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The Effect of Statin in Managing Cholelithiasis: A Systematic Review

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ABSTRACT

Introduction: Gallstone disease is a prevalent condition leading to numerous hospitalizations worldwide, with cholesterol gallstones comprising 80–90% of cases. While cholecystectomy remains the primary treatment, statins, known for reducing low-density lipoprotein cholesterol, may influence gallstone formation by altering biliary cholesterol levels. However, findings regarding their effectiveness in humans are inconsistent. This systematic review evaluates the role of statins in managing cholelithiasis.

Methods: A systematic review adhering to PRISMA guidelines included randomized controlled trials, cohort studies, and case-control studies examining statin use in adults without prior gallstone disease. Searches were conducted in Medline, Embase, and Cochrane Library. Data extraction and quality assessments were performed by two independent reviewers, resolving discrepancies by consensus.

Results: Among 1,007 references, eight studies involving 590,086 participants met inclusion criteria. Statin users, categorized by duration and usage status, exhibited a reduced risk of gallstone disease and cholecystectomy. Medium- and long-term statin users had the most significant protective effects, although findings varied due to differences in study designs, definitions of statin use, and gallstone outcomes.

Discussion: Statins demonstrated a potential protective role against gallstone formation and severity, consistent with previous meta-analyses. However, limitations, including observational study biases, variability in definitions, and confounding factors like lifestyle and comorbidities, necessitate cautious interpretation. Prospective studies are required to confirm these findings and address gaps such as the impact of statin discontinuation on gallstone recurrence.

Conclusion: Medium- and long-term statin use reduces gallstone and cholecystectomy risks, highlighting their potential in managing cholelithiasis. Future research should explore these effects further to refine clinical recommendations.

Keywords: Statin, cholelithiasis, gallstone disease

INTRODUCTION

Gallstone disease is a leading cause of hospital admissions in developed nations1, with its prevalence in Western populations ranging from 10–30%2. Cholecystectomy is the primary treatment for symptomatic cholelithiasis, with approximately 70,000 procedures performed in the U.S. in 20081,3. Gallstones are predominantly composed of cholesterol (80–90%) and pigment stones2. Statins, commonly prescribed to lower low-density lipoprotein cholesterol (LDL-C) and reduce cardiovascular risk, also inhibit cholesterol biosynthesis, potentially affecting biliary cholesterol levels4. While animal studies suggest statins may alter biliary lipid composition and reduce gallstone formation5,6, findings in human studies

vary. Some research supports statins' ability to lower bile cholesterol or dissolve gallstones, while others show minimal effects7,8. A 2015 meta-analysis concluded that statin use reduces gallstone disease risk but noted significant unexplored heterogeneity9. Variability in statin use duration and definitions of current/former users complicates findings10,11. Therefore, we conducted a systematic review to assess the association between statin use in managing cholelithiasis.

MATERIALS & METHODS

We performed a systematic review on the Cochrane Handbook for Systematic Reviews of Interventions12 and reported results per PRISMA guidelines. We searched Medline, Embase, and Cochrane Library databases for relevant studies up to August 2024. Eligible articles included randomized controlled trials, prospective studies, retrospective studies, or case-control studies involving adults without prior gallstone disease or cholecystectomy. Only studies examining statin use and reporting gallstone or cholecystectomy outcomes were included. Duplicate reports were excluded, favoring the most comprehensive data. Two independent reviewers extracted study details, including publication year, participant demographics, disease status, and statistical outcomes. Discrepancies were resolved through consensus or consultation with a senior reviewer.

RESULT

Our search identified 1,007 references from Medline, Embase, and the Cochrane Library. After screening titles and abstracts, we excluded duplicates (n = 49) and irrelevant references (n = 942), leaving 16 full-text articles for further review. Ultimately, six case-control studies10,11,13–16 and two retrospective cohort studies17,18 met the criteria for qualitative and quantitative synthesis. A flowchart detailing the study selection process is shown in Figure 1.

The eight included studies10,11,13–18, conducted between 1994 and 2012, collectively analyzed 590,086 participants. Five studies11,13,15–17 included patients who underwent cholecystectomy for gallstone disease, while the remaining three10,14,18 involved patients diagnosed with gallstone disease, as detailed in Tables 1.

Five studies10,11,13–15 classified patients as current, past, or non-users of statins. In contrast, the other three studies16–18 broadly defined statin users as those with any prescription before the index date, which was either the first diagnosis of gallstone disease or the date of cholecystectomy for patients without prior cholelithiasis records. Regarding statin use duration, three studies10,11,15 categorized it based on the number of prescriptions prior to the index date, as detailed in Tables 2.

Table 1. Characteristics of included studies

Study, year	Study type	Country	Inclusion period	Match method	Exclusion criteria	Case definition	Statin use
Biétry 2016 (Harville, 1977)	CC	Switzerland	2008～2014	1:4 matched on age, sex, and index date	Cancer or HIV	Cholecystectomy only	Prior to index date †, Current user: last prescription <180 days Former user: last prescription >180 days
Bodmer 2009 (Grant, 2014)	CC	UK	1994～2008	1:4 matched on age, sex, and index date	Alcoholism, drug abuse, cancer or HIV	First time diagnosed gallstone disease followed by cholecystectomy in 2 years; or cholecystectomy only	Prior to index date, Current user: last prescription <90 days Former user: last prescription >90 days
Chiu 2012 (Sterne et al., 2016)	CC	Taiwan	1996～2009	1:1matched on age, sex, and index date	Cancer	First time diagnosed gallstone disease followed by cholecystectomy in 2 years; or cholecystectomy only	Any prescription prior to index date
Erichsen 2010 (Biétry et al., 2016)	CC	Denmark	1996～2008	1:10 matched on age, sex	Preexisting gallstone disease or liver, bile duct or pancreatic cancer	Diagnosis of gallstone, cholecystitis or a record gallbladder surgery (cholecystectomy or drainage)	Prior to index date, Current user: last prescription <90 days; Former user: last prescription >90 days
González-Pérez 2007 (Julian Higgins et al., 2019)	CC	UK	1996～1996	1:4 matched on age and sex	Preexisting gallstone disease or cancer	Symptomatic gallstone	Prior to index date, Current user: last prescription <30 days; Former user: last prescription >30 days
Merzon 2010 (Erichsen et al., 2011)	CC	Israel	2003～2006	1:4 matched on age and sex	N/A	Cholecystectomy due to gallstone disease	Prior to index date, Last prescription <180 days prior to index date
Martin 2015 (Higgins, 2003)	RC	US	2003～2012	1:1 propensity matched	History of burn, trauma, statin use <90 days, or starting statin use after baseline period	Diagnosis of cholelithiasis	Statin use lasting over 90 days prior to index date
Tsai 2009 (Kan et al., 2015)	RC and PC	US	1994～2000	N/A	Prior cholecystectomy or gallstone disease or cancer	Self-reported cholecystectomy	Prior to index date, Current user: self-reported current use from inception to 2000, Former user: no present use in 2000

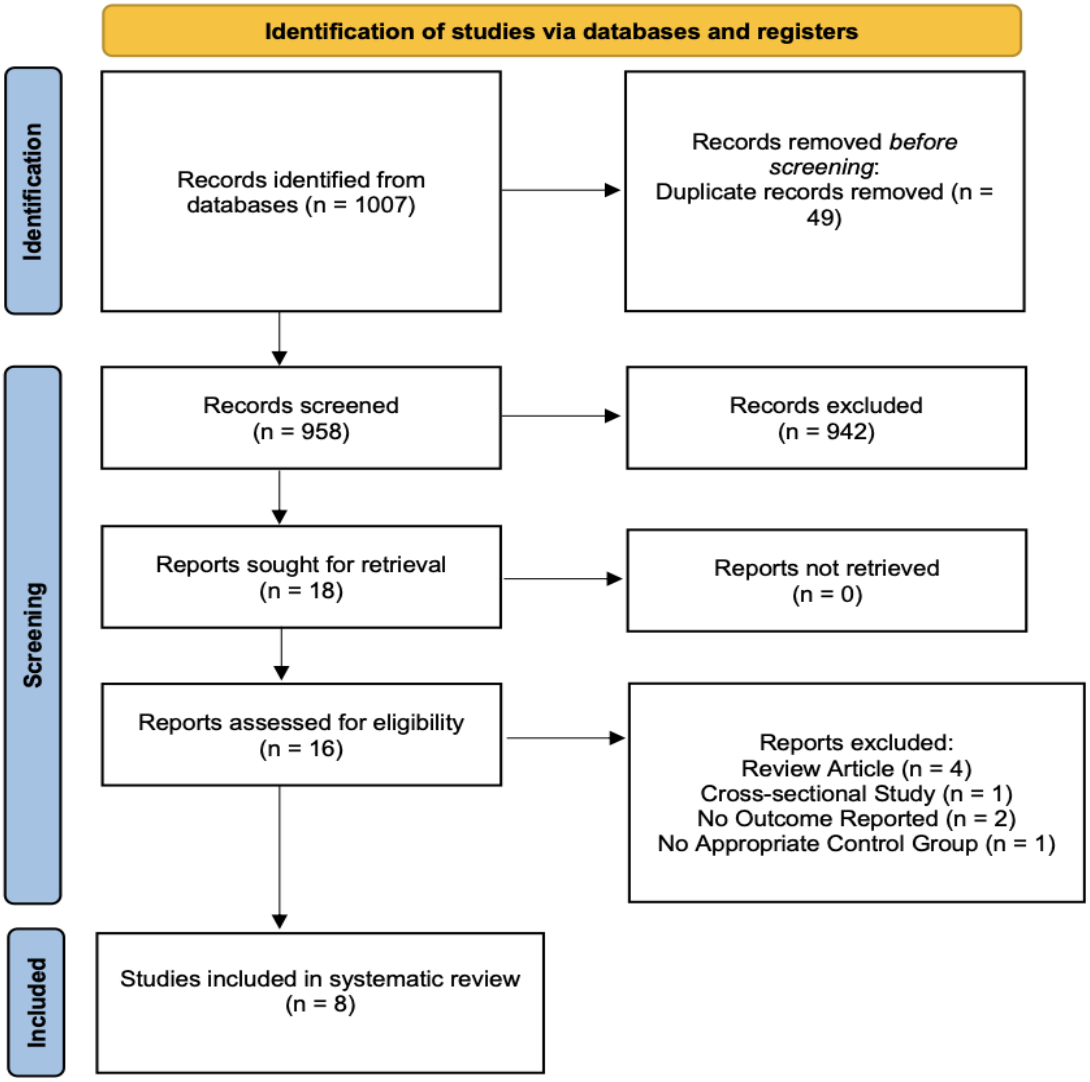

Figure 1. PRISMA flow diagram

Table 2. Studies reporting different duration of statin use (current users)

Study, year	1-4 prescriptions Overall, n (%)			1-4 prescriptions Men, n (%)			1-4 prescriptions Women, n (%)		
	Case	Control	AOR (95% CI)	Case	Control	AOR (95% CI)	Case	Control	AOR (95% CI)
Biétry 2016[23]	63 (2.8)	155 (1.7)	1.34 (0.99 to 1.83)	34 (1.5)	77 (0.9)	1.50 (0.98 to 2.32)	29 (1.3)	78 (0.9)	1.20 (0.77 to 1.88)
Bodmer 2009[19]	277 (1.0)	832 (0.8)	1.10 (0.95 to 1.27	89(0.3)	312 (0.3)	0.99 (0.77 to 1.26)	188(0 .7)	520(0.5)	1.19(0.99 to 1.42)
Erichsen 2010[17]	464 (1.4)	3443 (1.1)	1.17 (1.06 to 1.30)	185(0. 6)	1434 (0.4)	1.06(0.90 to 1.25)	279(0 .9)	2009(0.6)	1.25(1.1 to 1.42)
	5-19 prescriptions Overall, n (%)			5-19 prescriptions Men, n (%)			5-19 prescriptions Women, n (%)		
	Case	Control	AOR (95% CI)	Case	Control	AOR (95% CI)	Case	Control	AOR, 95 CI
Biétry 2016[23]	234 (10.5)	1005 (11.3)	0.77 (0.65 to 0.92)	124 (5.6)	546 (6.1	0.78 (0.61 to 1.00)	110 (5.0)	459 (5.2)	0.77 (0.61 to 0.99)
Bodmer 2009[19]	690 (2.6)	2550 (2.4)	0.8 (0.77 to 0.93)	256 (1.0)	959 (0.9)	0.89 (0.76 to 1.03)	434 (1.6)	1591 (1.5)	0.84 (0.75 to 0.94)
Erichsen 2010[17]	813 (2.5)	7368 (2.3)	0.89 (0.82 to 0.97)	349 (1.1)	3,188 (1.0)	0.84 (74 to 0.95)	464 (1.4)	4,180 (1.3)	0.93 (0.84 to 1.03)
	≥20 prescriptions Overall, n (%)			≥20 prescriptions Men, n (%)			≥20 prescriptions Women, n (%)		
	Case	Control	AOR (95% CI)	Case	Control	AOR (95% CI)	Case	Control	AOR, 95 CI
Biétry 2016[23]	99 (4.5)	367 (4.1)	0.88 (0.69 to 1.13)	60 (2.7)	211 (2.4)	0.98 (0.70 to 1.37)	39 (1.8)	156 (1.8)	0.79 (0.54 to 1.16)
Bodmer 2009[19]	865 (3.2)	3960 (3.7)	0.64 (0.59 to 0.70)	377 (1.4)	1636 (1.5)	0.70 (0.61-0.81)	488 (1.8)	2324 (2.2)	0.61 (0.55-0.69)
Erichsen 2010[17]	487 (1.5)	4769 (1.5)	0.76 (0.69 to 0.84)	207 (0.6)	2,111 (0.6)	0.69 (0.59 to 0.81)	280 (0.9)	2,658 (0.8)	0.81 (0.70 to 0.92)

1-4 prescriptions means the short-term use of statin, 5-19, medium-term, over 20, long-term, AOR, adjusted odds ratio, CI, confidence interval

DISCUSSION

Statins are widely used for the treatment and prevention of cardiovascular diseases19 and have also been suggested to lower the risk of urolithiasis20,21. Most studies defined gallstone cases based on the requirement for cholecystectomy. Statins may influence both gallstone formation and the severity of symptoms. For example, Suuronen et al.22 observed fewer overall cholecystectomies but a higher number of laparoscopic cholecystectomies (LCs) in statin users. They attributed this to an increased incidence of mild symptomatic gallstones prompting LC. While different surgical approaches may reflect disease severity, none of the included studies compared outcomes between open and laparoscopic cholecystectomy.

Despite their effectiveness in preventing cardiovascular disease, statins are often discontinued due to perceived side effects, particularly myopathy, which occurs in only 0.01% of users23. Non-compliance is frequently driven by a belief in stable health conditions24, which can lead to relapsing dyslipidemia after discontinuation, exacerbating cardiovascular and gallstone-related outcomes25,26. We hypothesize that this recurrence of dyslipidemia may offset the protective effects of statins, particularly among medium- and short-term users.

Compared to earlier analyses, such as Kan et al.9, our study included three additional studies11,14,18. Consistent with prior findings, we observed a reduced risk of gallstone disease among medium- and long-term statin users. However, our analysis addressed several gaps. We evaluated how discontinuation impacts gallstone risk, which was not clarified in earlier studies. We excluded cross-sectional studies, as they assess prevalence rather than incidence27. While such studies may not contribute significantly to statistical heterogeneity, they introduce conceptual variance. By addressing these factors, we provide a more nuanced understanding of statin use and gallstone disease risk.

The results of our systematic review should be interpreted with caution due to several limitations. First, the inclusion of case-control and retrospective cohort studies introduced potential biases, as confounding factors were often inadequately controlled. Second, while we examined the protective effect of statins on gallstone formation, the definitions of statin use and gallstone disease varied across studies, affecting consistency. Third, important baseline factors linked to gallstone risk, such as hyperlipidemia, estrogen exposure, or hormone therapy, were not reported in some studies, reducing the precision of our findings. Lastly, the "healthy user" and "adherence" effects represent significant yet often overlooked biases in observational studies28. Patients who take and adhere to statins are generally more likely to engage in health-promoting behaviors, which could contribute to the observed protective effects. These behaviors are difficult to account for in observational research, resulting in unmeasured confounding bias.

CONCLUSION

Medium- and long-term statin use appears to reduce gallstone disease and cholecystectomy risk, therefore effective in managing cholelithiasis but further prospective studies are needed to confirm these effects and address study limitations.

Declaration by Author

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