


ORIGINAL ARTICLE

Real-world evaluation of the impact of statin intensity on adherence and persistence to therapy: A Scottish population-based study

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Aim: To assess associations between statin intensity and adherence, persistence and discontinuation of statin therapy in Scotland.

Method: Retrospective cohort study, using linked electronic health records covering a period from January 2009 to December 2016. The study cohort included adult patients (≥ 18 years) newly initiating statins within Greater Glasgow and Clyde, Scotland. Study outcomes comprised adherence, discontinuation and persistence to treatment, stratified by three exposure groups (high, moderate and low intensity). Discontinuation and persistence were calculated using the refill-gap and anniversary methods, respectively. Proportion of days covered (PDC) was used as a proxy for adherence. Kaplan-Meier survival curves and Cox proportional hazard models were used to evaluate discontinuation, and associations between adherence/persistence and statin intensity were assessed using logistic regression.

Results: A total of 73 716 patients with a mean age of 61.4 ± 12.6 years were included; the majority (88.3%) received moderate intensity statins. Discontinuation rates differed between intensity levels, with high-intensity patients less likely to discontinue treatment compared to those on moderate intensity (prior cardiovascular disease [CVD]: HR 0.43 [95% CI 0.34-0.55]; no prior CVD: 0.80 [0.74-0.86]). Persistence declined over time, and high-intensity patients had the highest persistence rates. Overall, 52.6% of patients were adherent to treatment (PDC $\geq 80\%$), but adherence was considerably higher among high-intensity patients (63.7%).

Conclusion: High-intensity statins were associated with better persistence and adherence to treatment, but overall long-term persistence and adherence remain a challenge, particularly among patients without prior CVD. This needs addressing.

KEYWORDS

cardiovascular disease, drug utilisation, high-intensity therapy, medication adherence, Scotland, statins

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1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide.¹ In Scotland, whilst the mortality from coronary heart disease has been decreasing, treating and preventing CVD remains an important priority in health care, particularly as its population is projected to age considerably over the coming years, with an estimated 25% of the population aged 65 years or older by 2041.^{2,3} In addition, there is a high prevalence of risk factors associated with heart disease in Scotland, including smoking, poor diet and physical inactivity. Accordingly, in 2015, 15% of adults aged 16 years or above had a cardiovascular condition, which represents an estimated 670 000 people living with CVD in Scotland. Both incidence and prevalence of CVD are higher amongst men, the elderly and in deprived areas.^{2,4}

CVD prevention is seen as a cost-effective strategy in many scenarios.^{4,5} Evidence from clinical trials and epidemiological studies has shown a strong relationship between high low-density lipoprotein cholesterol (LDL-C) levels and the incidence of CVD; lipid-lowering therapy is associated with significant reductions in CVD morbidity and mortality.^{6–9} Consequently, the use of statins, competitively inhibiting **3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase**, is one of the cornerstones of CVD prevention.^{4,10,11}

Recent evidence has supported the higher efficacy of high-intensity statin therapy in comparison to low or moderate intensity,¹² therefore the Scottish guidelines now recommend high-intensity statin therapy, namely **atorvastatin** 80 mg, as the most clinically effective and cost-effective option for secondary prevention in patients with established coronary vascular disease.⁴ Nevertheless, there are concerns around the safety of high-intensity statins as high doses may increase the incidence of statin-related side effects such as myopathy, hepatotoxicity or diabetes,^{13–15} which in turn might impede patients' adherence and persistence to treatment,¹⁶ and subsequently potentially limit the clinical benefit of statins in reducing CVD.^{17–20} This is particularly important given that long-term adherence to statin therapy has already been shown to be far from optimal,^{21–25} and a significant proportion of patients stop taking their statins within 2 years of initiation.^{22,23} A wide range of factors, related to both the patient and the healthcare provider, has been shown to impact adherence to long-term treatment, for instance insufficient understanding of the disease, concerns about side effects or inconsistent information received from healthcare professionals.²⁶ There is, however, limited and controversial evidence to date with regard to the effect of statin intensity levels on treatment adherence/persistence.^{27–29} A recent systematic review of adherence and persistence with statins showed that only two of the 84 studies included reported information on the statin intensity regime and its correlation with adherence.³⁰

Prescribing and dispensing data drawn from administrative databases is particularly useful for conducting large observational studies aimed at analysing drug utilisation rates, including adherence/persistence to treatment.^{31,32} The National Health Service (NHS) Scotland, which provides universal health care with no co-payments for medicines for all residents in Scotland, offers a wide

What is already known about this subject

- Long-term adherence to statin treatment is low and discontinuation rates are high.
- Guidelines for cardiovascular disease (CVD) prevention increasingly recommend high-intensity statin therapy.
- As adverse events rates are likely higher with high-intensity treatment, this could have a negative effect on adherence rates, but evidence so far is scarce.

What this study adds

- Adherence to statin treatment was higher among patients treated with high-intensity statins and discontinuation rates were lower compared to moderate intensity.
- Patients with prior CVD (secondary prevention) had better adherence than those without (primary prevention).

array of routinely collected data suitable for drug utilisation research, including prescribing and dispensing data.³³

The aim of this study was to assess the association of statin therapy intensity with adherence, persistence and discontinuation to/of treatment, thereby covering two distinct phases of medication-taking behaviour according to the Ascertaining Barriers for Compliance (ABC) taxonomy: implementation and discontinuation.³⁴ This information is vital since there has been an increase in prescribing of high-intensity statins in Scotland in recent years following advice from the Scottish Government and Health Boards.^{4,35} The findings from this study will be discussed with key stakeholder groups in Scotland to instigate additional pertinent interventions if needed to further reduce CVD rates.

2 | METHODS

2.1 | Study design and data sources

This retrospective longitudinal cohort study spanned from January 2009 to December 2016, using linked electronic health records for patients registered within NHS Greater Glasgow & Clyde (NHS GGC), the largest Health Board in Scotland. NHS GGC covers approximately 1.1 million people, or about 20% of the total Scottish population.³⁶ It comprises both urban and rural areas, as well as some of the most deprived areas within Scotland. Although the share of elderly people (over the age of 65 years) is slightly lower than the Scottish average, NHS GGC is in general representative of Scotland overall, particularly with regards to the prevalence of cardiovascular diseases.^{37,38}

New statin users were identified using the Prescribing Information System (PIS), which covers all prescriptions dispensed within the community (primary care) setting. PIS data contains information with regards to both prescribing and dispensing (prescribed date and dispensed month/year, prescribed and dispensed quantities, and dispensed item name, strength and formulation), but due to the nature of the database, PIS does not contain information about prescriptions that have been issued but were not dispensed in a community pharmacy.³³ Data from PIS was linked to the Scottish Morbidity Records Outpatient attendance (SMR00) and Inpatient and Day Care (SMR01) datasets as well as to the Scottish death records using Community Health Index (CHI) numbers. The CHI number is a unique patient identifier used throughout Scotland and incorporated into all NHS Scotland datasets.³⁹

2.2 | Study cohort

The study population comprised all adult patients (≥ 18 years old) who newly initiated statin therapy (atorvastatin, **fluvastatin**, **pravastatin**, **rosuvastatin** or **simvastatin**) between January 2010 and December 2015 (cohort inclusion period); the date of first statin prescription was the index date. New use was defined as having no prescription records for any statin in the year prior to the index date (with the year 2009 used as a run-in period). Patients were excluded if they used a statin as part of a fixed-dose combination. In addition, patients were required to have at least 1 year follow-up time after the index date to ensure sufficient time to evaluate study outcomes. Individual patients were followed from the index date to either death or removal from a Scottish General Practitioner register for other reasons (such as emigration), with the date of emigration/death used as censor date where applicable, or until the study end date (31 December 2016), whichever occurred first. Patients were not censored when being admitted to a care home or hospital, as they are usually provided with medication through primary care or expected to bring their own chronic disease medication, respectively.

2.3 | Drug exposure

Detailed information about dispensed statin prescriptions was extracted from PIS and included the nonproprietary name, drug formulation, strength, prescription date and dispensed quantity. While the dispensed quantity was used to calculate patients' days of supply, the prescribing dates were used to estimate time periods between prescriptions as these dates are more accurate than the available dispensing dates (which default to the last day of each month). Statin users were stratified into three exposure groups based on the first statin received according to the current National Institute for Health and Care Excellence (NICE) classifications (high, moderate and low intensity) as detailed in Table 1.¹⁰ Only prescriptions for the first statin intensity level issued to patients were taken into consideration when calculating all outcome measures, with patients being allowed to

TABLE 1 Statin intensity levels according to the National Institute for Health and Care Excellence

Statin	High intensity	Moderate intensity	Low intensity
Atorvastatin	20-80 mg	10 mg	...
Fluvastatin	...	80 mg	20-40 mg
Lovastatin	...	40 mg	10-20 mg
Pravastatin	...	40-80 mg	10-20 mg
Rosuvastatin	20-40 mg	5-10 mg	...
Simvastatin	80 mg	20-40 mg	10 mg

switch between statins within the same level of intensity (eg, simvastatin 20 mg to atorvastatin 10 mg). Results therefore relate to the level of statin used at the index date.

2.4 | Outcome measures

Medication-taking behaviour consists of three elements: initiation, implementation, and discontinuation. While initiation and discontinuation represent the start and end of drug treatment, respectively, the process of implementation describes the extent to which a patient's medication intake corresponds to what has been prescribed.³⁴ Because of the nature of the data available, the outcome measures used in this study covered the latter two elements and comprised adherence, discontinuation and persistence to statin therapy, stratified by the three exposure groups.

Discontinuation – *to stop treatment* – was calculated using the refill-gap method, defined as a gap of more than 60 days without drug supply following the assumed end of a prescription, that is, the last day with assumed medication availability (grace period). Previous oversupply of medicines (eg, due to early refills) was taken into account.³² The period of 60 days was chosen based on observed prescribing patterns and the recommendation to have a grace period of at least the average prescription supply,⁴⁰ which was 56 days in this study. Patients were classified as having discontinued treatment when switching to a different level of statin intensity. In addition, to assess permanence of statin discontinuation, patients reinitiating treatment after an initial discontinuation event were identified, and levels of statin intensity prior and after this discontinuation were compared.

Persistence – *being on treatment* – was assessed at prespecified points in time (6, 12, 24 and 36 months after treatment initiation) using the anniversary method by assessing whether patients were in possession of drug supply covering specific dates. This method aims to account for both intermediary treatment interruptions and short-term changes in intensity of therapy (eg, due to temporary shortages of specific drugs).³² As patients were not censored when switching between different statins or intensity levels, permanent switch of intensity was classified as nonpersistence.

Proportion of days covered (PDC) was used as a proxy for adherence – *to take medication as prescribed*. PDC was calculated by dividing the total number of days covered by statin prescriptions by the

total number of days in the follow-up period, capped at 100%. To calculate days covered, dispensed quantities were used with an assumed intake of one tablet/capsule a day. Applying the most commonly used cut-off point, patients were classified as adherent when their PDC was $\geq 80\%$ and nonadherent with a PDC $< 80\%$.^{31,41} In addition, to be able to better distinguish between implementation and persistence, the compliance rate (CR) was calculated: the number of days covered by statin prescriptions (excluding the days' supply obtained at the last dispensation) divided by the number of days in the period up to, but not including, the last recorded prescription.⁴¹

2.5 | Covariables

Baseline patient characteristics were captured at index date and included sex, age, first statin prescribed, year of statin initiation, deprivation, comorbidities and overall frailty. Deprivation was measured using the Scottish Index of Multiple Deprivation (SIMD), ranked from 1 (most deprived) to 5 (least deprived).⁴² Comorbidities were assessed by calculating a Charlson comorbidity score⁴³ using International Classification of Diseases, 10th edition (ICD-10) codes, identified from SMR00 and SMR01 records. The Charlson score is the most widely used indicator of comorbidities and has been adapted by Quan et al for use with ICD-10 codes.⁴⁴ For the general measure of frailty, the number of in-hospital days – regardless of cause – was counted during the 2-year period prior to the index date, as recorded in SMR01.

2.6 | Statistical analysis

Descriptive statistics were used to assess baseline characteristics. Continuous variables were summarised using means and standard variation, while categorical variables were presented using absolute and relative frequencies.

Kaplan-Meier survival curves were plotted to calculate the median time to first discontinuation of statin use. Associations between adherence/persistence to treatment and statin intensity were assessed using logistic regression models; Cox proportional hazard models were used to evaluate time to discontinuation. Moderate intensity therapy was chosen as reference based on practical and clinical deliberations. All findings were adjusted for baseline covariables, using complete cases only (ie, excluding patients from the regression analyses when data were missing).

All analyses were performed using the full patient cohort, as well as stratified by whether a statin was prescribed for primary or secondary prevention. Secondary prevention was defined as having a diagnosis of myocardial infarction, angina, stroke or ischaemic heart disease – recorded in SMR00/SMR01 – within the year preceding the index date (ICD-10 codes I20-I24, I25.0, I25.1, I25.6, I25.8, I25.9, I51.6, I51.7, I60-I64, G45.0-G45.3, G45.8, G45.9, H34.1). Sensitivity analyses were performed for discontinuation and persistence using alternative admissible intervals without drug supply (ie, supply gaps) of 30, 90, 120 and 180 days (grace periods).

All data analyses were conducted using R Studio, version 3.3.0. For the extraction of PIS data, stored on an SQL server, the R package Open Database Connectivity (RODBC) was used.^{45,46} Data were anonymised, hosted and managed by the NHS GGC Safe Haven, and their use was approved by the appropriate Local Privacy Advisory Committee.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

During the study period, a total of 212 953 patients received at least one prescription for any statin. Of these, 139 237 patients were excluded due to being below the age of 18 years when initiating treatment, having been treated with statins during the run-in period, having received fixed dose combinations including statins or not having at least one full year of follow-up after the index date. This resulted in 73 716 patients subsequently being included in the study (Figure 1).

3.1 | Baseline characteristics

Of the 73 716 patients included in the study cohort, the majority (88.4%) were initiated on moderate intensity therapy, followed by 9.7% on high intensity and 1.9% on low intensity. Simvastatin was the most commonly prescribed statin, issued to 85.6% of all patients newly initiating treatment and accounting for 95.0% and 79.8% of all moderate and low-intensity therapy, respectively. In contrast, the vast majority (98.1%) of patients who started high-intensity treatment received atorvastatin. The mean age of all statin users was 61.4 years (SD 12.6) and 39.5% were elderly (≥ 65 years), with 16.3% being 75 years of age or older. Slightly over half the patients (52.3%) were male. The mean Charlson score was 0.77 (SD 1.32) and 45.2% of patients had hospital admissions in the 2-year period prior to cohort entry, with an average of 10.4 days (SD 26.1) of in-hospital stay. There were, however, differences between the three intensity exposure groups. With a mean age of 60.6 years (SD 12.7), patients on high-intensity therapy were on average younger than those initiating moderate (mean 61.4 years, SD 12.6) or low-intensity statins (mean 63.9 years, SD 13.3). High-intensity patients had, nevertheless, more comorbidities, with higher mean Charlson scores, higher proportions of patients with prior CVD (high intensity 25.6%, moderate intensity 13.4%, low intensity 4.8%) and higher proportions of patients with recent admissions to hospital (high intensity 50.3%, moderate intensity 44.7%, low intensity 38.9%). Details of baseline characteristics for

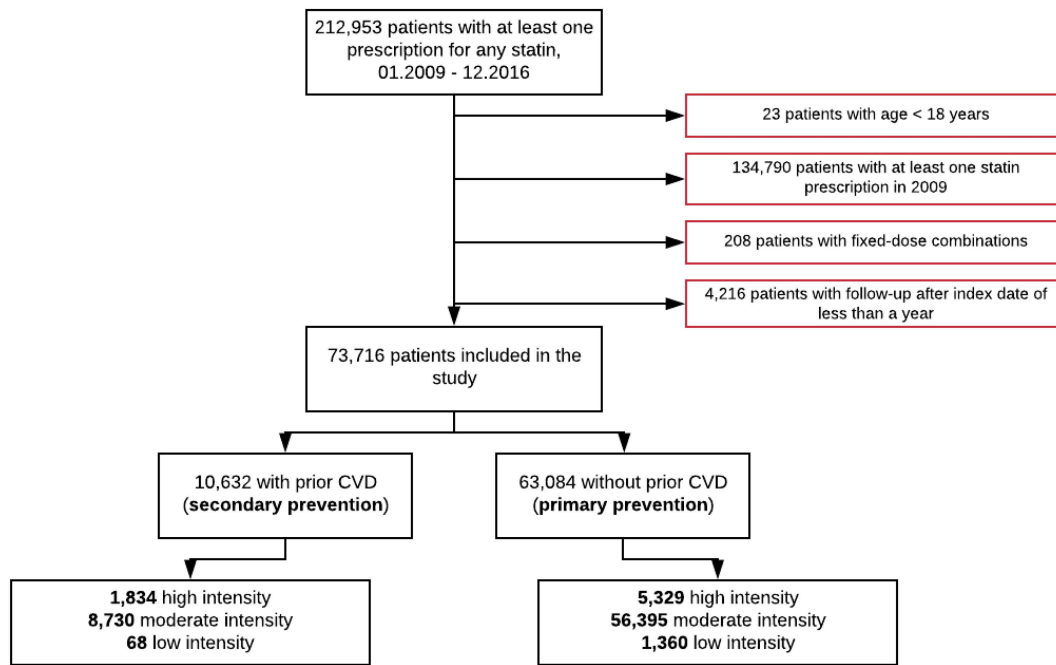


FIGURE 1 Study cohort identification flow chart

the full cohort – overall as well as by statin intensity – can be found in Supporting Information Table S1.

When stratifying by primary/secondary prevention, patients with prior CVD were older than those without (mean age 63.6 years [SD 14.2] vs 61.0 years [SD 12.3]), predominantly male (58.9% vs 51.1% among patients without CVD) and had a higher mean Charlson score (1.72 [SD 1.47] vs 0.55 [SD 1.17]). In addition, patients with prior CVD had all recently been hospitalised, with an average of 16.5 (SD 30.9) in-hospital days, in contrast to only 39.5% of patients subject to primary prevention, with an average of 7.6 (SD 23.0) in-hospital days. Differences between statin intensity levels were also observed in both stratified cohorts (for details, see Table 2).

3.2 | Discontinuation of treatment

During the study period, 46 730 patients (62.9%) discontinued statin treatment and the median time to first discontinuation was 522 days (95% confidence interval [CI] 510-535). Discontinuation rates as well as time to discontinuation differed between intensity levels, however, ranging from 50.9% with a median time to discontinuation of 911 days (95% CI 843-1007) among patients treated with high-intensity statins to 75.5% (median time to discontinuation 207 days (95% CI 168-244) among low-intensity patients (see also Supporting Information Figures S1 and S2). Discontinuation also differed considerably between patients with and without prior CVD, with overall rates of 48.0% and 65.4%, respectively. Similar to the overall cohort, discontinuation rates in both these subgroups were lowest among patients treated with high-intensity statins and highest among low-intensity statin patients. Time to discontinuation varied widely between the different

patient groups, but was consistently longer for secondary prevention (see Table 3 and Figure 2 for details).

After adjusting for baseline patient characteristics (year of treatment initiation, drug prescribed, sex, age category, deprivation (SIMD), Charlson score [0 vs ≥ 1], prior CVD yes/no and hospitalisation yes/no), patients on high-intensity statin therapy were less likely to prematurely discontinue treatment than those on moderate intensity therapy (Hazard Ratio [HR] 0.74, 95% CI 0.69-0.79). Although Hazard Ratios differed considerably between patients with and without prior CVD, stratified findings were in general similar to those observed in the complete cohort. Compared to moderate intensity, high-intensity statin patients were less likely to discontinue treatment regardless of prior CVD status (with prior CVD: HR 0.43, 95% CI 0.34-0.55; without prior CVD: HR 0.80, 95% CI 0.74-0.86) (Table 3).

3.3 | Reinitiation of treatment

Overall, 72.3% of patients reinitiated statin therapy after a first discontinuation event, the majority of which (72.7%) with the same statin intensity that was used prior to treatment interruption, and 4.7% of patients reduced and 23.2% increased statin intensity. The proportion of patients changing intensity levels differed, however, between patients with and without prior CVD (Figure 3).

3.4 | Persistence to treatment

In line with discontinuation rates, persistence to treatment also varied significantly between statin intensity levels, with considerable

TABLE 2 Baseline characteristics of new statin users by intensity level and prior CVD status (type of prevention)

	Prior CVD (secondary prevention) n = 10 632 (14.4%)			No prior CVD (primary prevention) n = 63 084 (85.6%)		
	Intensity, n (%)			Intensity, n (%)		
	High 1834 (17.2)	Moderate 8730 (82.1)	Low 68 (0.6)	High 5329 (8.4)	Moderate 56 395 (89.4)	Low 1360 (2.2)
Sex, n (%)						
Male	1196 (65.2)	5041 (57.7)	30 (44.1)	2931 (55.0)	28 728 (50.9)	608 (44.7)
Female	638 (34.8)	3689 (42.3)	38 (55.9)	2398 (45.0)	27 667 (49.1)	725 (53.3)
Age categories (years), n (%)						
<55	685 (37.4)	2484 (28.5)	9 (13.2)	1619 (30.4)	17 737 (31.5)	326 (24.0)
55-64	531 (29.0)	2068 (23.7)	16 (23.5)	1587 (29.8)	17 112 (30.3)	374 (27.5)
65-74	333 (18.2)	1740 (19.9)	18 (26.5)	1330 (25.0)	13 340 (23.7)	368 (27.1)
75+	285 (15.5)	2438 (27.9)	25 (36.8)	793 (14.9)	8206 (14.6)	292 (24.5)
Age (years), mean (SD)	59.7 (13.1)	64.4 (14.3)	68.3 (13.6)	60.9 (12.6)	60.9 (12.3)	63.7 (13.2)
Deprivation score (quintile), n (%) ^a						
1 (most deprived)	754 (41.1)	3534 (40.5)	18 (26.5)	2034 (38.2)	22 616 (40.1)	406 (29.9)
2	300 (16.4)	1548 (17.7)	13 (19.1)	928 (17.4)	10 112 (17.9)	221 (16.3)
3	233 (12.7)	1192 (13.7)	13 (19.1)	740 (13.9)	7229 (12.8)	187 (13.8)
4	210 (11.5)	976 (11.2)	11 (16.2)	680 (12.8)	6671 (11.8)	227 (16.7)
5 (least deprived)	307 (16.7)	1366 (15.6)	11 (16.2)	869 (16.3)	9025 (16.0)	298 (21.9)
Calendar year of the first statin prescription, n (%)						
2010	384 (20.9)	1566 (17.9)	17 (25.0)	748 (14.0)	11 513 (20.4)	315 (23.2)
2011	101 (5.5)	1753 (20.1)	16 (23.5)	396 (7.4)	9594 (17.0)	251 (18.5)
2012	140 (7.6)	1646 (18.9)	13 (19.1)	587 (11.0)	10 175 (18.0)	241 (17.7)
2013	251 (13.7)	1434 (16.4)	12 (17.6)	954 (17.9)	9515 (16.9)	214 (15.7)
2014	341 (18.6)	1332 (15.3)	5 (7.4)	1152 (21.6)	8370 (14.8)	210 (15.4)
2015	617 (33.6)	999 (11.4)	5 (7.4)	1492 (28.0)	7228 (12.8)	129 (9.5)
Charlson comorbidity score, n (%) ^{b, c}						
0	90 (4.9)	677 (7.8)	9 (13.2)	2327 (43.7)	28 482 (50.5)	616 (45.3)
≥ 1	1744 (95.1)	8053 (92.2)	59 (86.8)	1143 (21.4)	11 571 (20.5)	353 (26.0)
Charlson comorbidity score, mean (SD) ^{2, 3}	1.61 (1.31)	1.74 (1.49)	2.44 (2.15)	0.63 (1.25)	0.53 (1.15)	0.78 (1.44)
Hospitalization (yes), n (%) ^d	1834 (100)	8730 (100)	68 (100)	1768 (33.2)	20 402 (36.2)	487 (35.8)
General patient fragility, mean (SD) ⁴	12.3 (24.1)	17.3 (32.1)	24.6 (34.8)	6.8 (17.8)	7.6 (23.5)	8.5 (21.5)

Abbreviations: CVD, cardiovascular disease.

^a1.3% (n = 987) of missing data: secondary prevention n = 146 (1.4%), primary prevention n = 841 (1.3%).

^bBased on all ICD codes recorded in hospital records during the 2-year period preceding the index date.

^c25.2% (n = 18,592) of missing data: secondary prevention n = 0 (0%), primary prevention n = 18,592 (29.5%).

^dIn-hospital days, assessed during the 2-year period preceding the index date.

differences between patients with and without prior CVD. Persistence declined over time; nevertheless, patients subject to high-intensity therapy had the highest persistence rates at all analysed time points. Details are presented in Table 4.

In general, after adjusting for baseline characteristics, patients initiating high-intensity statins were more likely to still be on treatment at any point in time compared to patients initiating moderate intensity therapy (6 months: Odds Ratio [OR] 1.48, 95% CI 1.30-1.68; 12 months: OR 1.54, 95% CI 1.37-1.74; 24 months: OR 1.47, 95% CI 1.29-1.68).

Among patients with prior CVD, the ORs for being persistent with high-intensity statins as compared to moderate intensity were 3.41 (95% CI 2.24-5.12) after 6 months, 2.94 (95% CI 1.97-4.34) after 12 months and 2.82 (95% CI 1.82-4.34) after 24 months. Although differing in magnitude, the findings paint a similar picture for patients without prior CVD. Patients were more likely to be persistent with high-intensity statins when compared to moderate intensity (6 months: OR 1.38, 95% CI 1.20-1.57; 12 months: OR 1.41, 95% CI 1.24-1.60; 24 months: OR 1.36, 95% CI 1.18-1.56) (see Table 5 for details).

TABLE 3 Crude discontinuation rates, time to discontinuation and adjusted HRs by intensity level and prior CVD status (type of prevention)

	Crude discontinuation rate (%) ^a	Median time to first discontinuation (95% CI) (days) ^b	Hazard Ratio (95% CI), adjusted ^c
All patients	62.9	522 (510-535)	
Low intensity	75.5	207 (168-244)	1.56 (1.45-1.69)
Moderate intensity	63.9	504 (493-517)	1
High intensity	50.9	911 (843-1007)	0.74 (0.69-0.79)
Prior CVD (secondary prevention)	48.0	1232 (1168-1296)	
Low intensity	58.8	209 (87-NR)	1.85 (1.30-2.63)
Moderate intensity	50.4	1,126 (1064-1201)	1
High intensity	36.3	2,028 (1676-NR)	0.43 (0.34-0.55)
No prior CVD (primary prevention)	65.4	440 (429-450)	
Low intensity	76.3	203 (168-244)	1.55 (1.43-1.67)
Moderate intensity	66.0	435 (424-448)	1
High intensity	55.9	615 (561-705)	0.80 (0.74-0.86)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; NR, not reached.

^aRefill-gap method, admissible gap 60 days.

^bKaplan-Meier survival, unadjusted.

^cReference category is moderate intensity, adjusted for baseline variables: year of treatment initiation, drug prescribed, sex, age category, deprivation (SIMD), Charlson score (0 vs ≥1), prior CVD yes/no, hospitalisation yes/no.

FIGURE 2 Kaplan-Meier curves of time to first treatment discontinuation by CVD status (type of prevention)

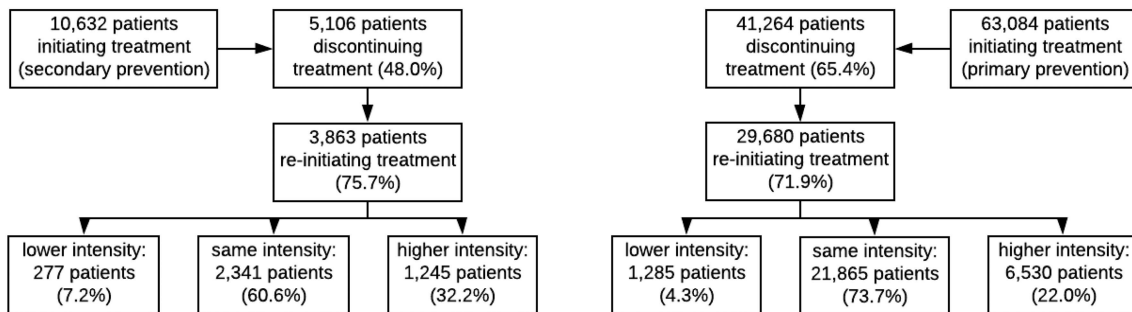
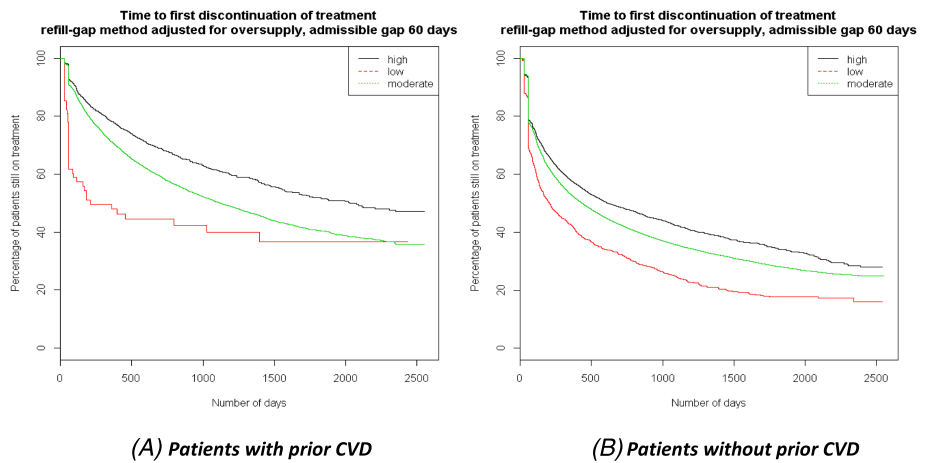


FIGURE 3 Discontinuation and reinitiation of treatment by CVD status (type of prevention)

TABLE 4 Crude persistence rates at specific points in time since treatment initiation by intensity level and prior CVD status (type of prevention)

Persistence rate (%) ^{a,b}	6 months	12 months	24 months	36 months
All patients	76.8	69.9	63.7	59.2
Low intensity	62.7	53.1	43.4	36.2
Moderate intensity	76.7	69.8	63.8	59.4
High intensity	80.1	74.7	68.0	63.3
Prior CVD (secondary prevention)	88.6	81.6	74.0	68.2
Low intensity	59.1	50.8	42.6	39.6
Moderate intensity	88.7	81.0	73.5	67.6
High intensity	89.7	85.5	78.0	73.5
No prior CVD (primary prevention)	74.8	68.0	62.1	57.8
Low intensity	62.9	53.2	43.4	36.1
Moderate intensity	74.9	68.1	62.3	58.2
High intensity	76.8	71.0	64.8	60.0

Abbreviations: CVD, cardiovascular disease.

^aAnniversary method, admissible gap 60 days.

^bDenominators are patients with sufficient follow-up time within a specific category.

TABLE 5 Adjusted ORs for persistence at specific points in time since treatment initiation by intensity level and prior CVD status (type of prevention)

OR (95% CI), adjusted ^{a,b}	6 months	12 months	24 months
All patients			
Low intensity	0.45 (0.39-0.52)	0.45 (0.40-0.52)	0.40 (0.34-0.46)
Moderate intensity	1	1	1
High intensity	1.48 (1.30-1.68)	1.54 (1.37-1.74)	1.47 (1.29-1.68)
Prior CVD (secondary prevention)			
Low intensity	0.17 (0.10-0.32)	0.22 (0.12-0.39)	0.23 (0.12-0.43)
Moderate intensity	1	1	1
High intensity	3.41 (2.24-5.12)	2.94 (1.97-4.34)	2.82 (1.82-4.34)
No prior CVD (primary prevention)			
Low intensity	0.47 (0.41-0.54)	0.47 (0.41-0.54)	0.41 (0.35-0.48)
Moderate intensity	1	1	1
High intensity	1.38 (1.20-1.57)	1.41 (1.24-1.60)	1.36 (1.18-1.56)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; OR, Odds Ratio.

^aAnniversary method, admissible gap 60 days.

^bReference category is moderate intensity, adjusted for baseline variables: year of treatment initiation, drug prescribed, sex, age category, deprivation (SIMD), Charlson score (0 vs ≥ 1), prior CVD yes/no, hospitalisation yes/no.

3.5 | Adherence to treatment

Only patients who had at least two dispensing records for the same statin intensity were included in the adherence analysis, totalling 66 248 patients (89.9% of all new statin users during the study period). Based on PDC, the overall adherence rate for the full cohort was 52.6%, but adherence to treatment was significantly higher among high-intensity statin users, with 63.7% classified as adherent in contrast to 51.6% and 40.5% among moderate- and low-intensity users, respectively. There were also differences in adherence between patients with and without prior CVD, with higher adherence rates

among patients subject to secondary prevention at all levels of statin intensity (Table 6).

When using the CR instead of the PDC, the overall adherence rate was considerably higher at 69.3% and differences between intensity levels were less pronounced, with between 68.5% and 76.1% of patients considered adherent to treatment. Again, patients with prior CVD had higher adherence rates at all levels of statin intensity (for details see Table 7).

After adjusting for baseline characteristics, compared to moderate intensity, patients on high-intensity statin therapy in general were more likely to be adherent to treatment, regardless of outcome

TABLE 6 Crude adherence rates, median PDC and adjusted ORs by intensity level and prior CVD status (type of prevention)

	PDC ≥ 80%	Median PDC (IQR)	OR (95% CI), adjusted ^a
All patients	52.6	83.3 (36.7-99.9)	
Low intensity	40.5	58.2 (16.8-96.8)	0.58 (0.50-0.68)
Moderate intensity	51.6	82.0 (35.6-99.5)	1
High intensity	63.7	93.4 (59.0-100.0)	1.54 (1.37-1.74)
Prior CVD (secondary prevention)	64.7	94.3 (58.4-100.0)	
Low intensity	58.3	97.4 (24.4-100.0)	0.78 (0.41-1.50)
Moderate intensity	62.7	93.1 (54.1-100.0)	1
High intensity	74.1	98.7 (78.7-100.0)	3.06 (2.10-4.46)
No prior CVD (primary prevention)	50.4	80.5 (34.0-99.1)	
Low intensity	39.6	56.4 (16.4-96.3)	0.57 (0.48-0.67)
Moderate intensity	49.7	79.7 (33.3-98.9)	1
High intensity	59.8	90.1 (51.7-100.0)	1.39 (1.22-1.58)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; IQR, inter-quartile range; OR, Odds Ratio; PDC, proportion of days covered.

^aReference category is moderate intensity, adjusted for baseline variables: year of treatment initiation, drug prescribed, sex, age category, deprivation (SIMD), Charlson score (0 vs ≥1), prior CVD yes/no, hospitalisation yes/no.

TABLE 7 Crude adherence rates, median CR and adjusted OR by intensity level and prior CVD status (type of prevention)

	CR ≥ 80%	Median CR (IQR)	OR (95% CI), adjusted ^a
All patients	69.3	93.2 (72.9-101.1)	
Low intensity	72.5	94.9 (76.9-103.2)	1.19 (1.00-1.41)
Moderate intensity	68.5	92.8 (71.9-101.0)	1
High intensity	76.1	96.0 (81.3-102.1)	1.27 (1.11-1.45)
Prior CVD (secondary prevention)	82.5	97.6 (87.6-103.1)	
Low intensity	85.4	99.7 (94.4-108.3)	1.19 (0.53-3.08)
Moderate intensity	81.9	97.4 (87.0-103.0)	1
High intensity	85.1	98.3 (89.8-103.2)	1.98 (1.25-3.08)
No prior CVD (primary prevention)	66.9	92.0 (70.1-100.7)	
Low intensity	71.9	94.5 (75.9-103.0)	1.19 (1.00-1.42)
Moderate intensity	66.3	91.7 (69.4-100.6)	1
High intensity	72.7	94.6 (77.4-101.7)	1.23 (1.06-1.41)

Abbreviations: CI, confidence interval; CR, compliance rate; CVD, cardiovascular disease; IQR, inter-quartile range; OR, Odds Ratio.

^aReference category is moderate intensity, adjusted for baseline variables: year of treatment initiation, drug prescribed, sex, age category, deprivation (SIMD), Charlson score (0 vs ≥1), prior CVD yes/no, hospitalisation yes/no.

measurement used (PDC: OR 1.54, 95% CI 1.37-1.74; CR: OR 1.27, 95% CI 1.11-1.45). Adherence was similar to the overall results when looking only at patients without prior CVD/primary prevention (PDC: OR 1.39, 95% CI 1.22-1.58; CR: 1.22, 95% CI 1.06-1.41), but was considerably higher among patients with prior CVD/secondary prevention (PDC: OR 3.06, 95% CI 2.10-4.46; CR: 1.98, 95% CI 1.25-3.08) (Tables 6 and 7).

3.6 | Sensitivity analyses

Results from the sensitivity analyses were consistent with the main analysis, although changing the length of permissible gaps had an

impact on absolute numbers of patients discontinuing treatment, as well as on the median time to treatment discontinuation. When allowing for a short gap of 30 days, the overall proportion of patients discontinuing treatment increased to 75.0%, with a median time to discontinuation of 256 days (95% CI 251-261). In contrast, extending the admissible gap to 90, 120 and 180 days resulted in decreased discontinuation rates of 56.0% (median time to discontinuation 798 days, 95% CI 778-818), 52.1% (median time to discontinuation 1029 days, 95% CI 1002-1052) and 47.5% (median time to discontinuation 1409 days, 95% CI 1372-1445), respectively. In line with these findings, overall persistence rates decreased when shortening the admissible gap and increased when expanding it. Overall trends and differences between patients with or without prior CVD, or between

different levels of statin intensity, were not affected (detailed results not shown).

4 | DISCUSSION

This longitudinal cohort study assessed the impact of statin intensity on all medication-taking behaviours (adherence, persistence and discontinuation) over a 7-year period. Unexpectedly, compared to moderate statin intensity, high-intensity statin therapy was associated with better adherence and persistence to treatment, and lower discontinuation rates. Nevertheless, in line with other published studies which evaluated discontinuation of and persistence to statins,^{21–25,30} discontinuation rates were high overall, persistence to treatment decreased over time, and adherence was in general suboptimal. However, none of these studies assessed the impact of statin intensity.

Although differences between intensity levels have previously been reported, albeit to varying degrees depending on the specific population studied (eg, a study conducted in Israel found adherence to be lowest among high-intensity statin users,²⁷ while a Japanese study observed both higher and lower adherence with high-intensity statin therapy in comparison to moderate intensity depending on the database used),²⁸ this is, to the best of our knowledge, the first study to comprehensively analyse all aspects of medication-taking behaviour (ie, discontinuation, persistence and adherence) with regard to statin therapy, taking into consideration both the level of statin intensity and whether patients have been subject to primary or secondary prevention.

Discontinuation was consistently lowest among high-intensity patients in the full cohort as well as in the subgroups when stratifying by primary/secondary prevention. This is encouraging given the initial concerns that discontinuation rates may be higher among high-intensity patients due to potentially increased side effects with increased dosage. Interestingly, atorvastatin, which accounted for the vast majority of high-intensity therapy in our study, has recently been associated with lower odds of discontinuing statin treatment than simvastatin in a study conducted in Australia.²⁵ This was despite atorvastatin having been linked with higher levels of adverse events in comparison to simvastatin.⁴⁷ Differences in discontinuation rates were still observed when adjusting for patients' baseline characteristics, potentially indicating that higher intensity statins are either not associated with a significantly higher occurrence of side effects; or that patients are more tolerant towards minor side effects than anticipated if there is sufficient motivation to continue treatment. Unfortunately, adverse events data were not available to confirm these hypotheses. Bearing in mind that a considerable proportion of patients (72.3%) reinitiated treatment after a first discontinuation event, the latter might at least partially explain the results, especially when considering that patients being treated with high-intensity statins will have a higher risk of serious cardiovascular events and thus might be more receptive to being prescribed a statin, while simultaneously prescribers might be more vigilant with continuing treatment in a high-risk patient group.

Persistence in all treatment groups decreased over time. While 76.8% of all patients were still on treatment after 6 months, this decreased to 69.9% after 1 year, albeit with significant differences between intensity levels, with persistence consistently highest among high-intensity patients. Similarly, adherence to statin therapy was poor overall, with only just over half of all patients (52.6%) categorised as adherent during the study period; again, high intensity patients generally displayed better adherence. When assessing adherence using CRs instead of the frequently applied PDC, a noticeably higher percentage of patients (overall 69.3%) was considered adherent to treatment. Differences between these two outcome measures were particularly marked within the low-intensity treatment groups, highlighting the potentially substantial impact of early treatment discontinuation on measurements of adherence. Remarkably, adherence remained higher among patients treated with high-intensity statins even when using CRs. As in previous studies, both persistence and adherence to treatment (regardless of measurement used) were higher among patients with a recent previous cardiovascular event such as a myocardial infarction or stroke.^{21,22,25,28,48}

Low adherence to long-term treatment may be related to a range of parameters involving prescribers, patients, or both, and it is conceivable that factors such as insufficient explanation about the treatment and the impact of noncompliance, an underestimation of disease risks or the probability of drug-related adverse events (which have all been shown to influence adherence to medication^{20,26,49}) are distributed differently between distinct patient groups, with subsequent effects on outcomes. These factors, however, could not be analysed in this study. Consequently, the reasons for the observed substantial differences in treatment adherence among the study participants remain unclear and need to be investigated further to enhance future adherence rates in Scotland.

Keeping the findings of not only this study but also results from other studies in mind, it seems pertinent to consider how best to increase adherence to statin therapy, as statins are a proven and cost-effective means of preventing cardiovascular diseases, which are, despite recent improvements, still a major cause of death and disability in Scotland.² Interventions to improve adherence that have been suggested include interactive voice response reminders, regular medication reviews by community pharmacists, and repeat disease counselling through nurses or physicians.⁵⁰ Several studies^{26,49,51} have highlighted that the patients who were most satisfied with their physician's explanations were more likely to remain current medicines users and to have better adherence. With pharmacists increasingly being introduced into GP practices in Scotland,⁵² there is scope to explore options for improving the dialogue between patients and healthcare professionals, and to potentially implement other interventions tailored to patients that could improve adherence to statins - such as providing verbal and written information about the disease and/or the treatment, adapting treatment regimens or using dispensing support tools such as dosette boxes, depending on context and reasons for nonadherence to therapy.⁵³ Most importantly, shared decisions about the initiation of treatment, discussing the potential risks and benefits of statin therapy, and shared management plans are

essential to improve adherence rates and quality of medicines use.^{20,26} We will be discussing the implications of our findings with key stakeholders in Scotland as a basis for debating possible future interventions that could be instigated to improve prescribing and adherence rates.

4.1 | Strengths and limitations

This is a population-based study assessing the association of statin intensity with the entire medication-taking behaviour process, hence providing unprecedented insight into adherence to statin treatment. Considering that access to health care is universal and electronic health records cover the entire population, some confounding factors present in other settings, such as missing out on sections of the population based on incomplete health insurance coverage or inaccessibility of treatment due to copayments, are not present in Scotland. Furthermore, PIS and SMR01 have previously been used for research, and data validity and accuracy have been established.⁵⁴

Nevertheless, this study has several limitations. First, study data were obtained from NHS Scotland information systems, which have been implemented for administrative purposes; hence, not all desirable data were available. Details about diagnoses and the indication for drug treatment, for instance, are not available in PIS. Consequently, the indication for the use of statins (ie, primary or secondary prevention) was estimated based on hospital records, potentially affecting the accuracy of findings based on stratification by the presence or absence of prior CVD. In addition, due to the lack of primary care data, the Charlson Comorbidity Index was calculated using hospital discharge records and since some comorbidities might not have been captured, Charlson scores might have been underestimated. Data regarding the number of medications taken by patients, occasionally used as a proxy for comorbidities but also an important factor when assessing adherence in itself, were also not available for analysis, with potential implications for the interpretation of results. Furthermore, data related to clinical or behavioural factors such as lipid control and other potentially confounding lifestyle variables (including smoking habits, diet and physical activity) were unavailable. Consequently, reasons for discontinuation of treatment (which could have been based on a decision made by the prescriber rather than the patient, particularly among low-risk patients being treated with low or moderate intensity statins) were unknown. Second, the lack of standardised definitions and methods for measuring adherence, discontinuation and persistence could hamper comparison of findings across studies, but this is a well-recognised issue in drug utilisation research.^{34,54} To accommodate the range of admissible gaps used in other studies, we conducted sensitivity analyses. Apart from changes in absolute numbers of patients discontinuing treatment, overall trends and differences between patients with and without prior CVD, or between levels of statin intensity, were not affected. Furthermore, based on applied definitions and calculations, adherence for individual patients could have been underestimated/discontinuation might have been overestimated if they intermittently received statin prescriptions

for a different intensity, but the impact on overall findings is likely to be small due to small numbers of observed instances. Finally, an important limitation is the underlying assumption that all dispensed medicines were taken by patients, which is not always the case. Although findings could have been impacted if patients continued to fill in prescriptions despite not actually taking the drugs, this limitation is difficult to address, especially considering the size of the study cohort. As with all observational research, unmeasured confounding cannot be ruled out.

5 | CONCLUSIONS

The study findings indicate higher long-term persistence and adherence among high-intensity statin users compared to moderate intensity, thus not supporting our initial concerns that high-intensity statin therapy might impede patients' persistence and adherence due to higher risks of side effects. However, the study findings reinforce current beliefs that long-term persistence and adherence to treatment with statins remain a challenge in the prevention of CVD, as this potentially leads to suboptimal treatment outcomes. Further research, potentially analysing laboratory data in combination with adverse events, is urgently needed to address these issues. Furthermore, steps need to be undertaken to encourage persistence and adherence in Scotland, particularly among patients without prior CVD where statins have been prescribed. We will be following up on this with key stakeholders to plan next steps given the continual high rates of CVD in Scotland.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

All authors contributed to the study concept and design. TM: data management, data analysis, drafting of the manuscript; RDN: data analysis, manuscript review; AK: data management, manuscript review. All authors contributed to the interpretation of the results and were involved in critically revising the text. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from NHS Scotland. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from NHS National Services Scotland, Information Services Division, with the permission of the Public Benefit and Privacy Panel for Health and Social Care.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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