Original research

Simvastatin in the prevention of recurrent pancreatitis: a triple-blinded randomised clinical trial (the SIMBA trial)

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ABSTRACT

Background Recurrent acute pancreatitis (RAP) or acute-on-chronic flares in chronic pancreatitis (CP) have limited preventive options beyond addressing the underlying aetiology. Statins, due to their anti-inflammatory properties, have been proposed as a potential prophylactic treatment.

Objective We aimed to evaluate whether simvastatin could reduce the recurrence of pancreatitis.

Design At 23 centres, we conducted a triple-blind, randomised, controlled, superiority trial enrolling patients with at least two episodes of RAP or CP flares in the previous 12 months. Participants were randomly assigned to receive simvastatin or placebo for 1 year. The primary endpoint was the recurrence of pancreatitis. The target sample size was 144 patients; however, an interim analysis was planned in the event of slow recruitment.

Results A total of 85 patients (42.1% women) were included in the interim analysis. In the intention-to-treat analysis, no significant differences were observed regarding recurrence: 46.2% simvastatin versus 44.4% placebo; OR 1.07, 95% CI 0.43 to 2.66; p=0.88, or time to recurrence. No statistically significant differences were observed in recurrence in per-protocol analysis (35.5% simvastatin vs 41.9% placebo; OR 0.76, 95% CI 0.27 to 2.12; p=0.60). Development of diabetes mellitus was more frequent in the simvastatin group (4 vs 0 patients; OR not calculable, p=0.04).

Conclusion This trial, evaluating simvastatin versus placebo for the prevention of pancreatitis, did not demonstrate a reduction in recurrence rate, although results might be underpowered due to early termination. The relationship between statins in these patients and new-onset diabetes requires further investigation.

Trial registration number NCT04021498.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recurrent acute pancreatitis (RAP) or acute-on-chronic flares in chronic pancreatitis (CP) have limited preventive options and new interventions are being tested.

WHAT THIS STUDY ADDS

⇒ Simvastatin does not reduce pancreatitis recurrence or time to recurrence compared with placebo, although these results might be underpowered. Exploratory data suggest that simvastatin may facilitate the development of diabetes in patients with RAP or CP.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The SIMBA trial did not demonstrate a reduction in recurrence rate of pancreatitis in patients with RAP or flares of CP when comparing simvastatin to placebo; results might be inconclusive due to low power. The possible higher incidence of diabetes in simvastatin users with pancreatitis is clinically relevant; however, further studies are needed to confirm these results.

INTRODUCTION

Recurrent acute pancreatitis (RAP) is defined as at least two distinct, documented episodes of acute pancreatitis (AP), separated by a period of complete symptom resolution (usually 3 months).[1] Its incidence is 8–10 per 100 000 per year.[2] Overall, after a first episode of AP, the recurrence rate is about 20%, but this varies by aetiology. In biliary AP, when cholecystectomy is performed, ideally during admission in mild cases, the recurrence rate is <10%.[3] However, in alcohol-related or idiopathic

cases, AP relapse is around 25%.[4] RAP has been described as a continuum stage from AP to chronic pancreatitis (CP), as a subset of patients with RAP (around 35%) will transition to CP, which is more frequent in smokers and heavy drinkers.[5] In these patients with CP, intermittent episodes of inflammation occur in about 45% of cases and are associated with impaired quality of life, work loss and increased healthcare costs due to hospital admissions and analgesic use.[6] To date, apart from removing the aetiological determinants of pancreatitis, there is no other treatment to reduce recurrence and progression to CP.[3]

Statins are primarily used to reduce cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, but they may also have anti-inflammatory and immune-modulating properties.[7 8] Although initially statins were thought to be a possible aetiologic factor for AP,[9] evidence was mainly from case reports; more recent evidence suggests against this hypothesis.[10 11] A reduced risk of AP in statin users has been shown in a case-control study,[12] a meta-analysis of randomised clinical trials[13] and a population-based study.[14] Moreover, in an animal model of CP, statins have been shown to reduce inflammatory pathways, suggesting that they may also help prevent its progression.[15]

In the SIMBA trial (SIMvastatin in the prevention of recurrent pancreatitis, a triple Blind rAndomized controlled multicentre trial), we hypothesised that simvastatin would reduce the recurrence of pancreatitis in patients with recurrent AP or acute-on-chronic inflammatory flares of CP.

METHODS

Trial participants and oversight

In this triple-blind randomised placebo-controlled, parallel-group, superiority, multicentre trial, we enrolled patients at 23 centres, 22 from Spain and 1 from India (ClinicalTrials.gov identification number NCT04021498). The complete trial protocol has been published previously (online supplemental file 1).[16]

Adult patients (≥18 years of age) with recurrent AP or acute-on-chronic inflammatory flares of CP (see definition in 'outcomes')[17] were assessed for eligibility. Exclusion criteria included: (1) less than two AP or CP flares in the last 12 months, (2) statin consumption in the last year or contraindications for its use, (3) cholelithiasis or choledocholithiasis diagnosed in the last episode of AP, (4) endoscopic sphincterotomy and/or cholecystectomy and/or pancreatic surgery between last episode of pancreatitis and recruitment or plan to undergo any of these procedures in the following year, (5) serum triglycerides >500 mg/dL without previous specific treatment before the last episode of pancreatitis or patients expected to have a change in their specific hypertriglyceridaemia treatment in <1 year, (6) primary hyperparathyroidism that has been operated between the last episode of pancreatitis and recruitment or will be operated in <1 year, (7) iatrogenic AP (caused by endoscopic retrograde cholangio-pancreatography (ERCP), surgery or other invasive treatment) did not count as an episode of AP/CP flare, (8) abstinence syndrome due to alcohol or drugs and/or delirium tremens in the last 6 months before recruitment, (9) previous (last year) failure to attend follow-up medical visits or lack of adherence to treatment, or social problems that may be associated with lack of adherence to the study treatment or to inadequate follow-up and (10) pregnancy or breastfeeding.

The trial protocol adhered to the Standard Protocol Items: Recommendations for Interventional Trials[18] guidelines, and this manuscript followed the Consolidated Standards of Reporting Trials[19] recommendations for reporting clinical trials. No patients were involved in the trial design. The SIMBA trial adheres to the principles outlined in the Declaration of Helsinki.[20] All patients provided informed consent. The trial had a Data Monitoring Committee (AV-R and PZ) and a Trial Steering Committee (VKS, BUW, PKG and GIP) to oversee and evaluate the trial's progress. All authors had access to the study data and reviewed and approved the final manuscript.

Patient and public involvement

Patients were not involved in the design or conduct of the study. Findings will be disseminated via the main international and national gastroenterology and pancreatology associations, as well as patient associations.

Trial procedures

Participants were randomly assigned in a 1:1 ratio to receive simvastatin 40 mg or placebo (once daily for 1 year). The 40 mg dose was based on the protocol of a pilot clinical trial ('Simvastatin in Reducing Pancreatitis in Patients With Recurrent, Acute or Chronic Pancreatitis', ClinicalTrials.gov Identifier: NCT02743364) designed by one of the co-authors (BUW). Randomisation was performed by a centralised, computer-generated randomisation system included in REDCap,[21] the online case report form used in SIMBA. Access to REDCap was provided by the Spanish Association of Gastroenterology (AEG) through its AEG REDCap node. The allocation sequence was kept hidden from the study team. The randomisation list, created by the Clinical Pharmacology department of Dr. Balmis General University Hospital (DBGUH), was based on a computer-generated list (one list per centre) of random numbers obtained using the block random-command number from the psych package[22] for R[23]; permuted blocks were used with each block containing eight patients for randomisation. Randomisation was stratified by (A) centre, (B) antecedent of more than three lifetime episodes of AP or CP flares and (C) alcoholic aetiology. The Pharmacy department of DBGUH performed masking. Both simvastatin and placebo (simvastatin's excipient, lactose) were masked in indistinguishable white capsules and distributed to other centres periodically. The trial coordinator (AV-R) oversaw the verification of randomisation lists and ensured the correct distribution of medication.

The treatment allocation was blinded to patients, investigators and the statistician until the statistical analysis was performed (the database had the treatment arms masked). This investigator-initiated trial was conducted independently of the pharmaceutical industry and funded through competitive grants from the Spanish government, a scientific society, a regional medical association and the sponsoring research institution (see Funding).

After assessment for eligibility by gastroenterologists at different participating centres and provision of informed consent, patient baseline characteristics were obtained and recorded. The patients were then randomised, and they received the study medication. Follow-up outpatient visits were scheduled after recruitment at months 1, 4, 8 and 12. The first visit was scheduled just after 1 month to detect possible adverse events early. Treatment adherence, adverse events, alcohol and tobacco use, the number and severity of recurrent episodes of AP or flares of CP, as well as other causes of hospitalisation, were recorded at each follow-up visit. Routine laboratory tests were conducted at every outpatient visit, while faecal elastase-1 and glycated haemoglobin were measured at baseline and at the final visit. A CT scan was also performed at both enrolment and the end of the follow-up period. Importantly, follow-up visits and assessments were carried out even for patients who discontinued

the study drug, to allow for an intention-to-treat analysis, unless they withdrew consent or were lost to follow-up.

As pre-specified in the published protocol,[16] an interim analysis was to be conducted in the event of slow recruitment. Following the enrolment of 89 patients between October 2017 and February 2024, the Trial Steering Committee recommended halting recruitment and initiating the interim analysis to evaluate the feasibility and scientific justification of continuing towards the target sample size.

Outcomes

The primary endpoint was the proportion of patients who experienced at least one recurrent episode of pancreatitis (AP or acute-on-chronic flare of CP) during the 12-month follow-up. This endpoint was defined as binary (yes/no), irrespective of the timing of the event, because our main clinical question was whether simvastatin reduces the 1-year risk of any recurrence, which is the key measure used by clinicians when deciding on preventive therapy, whereas the exact timing of recurrence within that period is of secondary importance. Recurrence was defined (both in recurrent AP or CP) following the 2012 Revision of the Atlanta Classification (RAC) diagnostic criteria of AP: at least two of the following: (A) typical epigastric pain, (B) pancreatic enzyme elevation ≥3 times the upper limit of normal or (C) imaging findings of pancreatitis (signs of AP or new inflammatory changes in CP, eg, peripancreatic fat stranding or liquid). In addition to the binary primary endpoint, the time to first recurrence was prospectively collected and analysed as a secondary exploratory endpoint using Kaplan-Meier curves and log-rank tests, as prespecified in the original protocol. A cumulative incidence function (CIF) analysis accounting for competing risks was subsequently added in the Statistical Analysis Plan (SAP) V.2, as an exploratory post-hoc analysis, defined before unblinding, to better describe recurrence over time in the presence of variable follow-up and competing events. These survival-type analyses were not used for sample size calculation and do not modify the primary endpoint or its analysis, but rather complement it. Secondary outcomes measuring progression of disease included new-onset diabetes mellitus (based on American Diabetes Association criteria,[24] with baseline glycated haemoglobin used as the main diagnostic criterion because many patients were enrolled during an acute episode of pancreatitis, which precluded the use of fasting glucose at baseline); new-onset of pancreatic exocrine insufficiency (defined as faecal elastase-1 at the end of follow-up <100 mcg/g in patients with baseline faecal elastase-1 >100 mcg/g); new-onset CP at the end of follow-up (calcifications and/or dilated duct ≥4 mm for those patients without those criteria at recruitment); number of all-cause hospital admissions; severity of recurrent AP (based on the RAC)[17]; variation in episode count between the pre-recruitment year and the trial year (for those who completed follow-up) and frequency of adverse events.

Statistical analysis

The sample size was determined based on an unpublished internal retrospective analysis, which included 106 patients who met the study inclusion and exclusion criteria over 15 years (2000–2015). This analysis showed a 1-year recurrence rate of 50% among patients who did not receive statins. Using the arcsine method, the study was powered to detect a 50% relative reduction in recurrence with simvastatin based on a previous meta-analysis.[13] Assuming a two-sided alpha level of 0.05, a statistical power of 80%, and accounting for a 20% loss to follow-up, a total of 144 patients (72 per group) were required.

Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and reported as means with SD or medians with IQRs, depending on distribution. Categorical variables were summarised as frequencies and percentages.

For the primary binary outcome, univariable association was assessed using χ^2 test, providing unadjusted ORs with 95% CI. Although timing was not incorporated into the primary endpoint definition, dates of recurrent episodes were prospectively collected. Kaplan-Meier analyses of time to first recurrence were prespecified as exploratory secondary analyses. Curves were generated, along with the log-rank test. Patients were censored at the time of loss to follow-up or at the end of the observation period, whichever occurred first. Additionally, a CIF analysis (as a post-hoc analysis, SAP-V2) was conducted to account for varying follow-up times and competing risks, offering a more accurate estimate of recurrence over time. Statistical differences between CIF of statins and placebo were assessed using the Gray's test. The time used to calculate the CIF curves corresponded to the time until the end of follow-up (1 year, date of loss to follow-up due to withdrawal or death) or to the first episode of pancreatitis.

Secondary outcomes were analysed using χ^2 (with Fisher correction when necessary), t-tests or paired t-tests, and non-parametric alternatives (Mann-Whitney U or Wilcoxon) when appropriate. Secondary outcomes were considered exploratory, as no correction for multiplicity was performed.

Subgroup analyses were conducted for: (A) patients with baseline CP, (B) baseline RAP, (C) alcohol aetiology, (D) non-alcoholic aetiology, (E) female sex, (F) male sex, (G) RAP with only two previous flares without CP and (H) RAP with three or more previous flares but without CP, which behaves similarly to early CP.[25] Subgroup analyses by sex and number of previous flares were considered post-hoc analyses.

A two-sided p value of <0.05 was considered to indicate statistical significance.

A blinded analysis was conducted, with the random assignment of labels 'A' or 'B' to the treatment arms instead of simvastatin and placebo, by the Clinical Pharmacology Department of DBGUH. This assignment was unblinded after statistical analysis to reveal the placebo or simvastatin groups. Primary analysis was performed on an intention-to-treat basis. A per-protocol analysis (patients who received the whole 1-year treatment) was also performed. A binary logistic regression in the case of significant baseline differences was planned. However, as there was not an imbalance, a logistic regression adjusted only by stratification variables was performed for the primary outcome to assess robustness of our results yielding the adjusted OR. Although the SAP originally specified the use of relative risk, for consistency between univariable and multivariable effect measures, we report OR throughout.

Missing data due to loss to follow-up for the primary outcome, and all other variables were comparable between groups. No imputation for missing data was performed.

Analyses were performed using SPSS software, V.29.0.2.0 (IBM), and R software V.4.1.2.

The SAP is available in online supplemental material. Post-hoc analyses and addenda to the SAP are included in SAP V.2, January 2025, which is also available in online supplemental material.

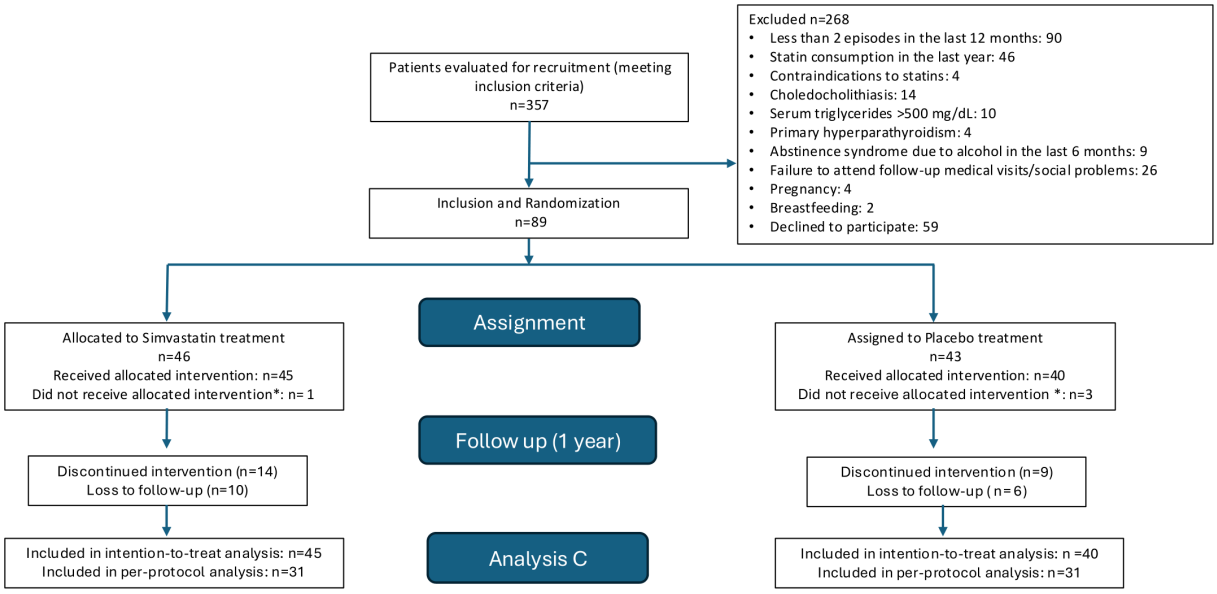

Figure 1 Flowchart of patients. *One patient in the simvastatin group and three patients in the placebo group withdrew consent before receiving any dose of the study drug.

RESULTS

From October 2017 until February 2024, 357 patients were assessed for eligibility (figure 1). From those, 89 were randomised to receive either simvastatin or placebo; however, 4 patients withdrew consent before receiving any dose of medication, leaving 85 patients included in the intention-to-treat analysis: 45 in the simvastatin group and 40 in the placebo group. 14 patients in the simvastatin group and 9 in the placebo group abandoned treatment, while 31 patients in each group completed the 1 year treatment.

Intention-to-treat analysis

The mean (SD) age was 54 (16) years, and 35 patients (41.2%) were women. 23 patients (27.1%) had CP at baseline, and the aetiology was alcohol in 28 patients (32.9%).

Baseline characteristics were equally distributed between both groups (table 1). Metabolic and aetiologic characteristics by treatment and pancreatitis type are detailed in (online supplemental material table 1s-2s). CP severity according to CT, diabetes and pancreatic exocrine insufficiency (PEI) is in online supplemental table 3s.

In the intention-to-treat analysis, no statistically significant difference was found in the primary outcome. Recurrent pancreatitis occurred in 18 patients (46.2%) in the simvastatin group compared with 16 patients (44.4%) in the placebo group with an OR of 1.07 (95% CI 0.43 to 2.66; p=0.88) over a median follow-up of 365 days (IQR: 313–365) and 365 days (IQR: 362–366), respectively. The number of recurrent AP episodes or flares was also comparable between groups, with a median of 0 (IQR: 0–1) in both groups (p=0.88).

Similarly, no significant difference was observed in time to recurrence based on Kaplan-Meier analysis (p=0.83; figure 2), and the cumulative incidence of episodes, as assessed by the CIF curve (online supplemental material figure 1s), showed no statistically significant differences between groups (p=0.83).

Regarding secondary outcomes, there were no statistically significant differences between groups in the intention-to-treat analysis, as shown in table 2, in CP development, PEI development, all-cause readmission, mild, moderate or severe recurrent episodes, or adverse events. However, a statistically significant difference (p=0.045) was observed in the development of diabetes mellitus at 12 months, with four cases in the simvastatin group and none in the placebo group. Of the four affected patients, three initiated metformin therapy—one in combination with insulin—while one patient was pending treatment initiation at the end of follow-up. Characteristics of patients with CP at the end of follow-up can be seen in online supplemental table 4s.

Specific adverse events are shown in online supplemental table 5s. Myalgia and arthralgia were the most reported adverse events in both groups, occurring in 11.1% of patients in the

Table 1 Baseline characteristics of included patients

Characteristic	Simvastatin (n=45)	Placebo (n=40)
Age, mean (SD), years	54 (17)	55 (16)
Female sex, n (%)	19 (42.2)	16 (40.0)
Body mass index, median (IQR) (kg/m^2)	24 (21–29)	23 (21–27)
Chronic pancreatitis, n (%)	11 (24.4)	12 (30.0)
Number of pancreatitis prior to recruitment, median (IQR)	4 (3–6)	4 (3–6)
Number of pancreatitis in the previous 12 months, median (IQR)	2 (2–4)	2 (2–4)
More than three pancreatitis episodes previous to recruitment, n (%)	31 (68.9)	25 (62.5)
Time in months from last episode to recruitment, median (IQR)	1 (0–3)	1 (0–3)
Alcohol aetiology, n (%)	16 (35.6)	12 (30.0)
Active alcohol intake, n (%)	15 (33.3)	15 (37.5)
Active smoker, n (%)	14 (31.1)	9 (22.5)
Diabetes at diagnosis, n (%)	8 (17.8)	6 (15.0)
Glycated haemoglobin, median (IQR)	5.5 (5.2–6.0)	5.5 (5.1–5.7)
Cholecystectomy, n (%)	18 (40.0)	17 (42.5)
Previous endoscopic sphincterotomy, n (%)	4 (9.0)	6 (15.0)
Pancreatic exocrine insufficiency, n (%)	11 (24.4)	10 (25.0)

Pancreatitis: recurrent episodes of acute pancreatitis or acute-on-chronic inflammatory flares of chronic pancreatitis.

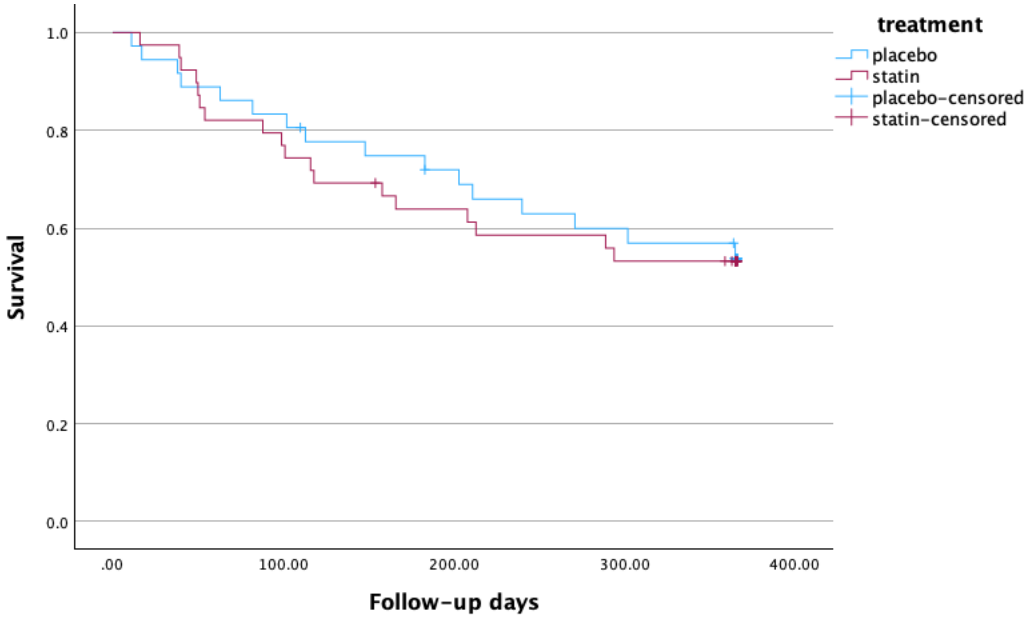

Figure 2 Kaplan-Meier analysis of time to recurrence in the intention-to-treat population. Log-Rank test: p=0.83.

statin group and 10% in the placebo group. These were followed by abdominal symptoms (mild abdominal pain or discomfort, abdominal distension, meteorism or constipation) (6.7% vs 7.5%) and elevations in liver enzymes (4.4% vs 0%) or creatine phosphokinase (0% vs 5.0%). A mild cutaneous allergic reaction to the study drug was observed in one patient receiving statin therapy. Adverse events led to treatment discontinuation in five patients in the statin group (one for allergy and myalgia, two for elevated liver enzymes or CPK, one for myalgia and one for transient hyperglycaemia) and in two patients in the placebo group (one for abdominal pain and one for myalgia).

A multivariate analysis adjusted by stratification variables for the primary outcome was performed with an adjusted OR of 0.82 (95% CI 0.27 to 2.56; p=0.74).

Per-protocol analysis

In the per-protocol analysis, no significant differences were observed in the primary outcome. Recurrent AP or CP flares occurred in 35.5% in the simvastatin group and 41.9% in the placebo group (OR 0.76; 95% CI 0.27 to 2.12; p=0.6). Time to recurrence was also similar (p=0.64; figure 3), as were secondary outcomes, except for diabetes development (table 3).

No significant differences were observed in the median change in episode number between the year before and after recruitment: 2 episodes (IQR 1–3) in the statin group and 2 episodes (IQR 1–2) in the placebo group (p=0.07). No deaths occurred among patients who completed follow-up.

Subgroup analysis

In the pre-specified subgroup analysis in patients with CP and RAP, no significant differences in recurrence were found between treatment arms (CP: OR 0.51, 95% CI (0.09 to 3.11); RAP: OR 1.36, 95% CI 0.47 to 3.99; p=0.66 and 0.57, respectively). DM development at 12 months was statistically significantly higher in patients with CP receiving simvastatin (p=0.03). No other significant differences were found across aetiologic, sex or flare-number subgroups (online supplemental tables 6-14s and figures 2-9s).

Table 2 Primary and secondary outcomes in the intention-to-treat analysis

Characteristic	Simvastatin, n=45	Placebo, n=40	OR (95% CI)	P value
Recurrence, n (%)	18 (46.2)	16 (44.4)	1.07 (0.43 to 2.66)	0.88
Development of CP at 12 months, n (%)*	6 (24.0)	4 (16.7)	1.58 (0.39 to 6.48)	0.73
PEI development, n (%)†	15 (44.1)	7 (23.3)	2.59 (0.88 to 7.67)	0.08
Development of DM at 12 months, n (%)‡	4 (14.3)	0 (0)	N.A.	0.045
Number of all cause readmission, median (IQR)	0 (0–1)	0 (0–1)	N.A.	0.50
Number of mild recurrent episodes, median (IQR)	1 (0–2)	0 (0–1)	N.A.	0.34
Number of moderate recurrent episodes, median (IQR)	0 (0–0)	0 (0–0)	N.A.	0.40
Number of severe recurrent episodes, median (IQR)	0 (0–0)	0 (0–0)	N.A.	0.37
Adverse events, n (%)	13 (32.5)	10 (27.0)	1.30 (0.49 to 3.47)	0.60

Odds Ratio (OR) could not be calculated as one of the groups had zero events; thus, OR is marked as N.A. (Not Applicable). OR is not applicable for non-parametric comparisons performed with the Mann-Whitney test and is accordingly marked as N.A

*Development of chronic pancreatitis at 12 months was calculated for those patients without baseline criteria for chronic pancreatitis: 25 in the simvastatin group and 24 in the placebo group.

†Development of PEI at 12 months was calculated for those without baseline PEI: 34 in the simvastatin group and 30 in the placebo group.

‡Development of DM at 12 months was calculated for those patients without baseline DM: 28 in the simvastatin group and 31 in the placebo group.

CP, chronic pancreatitis; DM, diabetes mellitus; PEI, pancreatic exocrine insufficiency.

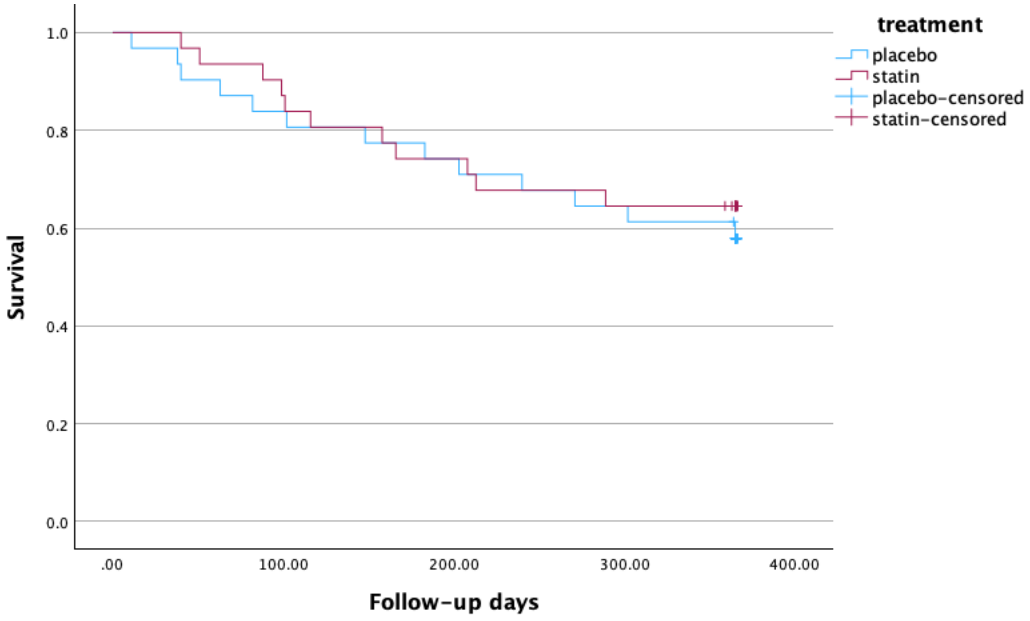

Figure 3 Kaplan-Meier analysis of time to recurrence in the per-protocol population. Log-Rank test: p=0.64

DISCUSSION

This interim analysis of the trial showed that simvastatin does not prevent recurrent episodes of AP in patients with RAP or acute inflammatory flares in patients with CP compared with placebo.

Statins were initially suspected of increasing the risk of AP based on case reports.[9] However, more recent meta-analyses and population studies not only refute this[10] but even suggest a protective effect.[12–14 26 27]

Based on this growing body of evidence, interest in statins as a potential protective factor against AP has increased. Several studies have explored their preventive role, particularly in the setting of post-ERCP AP. While early studies appeared to support a protective effect of statins,[27] more recent data have failed to confirm these findings,[28–30] even in prospective multicentre studies[28] and meta-analyses.[29]

The trial was primarily analysed on a binary endpoint (≥1 recurrence in 12 months), reflecting the clinically most relevant question of whether patients will suffer any recurrent episode over a 1 year horizon, rather than on finer differences in the timing of recurrence. Our study did not confirm the hypothesis that statins could prevent recurrent pancreatitis, thereby reinforcing previous evidence against their prophylactic role. While statins might exert different effects in patients with CP or RAP, this possibility was explored through subgroup analysis. No statistically significant differences or trends were found between treatment arms among patients with or without CP at baseline, nor those with an alcoholic aetiology, an established risk factor for recurrence.[5] To minimise the potential confounding effect of alcohol, randomisation was stratified by aetiology, and a dedicated subgroup analysis was conducted. However, these subgroup analyses were exploratory and underpowered; therefore, no definitive conclusions can be drawn from them.

Another finding from this trial is that statins may facilitate the development of diabetes compared with placebo, particularly among patients with baseline CP. While this should be considered as exploratory and interpreted with caution, also due to small numbers and some confounding factors such as changes

Table 3 Primary and secondary outcomes in a per-protocol analysis

Characteristic	Simvastatin, n=31	Placebo, n=31	OR (95% CI)	P value
Recurrence, n (%)	11 (35.5)	13 (41.9)	0.76 (0.27 to 2.12)	0.60
Development of CP at 12 months, n (%)*	5 (22.7)	4 (19.0)	1.25 (0.29 to 5.47)	1.00
PEI development, n (%)†	6 (26.1)	5 (19.2)	1.48 (0.39 to 5.71)	0.56
Development of DM at 12 months, n (%)‡	4 (16.0)	0 (0)	N.A.	0.04
Number of all cause readmission, median (IQR)	0 (0–1)	0 (0–1)	N.A.	0.84
Number of mild recurrent episodes, median (IQR)	1 (0–2)	1 (1-3)	N.A.	0.24
Number of moderate recurrent episodes, median (IQR)	0 (0–0)	0 (0–0)	N.A.	0.95
Number of severe recurrent episodes, median (IQR)	0 (0–0)	0 (0–0)	N.A.	0.34
Adverse events, n (%)	6 (19.4)	6 (19.4)	1.0 (0.28 to 3.53)	1.00

OR could not be calculated as one of the groups had zero events; thus, OR is marked as N.A. (not applicable). OR is not applicable for non-parametric comparisons performed with the Mann-Whitney test and is accordingly marked as N.A.
*Development of chronic pancreatitis at 12 months was calculated for those patients without baseline criteria for chronic pancreatitis: 22 in the simvastatin group and 21 in the placebo group.
†Development of PEI at 12 months was calculated for those without baseline PEI: 23 in the simvastatin group and 26 in the placebo group.
‡Development of DM at 12 months was calculated for those patients without baseline DM: 25 in the simvastatin group and 30 in the placebo group.
CP, chronic pancreatitis; DM, diabetes mellitus; PEI, pancreatic exocrine insufficiency.

in lipid treatment that could not be controlled in the trial, it aligns with previous evidence. The increased risk of new-onset diabetes was first reported in the JUPITER trial, a double-blind randomised clinical trial comparing rosuvastatin versus placebo in patients with normal levels of cholesterol but high levels of C-reactive protein, where the rosuvastatin group had a 27% significant increase in the risk of developing diabetes.[31] Subsequent meta-analyses of randomised clinical trials have reported an elevated risk of new-onset diabetes among statin users,[32] particularly in individuals already at higher baseline risk for diabetes,[33] mainly considering metabolic syndrome or obesity but without specific considerations for patients with CP or RAP up till now, which are also conditions associated with increased risk for diabetes. In fact, an OR of 1.89 (95% CI 0.95 to 3.77)[34] has been reported in a high-risk population, highlighting a potential concern that warrants further investigation. The information regarding patients with pancreatitis is limited to a population-based study that showed that statins may protect against the onset of diabetes after an episode of AP, reducing the development risk by 42%. However, this is a retrospective study conducted in patients with AP, including only individuals with a first episode who were already on statin therapy. Therefore, it is a different sample of patients with less tendency to have diabetes, as patients are in an early stage of disease compared with recurrent AP and relapsing CP.[35] For the first time, a clinical trial in patients with pancreatitis suggests that statins could increase new-onset diabetes in this population, which is characterised by a reduced beta cell reserve due to repeated or continuous inflammation and fibrosis.[36] An appropriate balance between the potential risk of developing diabetes in these patients and the anticipated benefits of cholesterol reduction and cardiovascular risk mitigation must be carefully considered until new evidence is available. Overall, when indicated, the cardiovascular benefits of statins outweigh the small absolute risk of incident diabetes. Nevertheless, in line with American Heart Association[37] guidance, at-risk patients should receive closer glucose monitoring. Nevertheless, and considering the conflicting available evidence, and the fact that type 2 diabetes and pancreatogenic diabetes may differ pathophysiologically,[38] we believe that new prospective research specifically addressing this question is warranted.

This trial has several limitations. first, slow recruitment, likely due to strict inclusion and exclusion criteria and the COVID-19 pandemic, has hampered participant enrolment, leading to an interim analysis and the early termination of the study. Consequently, the trial is underpowered to assess the primary outcome adequately and it should be interpreted with caution. Since it was initially hypothesised that statins could reduce the recurrence of AP or acute-on-chronic inflammatory flares of CP, the trial was designed with a target sample size of 144 patients. However, the interim analysis revealed that, in the intention-to-treat analysis, patients in the statin arm actually had a higher risk of recurrence, and the difference observed in the per-protocol analysis (6%) was much smaller than anticipated. With the interim trend for post-interim data, the conditional power is 0.003, and predictive probability of success is 0.016 which means that the conditional power is very low, well below the predefined threshold of 0.10, so it is highly unlikely (only about 0.016, ie, 1.6%) that a statistically significant result would be obtained even after including the remaining patients. So, although our results could be a false negative, because we did not reach the calculated sample size, with this calculation we demonstrate that this is very unlikely.

Given these findings and considering the potential increased risk of diabetes development observed in the statin group, which showed no efficacy in preventing new episodes of inflammation, the Data Monitoring Committee recommended to the Steering Committee that the trial be terminated. The rationale was that continuing would likely be futile and potentially expose patients to harm.

Other limitations of the trial include suboptimal adherence to the treatment protocol. Specifically, 14 patients in the simvastatin group and 9 in the placebo group discontinued treatment prematurely. This relatively high dropout rate, along with a considerable loss to follow-up, may reflect a perceived lack of treatment efficacy from the patients' perspective, leading them to abandon treatment. Moreover, adverse events—although mostly mild—were reported in nearly one-third of participants, a factor that likely contributed further to non-adherence to treatment and dropout.[39]

Regarding follow-up, the trial had already anticipated a dropout rate of approximately 20%—higher than typically observed in other trials—based on the characteristics of the study population, with low engagement in long-term medical regimens. However, actual loss to follow-up exceeded expectations despite specifically excluding participants with a documented history of poor adherence. This finding highlights a significant challenge in managing this patient population: the overall low adherence to both treatment and follow-up, regardless of the therapeutic strategy employed, which also reflects the general difficulty of conducting trials in patients with CP. In fact, new trials evaluating interventions in this group of patients are already assuming even higher drop-out rates (30%),[40] which are similar to our observations.

Another relevant aspect is that the SIMBA trial primarily aimed to evaluate recurrence and disease progression. However, pain patterns and their impact on quality of life were not assessed. Future studies should incorporate validated scales, such as the COMPAT score, to evaluate this.[41]

To conclude, in our randomised trial assessing the role of simvastatin versus placebo in preventing RAP or acute-on-chronic inflammatory flares of CP, the use of simvastatin did not prove to reduce recurrence, although the results may be underpowered due to early termination of the trial.

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