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Clinical Research Article

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# Statins Decrease the Risk of Orbitopathy in Newly Diagnosed Patients with Graves Disease

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**Abbreviations:** ATC, Anatomical Therapeutic Chemical; GD, Graves disease; GO, Graves orbitopathy; HMG CoA, 3-Hydroxy-3-methylglutaryl-coenzyme; HR, hazard ratio; ICD, International Classification of Diseases; IGF-1R, insulin-like growth factor 1 receptor; IQR, interquartile range; LDL, low-density lipoprotein; TSHR, thyrotropin receptor.

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## Abstract

**Context/objective:** The aim of this study was to examine the effect of statins and other lipid-lowering agents on the development of Graves orbitopathy (GO) in patients with newly diagnosed Graves disease (GD).

**Methods:** Our sample included the full adult population of individuals living in Sweden with newly diagnosed GD between 2005 and 2018 (n = 34 894). We compared the GO incidence in statin users (n = 5574) and nonusers (n = 34 409) by applying Cox regression with a time-varying exposure variable. We adjusted for age, sex, and treatment for hyperthyroidism in the multivariate analyses.

**Results:** Periods of nonusage lasted for a median of 4.3 years (interquartile range [IQR] 1.2-8.4), whereas periods of usage lasted for a median of 4.7 years (IQR 2.0-8.1). Among statin users, 77.1% had used simvastatin, 28.9% atorvastatin, and 8.2% had used other statins. Statin users were found to be significantly less likely to develop GO. In the main analysis based on the full cohort, the unadjusted hazard ratio (HR) was 0.74 (CI 0.65-0.84, $P < .001$), whereas full adjustment altered the effect to 0.87 (CI 0.76-1.00, $P = .04$). The main results were largely driven by men; the fully adjusted HR was 0.78 (CI 0.58-1.04, $P = .09$) for men and 0.91 (CI 0.79-1.06, $P = .24$) for women. Lipid-lowering agents other than statins did not exhibit a similar protective effect.

**Conclusion:** In newly diagnosed patients with GD, treatment with statins may protect against the development of GO. Statins should be investigated in a clinical trial as a preventive treatment for GO in newly diagnosed patients with GD.

**Key Words:** Graves disease, Graves orbitopathy, 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, statins

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Graves orbitopathy (GO) is the most common extrathyroidal manifestation of Graves disease (GD), occurring in 25% to 30% of GD patients (1). GO is a multifactorial disease caused by an interplay between endogenous and environmental factors, including age, sex, hypothyroidism, inadequate control of hyperthyroidism, radioiodine treatment, tobacco smoking, and certain drugs (2). It is believed to be an autoimmune disorder directed against the thyrotropin receptor (TSHR) (3); moreover, insulin-like growth factor 1 receptor (IGF-1R) also seems to be involved in the pathogenesis, probably by interplay with TSHR. Teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, has recently been approved for treatment of GO with very promising results (4-8). The pathological processes in GO include infiltration of the intraorbital structures by immunocompetent cells causing inflammation, increased production of glycosaminoglycans by orbital fibroblasts, and the expansion of intraorbital adipose tissue and intraocular muscles (1). GO is a debilitating disease, and the currently available treatments, such as corticosteroids, orbital irradiation, and immune modulators (9, 10), do not prevent the long-term consequences of GO and are associated with potentially severe side effects. Identifying modifiable risk factors that predispose GD patients to develop GO and producing novel therapies could significantly improve the quality of life of these patients.

3-Hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, commonly known as statins, reduce low-density lipoprotein (LDL) cholesterol levels, leading to a decreased cardiovascular risk. Apart from reducing cholesterol levels, the anti-inflammatory effects of statins have been widely debated. The frequently cited JUPITER study (11, 12) discovered the anti-inflammatory actions of statins, which were not related to their cholesterol-lowering effect. In that study, rosuvastatin reduced systemic markers of inflammation together with cholesterol levels and the number of cardiovascular events (13-15). Subsequently, statins have been proposed as a novel anti-inflammatory therapy for a number of conditions, including autoimmune diseases (16-24). In GO, Koch et al. (24) suggested that statins may be able to convert a primarily proinflammatory T cell response into an anti-inflammatory T cell response via upregulation of TH2 cells and regulatory T cells. Likewise, statins may be able to mobilize disease-specific proinflammatory T cells from the disease site into the blood, resulting in clinical remission (24).

Recently, Stein et al. retrospectively investigated a large cohort of patients with newly diagnosed GD to identify risk factors associated with the development of GO (25). In this study, thyroidectomy applied as a treatment for hyperthyroidism and exposure to statins lowered the risk of developing GO. In another recent cross-sectional study of patients with GD, a significant correlation was found between the occurrence of GO and both total and LDL-cholesterol in patients with a relatively short duration of GD, suggesting a role of cholesterol itself in the development of GO (26). Moreover, the authors found a correlation between the clinical activity score and serum lipids in untreated GO patients depending on the GO duration. However, this finding was not verified in a confirmatory study by the same group (27). A randomized clinical trial is now investigating whether lowering of cholesterol with atorvastatin in addition to the standard 12 weeks of treatment with intravenous steroids in hypercholesterolemic patients with moderate to severe and active GO is associated with a better outcome of GO (28).

The aim of our study was to examine the effect of the use of statins and other lipid-lowering agents on the development of GO in patients with newly diagnosed GD in the Swedish population and to investigate whether this effect is influenced by the type of lipid-lowering agent, dosage, duration, and time course of the treatment.

## Materials and Methods

Data were obtained from the Swedish National Board of Health and Welfare (*Socialstyrelsen*), and included information between 2005 and 2018 from 2 different official registers: the Prescribed Drugs Register (*Läkemedelsregistret*) and the National Patient Register (*Patientregistret*). The 2 registers were linked together by the use of personal identifiers. The Prescribed Drugs Register records all prescribed drugs dispensed at pharmacies in Sweden since July 2005 and includes information such as the Anatomical Therapeutic Chemical (ATC) code, date of purchase, number of tablets, and dose per tablet. The National Patient Register records all hospital visits in the country and includes information such as diagnostic codes (main diagnosis and up to 20 secondary diagnoses), codes for surgical procedures, and the dates of visit. Both registers also include the age and sex of the patient.

Our cohort consisted of all individuals with at least 1 hospital visit for GD (International Classification of Diseases [ICD]-10: E050, either as the main or secondary diagnosis) between 2005 and 2019, and who were at least 18 years of age at the time of their first diagnosis during this period. Notably, GD in Sweden is not being treated by general practitioners and private endocrinologists are few; thus, the included cohort includes the majority of Swedish GD patients diagnosed during this time period. Aiming to only include patients with newly diagnosed GD, individuals with a diagnosis of GD or GO (ICD-10: H062) prior to 2005 were excluded.

Individuals were followed from the time of their first recorded GD diagnosis until their first visit for GO, or

at most until December 31, 2018. Cox regression was applied, with "statin user" as a time-varying treatment variable. In the main analysis, a person was defined as a statin user if the person had, so far, obtained at least 2 prescriptions of 3-Hydroxy-3-methylglutaryl-coenzyme (HMG CoA) reductase inhibitors (ATC: C10AA) since the point in time 3 months prior to their first GD diagnosis. Individuals could thus be reclassified from nonstatin users to statin users, but not the other way around. In the complementary analyses, individuals could also be reclassified from statin user to "recent statin user" when the elapsed time since the last prescription was 4-6 months (suggesting no usage during the last 1-3 months) and "former statin user" when the elapsed time since the last prescription was more than 6 months (suggesting no usage during the last 3 months or more). Any number of moves across these 3 categories were allowed in this complementary analysis. As GO frequently develops within 12 months from the GD diagnosis (29), in separate sensitivity analyses, individuals were only classified as statin users if they obtained their second statin prescription up to 3 or 12 months following their first GD diagnosis.

The time variable in the Cox regressions represented the time since baseline, that is since the first GD diagnosis. Adjusted models included the age and sex at baseline (age was divided into 7 categories: 18-29, 30-39, 40-49, 50-59, 60-60, 70-79, and 80 or higher). Additional models also included time-varying adjustment for whether the individual had undergone treatment with thyroidectomy or radioiodine, or whether the individual had at least 2 records of obtaining antithyroid drugs. For each adjustment variable, the proportional hazards assumption was examined, and a stratified Cox model was used instead of regression adjustment whenever the proportional hazards assumption was not fulfilled. The main analysis was conducted separately for men and women.

To contrast the effects of statins and other lipid-lowering agents (ATC: C10A, except C10AA), a separate analysis was conducted, including statins and other lipid-lowering agents as separate treatment variables. Moreover, to examine the potentially different effects of different types of statins—simvastatin (ATC: C10AA01), atorvastatin (ATC: C10AA05), and others—an analysis was conducted using separate indicators for each of these 3 types. To account for differences in dosages across patients using different types of statins, this analysis was also conducted with adjustment for "equivalent dosage," which represented the average dosage per tablet obtained by the patient, where the dosage of atorvastatin was given twice the weight of that of simvastatin (30). Before the initiation of statin treatment, the dosage variable was set to 0. Users of statins other than atorvastatin and simvastatin were excluded from the dosage-adjusted analysis.

Finally, as an alternative to the GO indicator, the main analysis was replicated with "surgical treatment for severe GO" as the outcome variable. The outcome included any of the surgical orbital decompression procedures (CAC20, CAC30, CAC40, CAC42, and CAC44).

This study was approved by the Swedish Ethical Review Authority (Dnr: 2019–03737).

## Results

Our cohort included 34 894 unique individuals with GD. Of these, 34 409 were nonusers of statins for at least some part of the follow-up period, whereas 5574 were users (Table 1). Periods of nonusage lasted for a median of 4.3 years (IQR 1.2-8.4), whereas periods of usage lasted for a median of 4.7 years (IQR 2.0-8.1).

Substantial differences in background characteristics were observed across users and nonusers of statins. Users were older than nonusers (89% vs 45% above age 50). Statin users were also more likely than nonusers to be male (25.2% vs 17.1%). Statin users were more likely than nonusers to have been treated with radioiodine (5.5% vs 3.3%), whereas nonstatin users were more likely than statin users to have been treated with thyroidectomy (2.3% vs 1.1%) or antithyroid drugs (61.5% vs 48.4%). Statin users were more likely than nonusers to have been using other lipid-modifying agents (4.8% vs 0.1%). Among statin users, 77.1% had used simvastatin, 28.9% atorvastatin, and 8.2% had used other statins.

Users of statins were found to be significantly less likely to develop GO (Table 2). In the main analysis based on the full cohort, the unadjusted hazard ratio (HR) was 0.74 (CI 0.65-0.84, $P < .001$). Adjustment for age and sex produced an HR of 0.85 (CI 0.75-0.98, $P = .02$), whereas further adjustment altered the effect only slightly to 0.87 (CI 0.76-1.00, $P = .04$).

The main results were largely driven by men, although the results for both men and women were nonsignificant at the 5% level in the models with full adjustment. The fully adjusted HR amounted to 0.78 (CI 0.58-1.04, $P = .09$) for men and to 0.91 (CI 0.79-1.06, $P = .24$) for women.

Sensitivity analyses only counting statin initiation up to 3 or 12 months following the first GD diagnosis yielded similar results as the main analysis. Moreover, the results were virtually unaffected by different restrictions on the follow-up period.

Figure 1 displays the fully adjusted survival curves, based on the main analysis, drawn for statin and nonstatin users separately. Both curves were drawn for a representative

woman aged 50-59, with zeros on the other covariates. In line with the previously reported results, the incidence of GO was clearly lower in statin users.

Dividing the previously used indicator for "ever, so far" usage of statins into "current—less than a year," "current—more than a year" "recent," and "past" usage (Table 3) showed that the effects of current usage were similar to the main results previously established. The fully adjusted model yielded an HR of 0.72 (CI 0.52-1.00, $P = .05$) for current users having used statins for more than a year and 0.90 (CI 0.77-1.05, $P = .17$) for current users having used statins for less than a year, suggesting a stronger protective effect with a longer duration of treatment. Estimates for recent users and past users tended to be similar but were estimated with much less precision; the estimates were clearly nonsignificant but at the same time statistically indistinguishable from the effects of current usage.

Comparing different types of statins showed clear effects of atorvastatin but not of simvastatin when adjusting for age, gender, and other covariates except dosage (Table 4). As this could be a result of the higher potency of atorvastatin, we then performed a dose-adjusted analysis where atorvastatin was given twice the weight of simvastatin. In a fully adjusted model including dosage, the effect of dosage was marginally significant, with a protective effect (HR 0.89, CI 0.78-1.00, $P = .06$ per 20 mg of simvastatin or 10 mg of atorvastatin). The effects of both simvastatin and atorvastatin themselves were nonsignificant, with HRs close to 1 in this analysis.

Comparing current usage of statins with current usage of other lipid-lowering agents (Table 5) produced significant effects for statin usage only, although the effect was only marginally significant at the 5% level in the fully adjusted model (HR = 0.87, CI 0.75-1.01, $P = .06$). The effects of other lipid-lowering agents as well as the effects of combining statins and other lipid-lowering agents were imprecisely estimated with broad confidence

**Table 1.** Characteristics of patients with newly diagnosed Graves disease included in the study

| | Use of statins | No use of statins |
|---|---|---|
| Distinct individuals | 5574 | 34 409 |
| Follow-up time, years (median; IQR) | 4.7 (2.0-8.1) | 4.3 (1.2-8.4) |
| **Background characteristics (%) by statin use** | | |
| Age 18-29 | 0.7 | 15.1 |
| Age 30-39 | 2.3 | 19.9 |
| Age 40-49 | 8.1 | 20.2 |
| Age 50-59 | 20.3 | 16.5 |
| Age 60-69 | 32.1 | 12.7 |
| Age 70-79 | 26.2 | 9.0 |
| Age 80+ | 10.3 | 6.6 |
| Male | 25.2 | 17.1 |
| Use of antithyroid preparations | 48.4 | 61.5 |
| Thyroidectomy | 1.1 | 2.3 |
| Radioiodine | 5.5 | 3.3 |
| Use of other lipid-modifying agent | 4.8 | 0.1 |
| Statin use: simvastatin | 77.1 | — |
| Statin use: atorvastatin | 28.9 | — |
| Statin use: other | 8.2 | — |

Prevalences of background characteristics were calculated with person–time as the unit of observation. "Use of statins" means that the individual has so far obtained at least 2 packages of statins since the point in time 3 months before their first Graves disease diagnosis. Use of antithyroid preparations was defined analogously, and procedures were tracked from the point of Graves disease diagnosis. Age refers to age at the individual's first Graves disease diagnosis. There are 34 894 individuals in total.

**Table 2.** Hazard of developing Graves orbitopathy in statin users compared with nonusers

| | Unadjusted HR (95 % CI) | HR adjusted for age and gender (95% CI) | Additionally adjusted HR (95% CI) |
|---|---|---|---|
| Main analysis | 0.74 (0.65-0.84), $P < .001$ | 0.85 (0.75-0.98), $P = .02$ | 0.87 (0.76-1.00), $P = .04$ |
| Only women | 0.80 (0.69-0.92), $P = .002$ | 0.90 (0.76-1.05), $P = .17$ | 0.91 (0.79-1.06), $P = .24$ |
| Only men | 0.59 (0.45-0.78), $P < .001$ | 0.74 (0.55-1.00), $P = .05$ | 0.78 (0.58-1.04), $P = .09$ |
| Only counting statin initiation within 3 months | 0.67 (0.57-0.80), $P < .001$ | 0.81 (0.68-0.96), $P = .01$ | 0.81 (0.69-0.96), $P = .02$ |
| Only counting statin initiation within 1 year | 0.72 (0.63-0.83), $P < .001$ | 0.86 (0.74-0.99), $P = .03$ | 0.87 (0.76-1.00), $P = .06$ |
| Follow-up limited to 1 year | 0.70 (0.58-0.84), $P < .001$ | 0.81 (0.67-0.98), $P = .03$ | 0.81 (0.67-0.98), $P = .03$ |
| Follow-up limited to 2 years | 0.74 (0.63-0.86), $P < .001$ | 0.82 (0.70-0.97), $P = .02$ | 0.83 (0.71-0.98), $P = .02$ |
| Follow-up limited to 3 years | 0.75 (0.65-0.86), $P < .001$ | 0.83 (0.72-0.97), $P = 0.02$ | 0.84 (0.72-0.98), $P = .02$ |

Each cell corresponds to a separate regression. Estimates were obtained from Cox regressions with adjustment for age and gender (grouped) at the time of first Graves disease diagnosis, and in the additional analysis whether the individual had undergone treatment with thyroidectomy or radioiodine, or whether the individual has had at least 2 records of obtaining antithyroid preparations.

intervals; the results were both consistent with no effects of other treatments and with those having the same or greater effects as statins only. It was not possible to separate this analysis into separate analyses of the effects of different subtypes of lipid-lowering agents such as PCSK9-inhibitors, fibrates, ezetimibe, cholestyramine, and others, due to the low numbers of subjects in the subgroups.

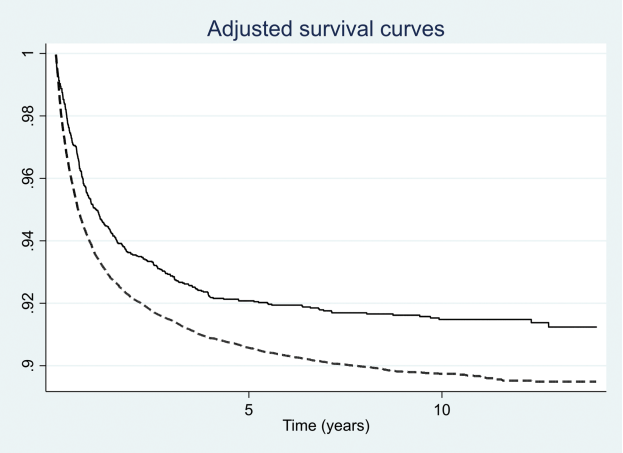


**Figure 1.** Adjusted survival curves (time until Graves orbitopathy) for statin users and nonusers, separately. The solid line represents statin users and the dashed line nonusers. The curves represent females in the 50-59 age group at baseline with zeros on all other covariates.

Finally, the analysis of surgical treatment for severe GO yielded very imprecise and nonsignificant estimates due to the outcome being rare (results not shown).

## Discussion

Few studies have examined the effect of statin therapy on the development of GO in patients with GD. In this large register-based study including 34 894 adult Swedish patients with newly diagnosed GD between 2005 and 2018, we examined the effect of statin therapy on the incidence of GO. The main finding is that statin users had a significantly lower incidence of GO than nonusers, a finding that confirms the conclusions of an earlier smaller study from the United States (25).

The aforementioned study by Stein et al. (25) enrolled 8404 adults with newly diagnosed GD over 8 years. Like in our study, ICD codes were used to identify subjects who developed GD and GO in a medical database. Multivariable Cox regression was used to determine the hazard of developing GO with adjustment for sociodemographic factors, systemic medical conditions, thyroid-stimulating hormone levels, and medical and surgical interventions for the management of hyperthyroidism. After adjustment for potential confounders, surgical thyroidectomy (HR 0.26), and statin use (HR 0.60) were associated with a decreased hazard of developing GO. In our study, we

**Table 3.** Hazard of developing Graves orbitopathy in current, recent, and previous statin users compared to nonusers

| | Unadjusted HR (95 % CI) | HR also adjusted for age and gender (95% CI) | Additionally adjusted HR (95% CI) |
|---|---|---|---|
| Current user—less than a year | 0.77 (0.66-0.89) *P* = .001 | 0.89 (0.76-1.03) *P* = .12 | 0.90 (0.77-1.05) *P* = .17 |
| Current user—more than a year | 0.62 (0.45-0.86) *P* = .004 | 0.70 (0.51-0.98) *P* = .04 | 0.72 (0.52-1.00) *P* = .05 |
| Recent user | 0.69 (0.40-1.19) *P* = .18 | 0.78 (0.45-1.36) *P* = .38 | 0.81 (0.47-1.41) *P* = .46 |
| Past user | 0.79 (0.55-1.15) *P* = .22 | 0.96 (0.66-1.39) *P* = .83 | 0.98 (0.68-1.42) *P* = .92 |

The reference group is "never user." The 4 types of usage (current, current more than a year, recent, and past) were entered simultaneously in all regressions; results reported on different rows in the same column were obtained from the same analysis. Estimates were obtained from Cox regressions with adjustment for age and gender (grouped) at the time of first Graves disease diagnosis, and in the additional analysis whether the individual had undergone treatment with thyroidectomy or radioiodine, or whether the individual has had at least 2 records of obtaining antithyroid preparations.

**Table 4.** Hazard of developing Graves orbitopathy in users of different types of statins compared with nonusers

| | Unadjusted HR (95 % CI) | HR also adjusted for age and gender (95% CI) | Additionally adjusted HR (95% CI) |
|---|---|---|---|
| Simvastatin | 0.77 (0.66-0.90), *P* = .001 | 0.90 (0.77-1.06) *P* = .20 | 0.94 (0.80-1.10), *P* = .41 |
| Atorvastatin | 0.64 (0.48-0.85), *P* = .002 | 0.71 (0.53-0.95) *P* = .02 | 0.71 (0.53-0.95), *P* = .02 |
| Other statins | 0.86 (0.54-1.36), *P* = .52 | 0.97 (0.61-1.55) *P* = .91 | 1.01 (0.64-1.61), *P* = .96 |

The reference group is "never user." The 3 types of statins (simvastatin, atorvastatin, and other) were entered simultaneously in all regressions; results reported on different rows in the same column were obtained from the same analysis. Users of more than 1 type of statin (simvastatin, atorvastatin, and other) were omitted. Estimates were obtained from Cox regressions with adjustment for age and gender (grouped) at the time of first Graves diagnosis, and in the additional analyses in the last column whether the individual had undergone treatment with thyroidectomy or radioiodine, or whether the individual has had at least 2 records of obtaining antithyroid preparations.

**Table 5.** Hazard of developing Graves orbitopathy in users of statins, nonstatin lipid-lowering agents, and both statins and nonstatin lipid-lowering agents compared with nonusers

| | Unadjusted HR (95 % CI) | HR also adjusted for age and gender (95% CI) | Additionally adjusted HR (95% CI) |
|---|---|---|---|
| Statins | 0.74 (0.65-0.85) $P < .001$ | 0.86 (0.74-0.99) $P = .04$ | 0.87 (0.75-1.01) $P = .06$ |
| Lipid-lowering agents other than statins | 0.98 (0.44-2.18) $P = .96$ | 1.04 (0.47-2.33) $P = .92$ | 0.99 (0.44-2.20) $P = .97$ |
| Both statins and other lipid-lowering agents | 1.07 (0.44-2.59) $P = .89$ | 0.94 (0.39-2.29) $P = .89$ | 0.89 (0.37-2.16) $P = .80$ |

The reference group is "never user of statins nor other lipid-lowering agents." The 3 explanatory variables reflect (1) current use of statins but not other lipid-lowering agents, (2) current use of other lipid-lowering agents but not statins, and (3) current use of both statins and other lipid-lowering agents. Former users were excluded. Estimates were obtained from Cox regressions with adjustment for age and gender (grouped) at the time of first Graves disease diagnosis, and in the additional analysis whether the individual had undergone treatment with thyroidectomy or radioiodine, or whether the individual has had at least 2 records of obtaining antithyroid preparations.

report a somewhat weaker relationship, possibly due to the different structure of the population and differences in other important parameters such as the prevalence of tobacco smoking, which is higher in the United States (14% in 2018) (31) than in Sweden (7% in 2018) (https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/tolkad-rapportering/folkhalsans-utveckling/resultat/levnadsvanor/tobaksrokning-daglig/).

An interesting result is the difference in the statin effect depending on gender, with men having a stronger protective effect of statin treatment on the development of GO in our study. A recent large meta-analysis (32) demonstrated similar absolute effects of statins on lipid concentrations in both genders, suggesting that this difference was not caused by the lipid reduction itself. It is known that men more frequently develop severe forms of GO (33), which has previously at least partly been explained by the higher prevalence of smokers among men (2). However, the prevalence of smokers in Sweden in the recent years has been similar among the sexes. Thus, the mechanism behind the difference between genders remains unclear.

Regarding the effect of different types of statins, the results were clearly driven by atorvastatin. However, after dose adjustment, there was no evidence of atorvastatin being superior to simvastatin.

Despite the emerging evidence on the beneficial effects of statins in GO, the mechanism by which statins modify the GO risk is not fully understood. The study by Stein showed a beneficial effect of statins but no such effect was found for nonstatin cholesterol-lowering drugs. This finding made the authors conclude that it was probably the pleiotropic anti-inflammatory effects of statins, and not their cholesterol-lowering effect, that was responsible for the protective effect against GO. Rheumatoid arthritis is an autoimmune condition that shares some pathogenetic mechanisms and risk factors with GD (34). Interestingly, the results of a recent systematic review and a meta-analysis of 15 randomized controlled clinical trials strongly suggested that statins decrease disease activity and improve rheumatoid arthritis symptoms by suppressing the inflammatory reaction alongside its lipid-lowering effect, atorvastatin being superior to simvastatin (35).

Despite the fact that the study by Stein et al. did not demonstrate any protective effect of nonstatin cholesterol-lowering drugs, it has been hypothesized that cholesterol itself may have a role in the pathogenesis of GO. In 2 recent Italian studies published by the same group in patients with GD, a significant correlation was found between the occurrence of GO and both total and LDL-cholesterol in patients with a relatively short duration of GD (26, 27). However, even here, the authors speculated that the altered inflammatory state of hypercholesterolemia is probably the main cause of this effect (26, 27, 36) and the effect of lowering cholesterol was not examined in these studies. In our study, we compared the usage of statins only to statin combined with a different kind of lipid-lowering agent. The results did not provide evidence for a better effect of the combined treatment, suggesting that mechanisms other than a cholesterol-lowering effect are responsible for the protective effect of statins in GO. Unfortunately, it was not possible to divide this analysis into separate analyses of the effects of different subtypes of lipid lowering agents due to low numbers of subjects in the subgroups.

Interestingly, in contrast to statins, other anti-inflammatory drugs such as COX-2 inhibitors did not reduce the hazard of GO in the American study (25), suggesting that there might also be other mechanisms than the reduction of inflammation contributing to the protective effect of statins. Bifulco and Ciaglia suggested that statins reduce GO risk mainly by modulating both apoptosis and autophagy activities in patients with GD (37). Another possible mechanism could be the reduction of adipogenesis concomitantly with the anti-inflammatory effect, as adipogenesis is 1 of the main

pathogenetic processes in GO (1). Indeed, in experiments in 3T3-L1 preadipocytes and human orbital fibroblasts, our group showed that simvastatin had a very strong suppressive effect on mRNA expression of both early and late adipogenic genes, which resulted in a decreased number of mature adipocytes (38).

Our study is subject to some limitations. The main drawback is the lack of individual clinical data such as the levels of thyroid hormones and TSH-receptor antibodies or smoking status, all of which can influence the risk of developing GO. However, it is unlikely that the laboratory parameters would systematically differ between statin users and nonusers. On the other hand, given that statins in Sweden are predominantly prescribed to individuals at high cardiovascular risk, one can speculate that the percentage of smokers could theoretically differ between the groups. Identification of subjects with GD and GO relied on diagnostic coding and is therefore subject to some uncertainty. The diagnosis of GD is usually straightforward. However, individuals with mild GO that did not contact healthcare providers because of their symptoms might have been missed and this study therefore probably includes mainly those with more severe disease. Furthermore, our study had no access to data on medication compliance; however, given the size of our population, it is unlikely that this would have influenced our results. Unfortunately, we lack information on the severity and activity of GO, which makes it impossible to comment on the relationship between statin use and the course of GO, as reported by others (26, 27). We tried to substitute the lack of data on severity by analyzing the association of statin use with surgical treatment for severe GO (decompression surgery). Unfortunately, this analysis yielded very imprecise and nonsignificant estimates due to the outcome being rare.

In conclusion, in patients with newly diagnosed GD, statin therapy may protect against the development of GO in a dose-dependent manner. No such effect was observed for other lipid-lowering agents. We suggest that preventive treatment with statins in newly diagnosed patients with GD should be examined in a prospective clinical trial.

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## Additional Information

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***Disclosures:*** The authors have nothing to disclose.

***Data Availability:*** Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

## References

1. Bahn RS. Current insights into the pathogenesis of Graves' ophthalmopathy. *Horm Metab Res*. 2015;**47**(10):773-778.
2. Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid*. 2002;**12**(10):855-860.
3. Bahn RS, Dutton CM, Natt N, Joba W, Spitzweg C, Heufelder AE. Thyrotropin receptor expression in Graves' orbital adipose/connective tissues: potential autoantigen in Graves' ophthalmopathy. *J Clin Endocrinol Metab*. 1998;**83**(3):998-1002.
4. Smith TJ, Janssen JAMJL. Insulin-like growth factor-I receptor and thyroid-associated ophthalmopathy. *Endocr Rev*. 2019;**40**(1):236-267.
5. Lanzolla G, Ricci D, Nicolì F, et al. Putative protective role of autoantibodies against the insulin-like growth factor-1 receptor in Graves' disease: results of a pilot study. *J Endocrinol Invest*. 2020;**43**(12):1759-1768.
6. Marinò M, Rotondo Dottore G, Ionni I, et al. Serum antibodies against the insulin-like growth factor-1 receptor (IGF-1R) in Graves' disease and Graves' orbitopathy. *J Endocrinol Invest*. 2019;**42**(4):471-480.
7. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;**382**(4):341-352.
8. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;**376**(18):1748-1761.
9. Yang M, Perros P. Management plan and delivery of care in Graves' ophthalmopathy patients. *Best Pract Res Clin Endocrinol Metab*. 2012;**26**(3):303-311.
10. Kahaly GJ, Riedl M, König J, et al.; European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. *Lancet Diabetes Endocrinol*. 2018;**6**(4):287-298.
11. Ridker PM, Danielson E, Fonseca FA, et al.; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;**359**(21):2195-2207.
12. Ridker PM; JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation*. 2003;**108**(19):2292-2297.
13. Fonseca FA, Izar MC. Primary prevention of vascular events in patients with high levels of C-reactive protein: the JUPITER study. *Expert Rev Cardiovasc Ther*. 2009;**7**(9):1041-1056.
14. Kones R. The Jupiter study, CRP screening, and aggressive statin therapy-implications for the primary prevention of cardiovascular disease. *Ther Adv Cardiovasc Dis*. 2009;**3**(4):309-315.
15. Verma A, Lavie CJ, Milani RV. C-reactive protein: how has JUPITER impacted clinical practice? *Ochsner J*. 2009;**9**(4):204-210.

16. Chang JW, Yang WS, Min WK, Lee SK, Park JS, Kim SB. Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients. *Am J Kidney Dis*. 2002;**39**(6):1213-1217.
17. Stüve O, Prod'homme T, Slavin A, et al. Statins and their potential targets in multiple sclerosis therapy. *Expert Opin Ther Targets*. 2003;**7**(5):613-622.
18. Stüve O, Youssef S, Steinman L, Zamvil SS. Statins as potential therapeutic agents in neuroinflammatory disorders. *Curr Opin Neurol*. 2003;**16**(3):393-401.
19. Walsh GM. Statins as emerging treatments for asthma and chronic obstructive pulmonary disease. *Expert Rev Respir Med*. 2008;**2**(3):329-335.
20. Huang CC, Chan WL, Chen YC, et al. Statin use in patients with asthma: a nationwide population-based study. *Eur J Clin Invest*. 2011;**41**(5):507-512.
21. McCarey DW, McInnes IB, Madhok R, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *Lancet*. 2004;**363**(9426):2015-2021.
22. Hu Y, Tong G, Xu W, et al. Anti-inflammatory effects of simvastatin on adipokines in type 2 diabetic patients with carotid atherosclerosis. *Diab Vasc Dis Res*. 2009;**6**(4):262-268.
23. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. *Nat Rev Drug Discov*. 2005;**4**(12):977-987.
24. Koch CA, Krabbe S, Hehmke B. Statins, metformin, proprotein-convertase-subtilisin-kexin type-9 (PCSK9) inhibitors and sex hormones: Immunomodulatory properties? *Rev Endocr Metab Disord*. 2018;**19**(4):363-395.
25. Stein JD, Childers D, Gupta S, et al. Risk factors for developing thyroid-associated ophthalmopathy among individuals with Graves disease. *JAMA Ophthalmol*. 2015;**133**(3):290-296.
26. Sabini E, Mazzi B, Profilo MA, et al. High serum cholesterol is a novel risk factor for Graves' orbitopathy: results of a cross-sectional study. *Thyroid*. 2018;**28**(3):386-394.
27. Lanzolla G, Sabini E, Profilo MA, et al. Relationship between serum cholesterol and Graves' orbitopathy (GO): a confirmatory study. *J Endocrinol Invest*. 2018;**41**(12):1417-1423.
28. Marinò M. Effects of Atorvastatin in Graves' Orbitopathy (GO). https://ClinicalTrials.gov/show/NCT03110848. Accessed February 22, 2021.
29. Wiersinga WM, Smit T, van der Gaag R, Koornneef L. Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. *J Endocrinol Invest*. 1988;**11**(8):615-619.
30. Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. *Am J Cardiol*. 1997;**80**(1):106-107.
31. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;**68**(45):1013-1019.
32. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet*. 2015;**385**(9976):1397-1405.
33. Perros P, Crombie AL, Matthews JN, Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. *Clin Endocrinol (Oxf)*. 1993;**38**(4):367-372.
34. Carmona L, Cross M, Williams B, Lassere M, March L. Rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2010;**24**(6):733-745.
35. Li GM, Zhao J, Li B, et al. The anti-inflammatory effects of statins on patients with rheumatoid arthritis: a systemic review and meta-analysis of 15 randomized controlled trials. *Autoimmun Rev*. 2018;**17**(3):215-225.
36. Lanzolla G, Vannucchi G, Ionni I, et al. Cholesterol serum levels and use of statins in Graves' orbitopathy: a new starting point for the therapy. *Front Endocrinol (Lausanne)*. 2019;**10**:933.
37. Bifulco M, Ciaglia E. Statin reduces orbitopathy risk in patients with Graves' disease by modulating apoptosis and autophagy activities. *Endocrine*. 2016;**53**(3):649-650.
38. Shahida B, Johnson PS, Jain R, et al. Simvastatin downregulates adipogenesis in 3T3-L1 preadipocytes and orbital fibroblasts from Graves' ophthalmopathy patients. *Endocr Connect*. 2019;**8**(9):1230-1239.