has not been a study that directly demonstrates the antimicrobial effect of statins on *C. difficile.* Third, a mouse study has demonstrated that use of statins has an influence on gut microbiota and could change the gut microbial composition through the alteration of transcription of genes encoding factors involved in gut homeostasis[28]. This change could affect the risk of developing *C. difficile* infection through competition with the normal colonic bacterial flora[29].

Alternatively, the use of statins may only decrease the inflammatory response to *C. difficile* infection, as statins are known to have anti-inflammatory properties through the inhibition of the mevalonate pathway which would result in decreased production of isoprenoids, a compound essential for the function of the innate and adaptive immunity[30]. Studies have demonstrated that use of statins is associated with decreased inflammatory cell influx[31], reduction of pro-inflammatory cytokine production and reduction of T-cell activation[32]. The reduced inflammatory response may lead to the decreased severity of *C. difficile* infection and, thus, fewer clinically evident cases.

Though most of the included studies were of high quality as reflected by the high Newcastle–Ottawa Score, our meta-analysis had some limitations. First, the between-study heterogeneity of this meta-analysis was high. As suggested by the sensitivity analyses, perhaps the different study designs and background populations were partially responsible for this high heterogeneity. Second, known risk factors for *C. difficile* infection were not adjusted in some primary studies. Therefore, it might be possible that the observed association was a result of a confounding effect. However, sensitivity

analysis including only studies that adequately adjusted their effect estimates continued to show a significantly negative association between exposure to statins and risk of *C. difficile* infection. Third, generalizability of this study may be limited as the number of the included studies was relatively small and all but one included study were conducted in the US. Thus, the observations may not be applicable to other populations as the epidemiology of *C. difficile* infection varies across regions. Finally, the data on the effect of statin use on C. *difficile* carriage were not available.

In summary, although the results from primary studies varied considerably, this meta-analysis was able to demonstrate a significantly decreased risk of *C. difficile* infection among statin users versus non-users. As the current study was observational in nature, studies with more rigorous design (*i.e.*, randomized controlled trial) are required to prove the efficacy of statins for the prevention of *C. difficile* infection before it can be recommended in clinical practice.

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***Conflicts of Interest*:** None.

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