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FULL RESEARCH PAPER
Lipids & atherosclerosis

Trends in atherosclerotic cardiovascular disease and lipid management: a population-level observational cohort study in Wales

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Aims European clinical guidelines recommend that patients with atherosclerotic cardiovascular disease (ASCVD), including ischaemic heart disease (IHD), stroke, and peripheral arterial disease (PAD), are prescribed lipid lowering treatment (LLT) and treated to target low-density lipoprotein cholesterol (LDL-C) levels. This study aimed to document trends in ASCVD, including treatment, monitoring, and achievement of target LDL-C.

Methods and results A retrospective observational population study was performed using linked healthcare data (2010–22). Over the study period, the number of patients with ASCVD increased from 181 153 to 207 747 (8882 to 9398 per 100 000). The proportion of patients prescribed LLT decreased from 75.3% in 2010 to 67.1% in 2022; high-intensity statin therapy increased from 9.4 to 25.2%, while non-high-intensity statin therapy decreased from 59.6 to 38.2%. The prescription of high-intensity statin therapy was consistently higher amongst patients with IHD (10.9% in 2010 increasing to 28.0% in 2022) than in patients with stroke (4.7–21.6%) or PAD (3.9–10.6%).

The proportion of cases with documented LDL-C decreased from 58.0% in 2010 to 49.3% in 2022. Of those with documented LDL-C in 2022, 44.0% achieved LDL-C < 1.8 mmol/L, including 45.2% of those with IHD, 42.0% of those with stroke, and only 32.8% of those with PAD.

Conclusion Prescription of LLT, including high-intensity statin therapy, documentation of LDL-C, and achievement of target LDL-C levels was relatively low, especially in PAD patients. Although target achievement in 'tested patients' increased over time, the proportion of patients undergoing lipid testing declined. More rigorous lipid management requires prioritisation, especially for PAD and stroke patients.

Lay summary We analysed trends in the presentation of atherosclerotic cardiovascular disease and lipid management in a population between 2010 and 2022.

- The number of patients with atherosclerotic cardiovascular disease increased by 14%, but the proportion receiving lipid lowering therapy decreased.
- Patients with ischaemic heart disease were more effectively managed than patients with stroke.
- Patients with peripheral arterial disease were the least effectively managed.

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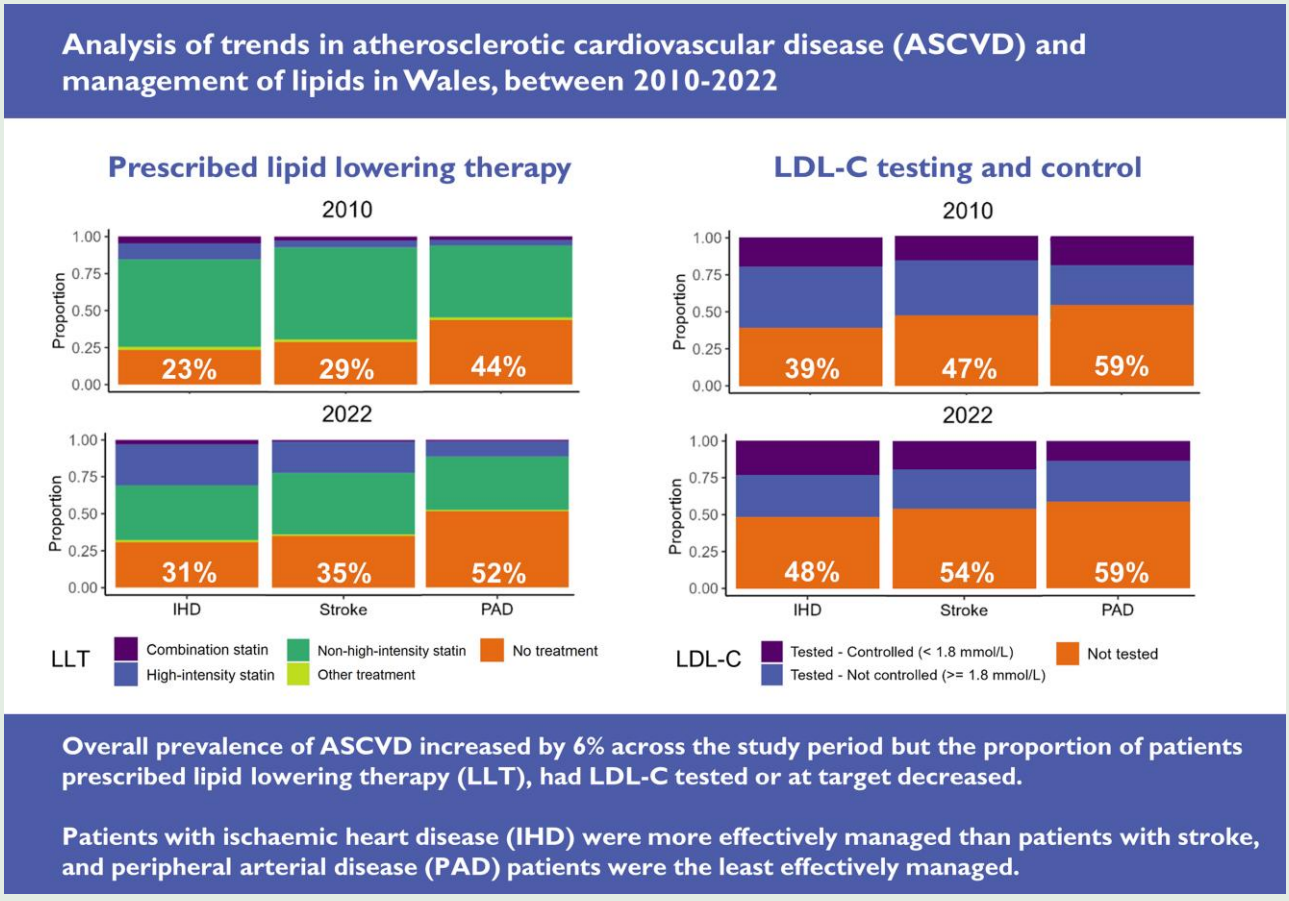
Graphical Abstract



Keywords Lipids • Cholesterol • Atherosclerosis • Statin • Pharmacoepidemiology

Introduction

In patients with established atherosclerotic cardiovascular disease (ASCVD), lipid lowering with statins, with or without additional lipid lowering therapy (LLT), improves clinical outcomes.[1–3] This practice is well established and endorsed by major clinical guidelines.[4–6]

A better understanding of the current trends in the clinical presentation of ASCVD, prescription of LLT, and achievement of guideline-recommended LDL-C targets will help determine not only the 'therapeutic gap' in lipid management for CVD prevention in routine practice, but also the potential opportunity of improving CVD risk management across the ASCVD spectrum. The aim of this study was to use routinely collected linked community and hospital health data to document population-scale trends in (i) the incidence and prevalence of ASCVD, including coronary, cerebro-, and peripheral and poly-vascular disease subgroups, (ii) prescription of LLT, (iii) monitoring of lipid levels, and (iv) achievement of the European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) recommended LDL-C targets[7] in the population of Wales, UK since 2010.

Methods

A retrospective observational cohort study was conducted using linked anonymised population-scale, individual-level electronic health record (EHR) data sources for patients with ASCVD in Wales, United Kingdom between 2010 and 2022, extracted from the Secure Anonymised Information Linkage (SAIL) Databank.[8,9]

Study inclusion and censor criteria

Patients were included if identified with ASCVD in their primary[10] or secondary care[11] record between January 2000 and December 2022 and aged ≥18 years old at first diagnosis (see Supplementary material for details of data sources).

Patients identified with ASCVD between 1 January 2000 and 31 December 2009 who were alive during the study observation period (1 January 2010–31 December 2022) were characterised as prevalent cases. Patients first identified with ASCVD during the study period were included as incident cases. Patients first identified with ASCVD before 2000 whose diagnoses were reconfirmed between 2000 and 2009 were also included as prevalent cases; otherwise, they were excluded due to data quality concerns. Prevalent cases entered the study on 1 January 2010. Incident cases entered on the date they were first identified with ASCVD (see Supplementary material for additional inclusion criteria).

Patients were censored at the date of (i) death, (ii) moving to a General Practice (GP) that does not provide data to the SAIL Databank for a period greater than 90 days, or (iii) moved out of Wales for a period greater than 90 days.

Characterising ASCVD

Patients with ASCVD, including ischaemic heart disease (IHD), stroke, and/or peripheral arterial disease (PAD), were identified from either their

primary or secondary care records (see Supplementary material online, *Tables S1 and S2* for diagnostic codes). Patients were classified as poly-vascular disease in the year that an ASCVD patient received a further diagnosis of ASCVD in an additional vascular territory (further diagnoses within the same vascular territory were not included as poly-vascular disease).

Medical history and demographic information

Age and deprivation quintiles were assigned at the index date. Primary care EHR data[10] were used to identify the following prior to the inclusion date: presence of diabetes mellitus, dementia, respiratory disease, including chronic obstructive pulmonary disease (COPD) or asthma, chronic kidney disease (CKD) stage 3+, chronic liver disease (including cirrhosis, fibrosis, chronic hepatitis, fatty liver, sclerosis of the liver, unspecified alcoholic liver damage, or hepatic failure), hypertension, smoking status, and body mass index (BMI) (see Supplementary material for the classification of the smoking status and the BMI).

Reporting of incidence and prevalence

The incidence of ASCVD was reported as the number of patients receiving a first diagnosis of ASCVD within each year of the observation period. Patients developing ASCVD within two or more territories within the incident year were recorded as incident poly-vascular disease.

The prevalence of ASCVD was reported as the number of patients living with disease at the beginning of each year. If a patient was censored during a particular year, they were excluded from the prevalence count for the following year. Patients who developed ASCVD in more than one territory were classified as poly-vascular disease within the year they were thus identified. We expressed incidence and prevalence per 100,000, the denominator being the number of patients resident in Wales, registered with a GP submitting records to SAIL, and aged ≥18 in 1 January of the relevant year.

Lipid lowering therapy, testing, and control of lipids

Prescriptions for LLT and lipid results were identified from the primary care data. In each year of the study, we reported the (i) prescribed LLT regimen, (ii) documentation of lipid testing and lipid levels for each patient with follow-up data from the start to the end of each year (prevalent cases) and for incident cases with a full year of follow up data after the date of first diagnosis, (iii) the number and proportion achieving the ESC/EAS LDL-C target of <1.8 mmol//L (or ≥1.8 mmol/L), and (iv) the respective LLT regimen in the 90 days prior to the lowest documented LDL-C for each year.

Prescriptions for lipid lowering therapy (LLT), including statins, ezetimibe, fibrates, and prescription grade N-3 supplements, were identified. LLT was classified as follows: high-intensity statin (HI-statin), namely, atorvastatin ≥40 mg/d and rosuvastatin ≥20 mg/d; non-high-intensity (NI-statin), namely, any other statin prescription; combination statin, namely, a combination of ezetimibe and/or fibrate with either HI- or NI-statin; other treatments, namely, ezetimibe and/or fibrate without a co-prescription of a statin; and no lipid lowering treatment.

Statistical analysis

Multivariable binary logistic regression modelling was conducted to identify variables associated with (i) a prescription for HI-statin, (ii) a documented LDL-C in the incident year, and (iii) achievement of an LDL-C <1.8 mmol/L. In each set of models, the analysis was performed for incident ASCVD only, and the outcome was determined over the 12 months following entry into the cohort. In each case, a final model was determined by minimising the Akaike information criterion. The odds ratios for the outcome were estimated for each variable in the final model. Analyses were carried out using R version 3.5. All scripts used to generate the findings presented in this study are available in a GitHub repository for others to access: https://github.com/SwanseaUniversityDataScience/1483_ASCVD-Lipid-Management.

Results

A total of 370 971 patients with ASCVD were included in this study (see Supplementary material online, *Figure S1*), of whom 165 659 patients entered as a prevalent case (documented diagnosis of ASCVD between 1 January 2000 to 31 December 2009) and 205 312 patients received a first diagnosis of ASCVD during the study period (incident cases).

The mean age of incident cases was 68.3 (SD ±13.9) years, and 54.3% were male. In 2010, 15.7% of the incident cases had prior diagnoses of diabetes mellitus, increasing to 20.7% of incident cases in 2022. The mean age of prevalent cases (on entry into the study) was 71.4 (SD ±12.5) years; 55.2% were male, and 22.0% had a prior diagnosis of diabetes mellitus (*Table 1*).

Temporal trends in ASCVD

Prevalence

During the study period, the overall prevalence of ASCVD increased from 181 153 (8882 per 100 000) in 2010 to 207 747 (9398 per 100 000) in 2022 (*Figure 1A, 1B* and Supplementary material online, *Table S4*). Over the same period, the prevalence of IHD increased from 99 471 to 101,596, but the proportion of ASCVD patients with IHD decreased from 4877 to 4596 per 100 000; the prevalence of stroke increased from 33 588 to 45 492 (1647 to 2058 per 100 000); and PAD increased from 15 276 to 24 778 (749 to 1121 per 100 000). There was a less notable change in the prevalence of poly-vascular disease from 32 818 to 35 881 (1609 to 1623 per 100 000), of whom IHD was present in 90% in 2010 and 87% in 2022 (see Supplementary material online, *Table S4*). We have presented age-stratified incidence and prevalence across the study period in Supplementary material online, *Table S2* and Supplementary material online, *Figure S4*, including those with early onset (aged <60 years) and the very elderly (>85 years).

Incidence

In 2010, there were 15 512 incident cases of ASCVD (761 per 100 000 per year), increasing to 16 703 (772 per 100 000 per year) in 2019 (*Figure 1C, 1D*). In 2020, the first year of the COVID-19 pandemic, there was a decrease in the number of new ASCVD cases to 14 667 (673 per 100 000 per year), followed by an increase in 2021 to 16 206 (739 per 100 000 per year) and 16 394 (742 per 100 000 per year) in 2022 (see Supplementary material online, *Table S4*).

The annual incidence of IHD decreased from 8146 in 2010 to 7420 in 2022 (399 to 336 per 100 000 per year). Over the same period, the incidence of stroke and PAD increased from 4427 to 5014 (217 to 227 per 100 000 per year) and from 2213 to 3170 (109 to 143 per 100 000 per year), respectively. There was a less marked increase in the incidence of poly-vascular disease from 726 cases in 2010 to 790 in 2022 (36 per 100 000 per year in 2010 and 2022). Of the patients with incident poly-vascular disease, IHD was present in 86% in 2010, which decreased to 77% in 2022 (see Supplementary material online, *Table S5*).

Trends in LLT prescribing, lipid testing and control

Of the 370 091 patients identified with ASCVD, 315 754 patients had at least 1 year of follow-up data, including 154 235 (93.1%) prevalent cases identified prior to the study period and 161 519 (78.7%) incident cases during the study period (see Supplementary material online, *Figure S1* and Supplementary material online, *Table S6*). Incident patients who died within 1 year of first ASCVD diagnosis were older than those with at least 1 year follow-up (78.8 years (SD ± 12.0) vs. 66.6 years (SD ± 13.4)) and had higher rates of dementia (8.9% vs. 2.0%), diabetes

Table 1 Cohort baseline characteristics at entry into the study

	Prevalent	Incident													Overall
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	
	n =	n =	n =	n =	n =	n =	n =	n =	n =	n =	n =	n =	n =	n =	n =
	165659	15511	15037	15387	15525	15469	15678	16116	16153	16477	16704	14664	16204	16387	370971
Sex N (%)															
Male	91412	8219	7902	8175	8513	8516	8427	8638	8914	8989	9047	8162	8859	9103	202876
	(55.2%)	(53%)	(52.6%)	(53.1%)	(54.8%)	(55.1%)	(53.8%)	(53.6%)	(55.2%)	(54.6%)	(54.2%)	(55.7%)	(54.7%)	(55.6%)	(54.7%)
Age (years) (standard deviation)															
Entry to study	71.4	68.4	68.2	68.6	68.3	68.2	68.4	68.2	68.2	68.2	68.2	68.3	68.3	68.3	69.7
	(12.5)	(14.2)	(14.2)	(14.1)	(13.9)	(13.9)	(13.8)	(13.9)	(13.8)	(13.8)	(13.7)	(13.6)	(13.7)	(13.4)	(13.3)
Comorbidities N (%)															
Respiratory	35539	2942	2914	3057	3144	3143	3349	3388	3494	3656	3743	3155	3616	3636	78776
disease	(21.5%)	(19.0%)	(19.4%)	(19.9%)	(20.3%)	(20.3%)	(21.4%)	(21.0%)	(21.6%)	(22.2%)	(22.4%)	(21.5%)	(22.3%)	(22.2%)	(21.2%)
Dementia	5923	413	452	457	437	441	456	433	464	489	507	481	505	439	11897
	(3.6%)	(2.7%)	(3.0%)	(3.0%)	(2.8%)	(2.9%)	(2.9%)	(2.7%)	(2.9%)	(3.0%)	(3.0%)	(3.3%)	(3.1%)	(2.7%)	(3.2%)
Chronic kidney	35800	2150	2101	2223	2357	2219	2193	2098	1971	1978	1931	1658	1703	1654	62036
disease stage 3+	(21.6%)	(13.9%)	(14.0%)	(14.4%)	(15.2%)	(14.3%)	(14.0%)	(13.0%)	(12.2%)	(12.0%)	(11.6%)	(11.3%)	(10.5%)	(10.1%)	(16.7%)
Liver disease	1746	196	188	195	223	251	242	287	352	401	443	407	509	538	5978
	(1.1%)	(1.3%)	(1.3%)	(1.3%)	(1.4%)	(1.6%)	(1.5%)	(1.8%)	(2.2%)	(2.4%)	(2.7%)	(2.8%)	(3.1%)	(3.3%)	(1.6%)
Diabetes	36403	2434	2358	2554	2660	2709	2912	2967	3055	3202	3345	2986	3332	3396	74313
	(22.0%)	(15.7%)	(15.7%)	(16.6%)	(17.1%)	(17.5%)	(18.6%)	(18.4%)	(18.9%)	(19.4%)	(20.0%)	(20.4%)	(20.6%)	(20.7%)	(20.0%)
Hypertension	98924	7554	7369	7612	7652	7577	7603	7897	7825	7919	8152	7353	7687	7698	198822
	(59.7%)	(48.7%)	(49.0%)	(49.5%)	(49.3%)	(49.0%)	(48.5%)	(49.0%)	(48.4%)	(48.1%)	(48.8%)	(50.1%)	(47.4%)	(47.0%)	(53.6%)
Smoker status N (%)															
Active smoker[a]	30111	3736	3824	3871	3947	3717	3771	3756	3686	3736	3773	3290	3738	3617	78573
	(18.2%)	(24.1%)	(25.4%)	(25.2%)	(25.4%)	(24.0%)	(24.1%)	(23.3%)	(22.8%)	(22.7%)	(22.6%)	(22.4%)	(23.1%)	(22.1%)	(21.2%)
Weight N (%)															
Obese[a]	51402	4135	4189	4198	4440	4462	4624	4848	4971	5189	5306	4688	4988	5253	112693
	(31.0%)	(26.7%)	(27.9%)	(27.3%)	(28.6%)	(28.8%)	(29.5%)	(30.1%)	(30.8%)	(31.5%)	(31.8%)	(32.0%)	(30.8%)	(32.1%)	(30.4%)

[a]See Supplementary material online, *Table S3* for further cohort characteristics of weight, smoking status, and deprivation quintile.

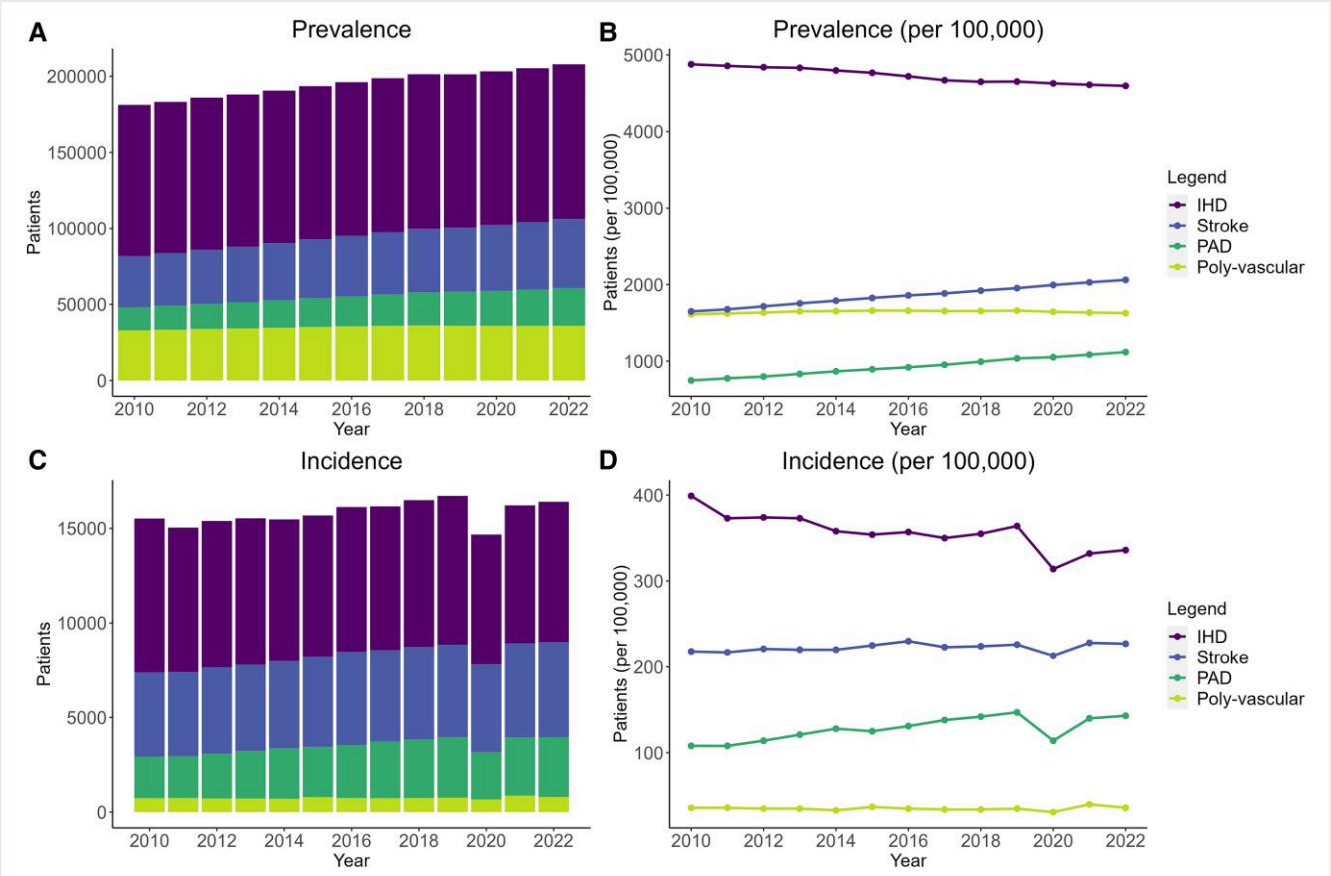


Figure 1 Prevalence and incidence of atherosclerotic cardiovascular disease according to vascular disease territory. Prevalence (top) and incidence bottom between 2010 and 2022. Absolute numbers (left) and per 100 K of the population (right).

(21.3% vs. 17.9%), and CKD (24.3% vs. 11.2%). A lower proportion comprised male patients (46.9% vs. 55.4%) (see Supplementary material online, *Table S6*).

Prescription of lipid lowering therapy

LLT prescription in prevalent ASCVD patients

Over the study period, the proportion of prevalent patients prescribed LLT decreased from 75.3% in 2010 to 67.1% in 2022. The proportion prescribed combination LLT decreased across the study period from 4.3% in 2010 to 2.4% in 2022; the proportion prescribed HI-statin therapy increased from 9.4 to 25.2%; NI-statin prescription decreased from 59.6 to 38.2%; other LLT decreased from 1.9 to 1.3%; and the proportion of patients receiving no LLT increased from 24.7 to 32.9% (*Figure 2* and Supplementary material online, *Table S7*).

Of the prevalent patients not prescribed HI-statin in 2010 and 2022, only 6.5% of this group in 2010 and 15.1% in 2022 had a previously documented prescription for HI-statin (see Supplementary material online, *Table S8a*).

HI-statin prescription was consistently higher amongst patients with IHD (increasing from 10.9% in 2010 to 28.0% in 2022) and poly-vascular disease (11.8% in 2010 increasing to 31.0% in 2022) across the whole study period than in patients with stroke (4.7% in 2010 to 21.6% in 2022) or PAD (3.9% in 2010 to 10.6% in 2022) (*Figure 3* and Supplementary material online, *Table S7*). Notably, in poly-vascular patients with both PAD and IHD, the prescription of HI-statin therapy was higher (11.8% in 2010 increasing to 30.7% in 2022) compared to those with PAD alone (see Supplementary material online, *Table S9*).

A greater proportion of the prevalent patients with PAD were not prescribed any LLT (43.6% in 2010 increasing to 51.7% in 2022) when compared to patients with IHD (23.4% in 2010 increasing to 30.8% in 2022), stroke (28.9% in 2010 increasing to 35.0% in 2022), or poly-vascular disease (16.5% in 2010 increasing to 24.3% in 2022). Furthermore, a lower proportion of poly-vascular patients with the combination of IHD and PAD were not prescribed any LLT (30.2% in 2010, increasing to 31.3% in 2022) compared to those with PAD alone.

LLT prescription in incident ASCVD cases

Amongst the incident cases, 70.6% were prescribed LLT in 2010 and 69.1% in 2021. Across this period, the proportion of incident ASCVD patients prescribed combination therapy increased from 2.4 to 2.6%; HI-statin therapy increased from 10.0 to 37.7%; NI-statin decreased from 57.3 to 28.1%; and the proportion of patients who were not prescribed any LLT increased from 29.4 to 30.9% (*Figure 3* illustrating 2010 and 2021 and data in Supplementary material online, *Table S7*).

Only 1.8% of those with an incident diagnosis of ASCVD in 2010 who were not prescribed HI-statin LLT had a previously documented prescription for HI-statin, increasing slightly to 3.8% of those incident cases in 2021 (see Supplementary material online, *Table S8b*).

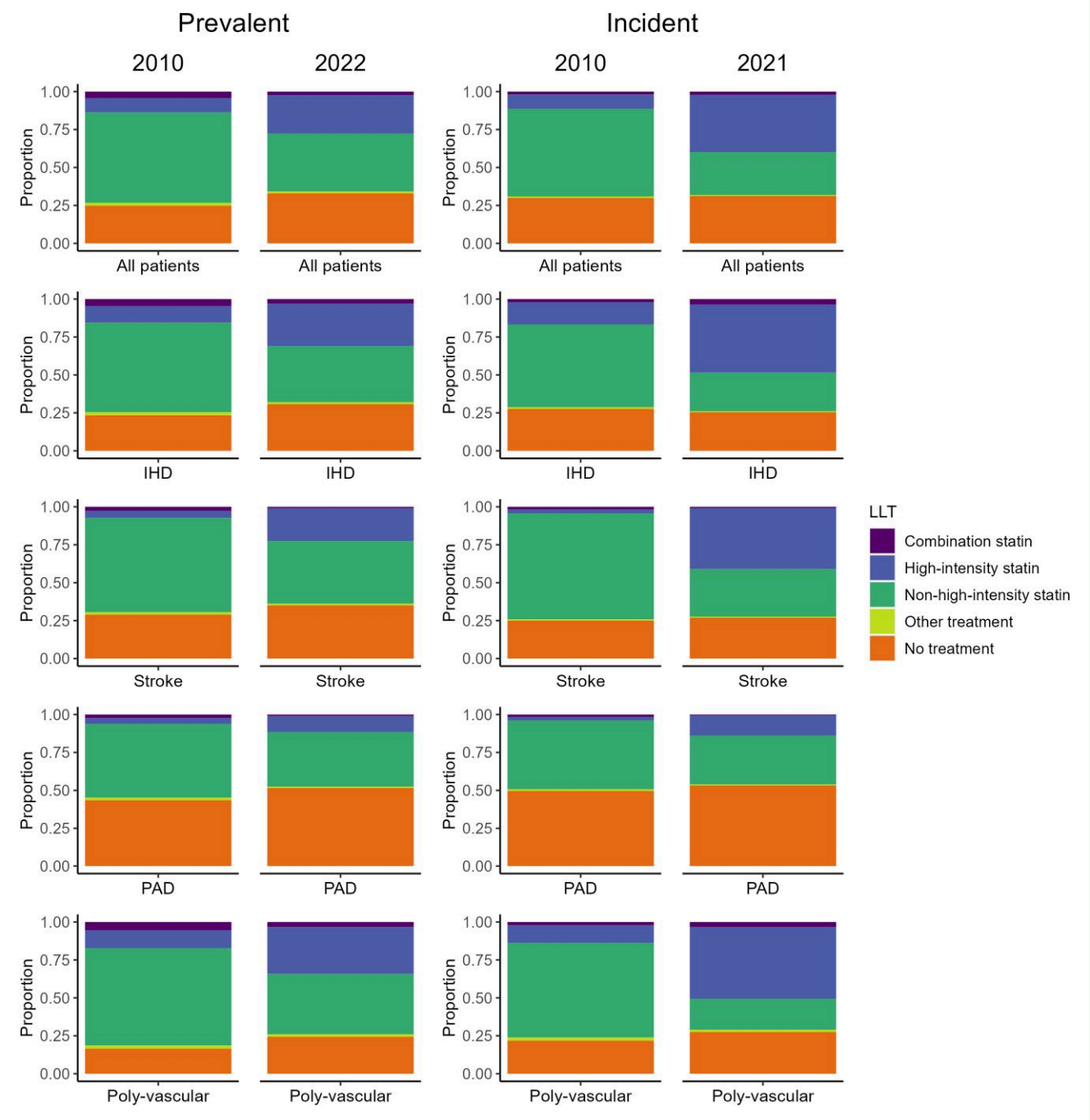


Figure 2 Prescribed lipid lowering treatment in prevalent and incident cases in the whole ASCVD population and according to the vascular disease territory (during the first and last years of study where 1 year of complete follow-up data was available).

Throughout the study period, the prescribing of HI-statins was consistently higher amongst patients with an incident diagnosis of IHD (increasing from 15.3% in 2010 to 44.8% in 2021) or poly-vascular disease (12.6% in 2010 increasing to 48.4% in 2021) than patients with stroke (3.2% in 2010 increasing to 40.6% in 2021) or PAD (2.7% in 2010 increasing to 13.0% in 2021) (*Figure 3* and Supplementary material online, *Table S7*).

In the same period, a greater proportion of patients with incident PAD were not prescribed any LLT (48.6% in 2010 to 53.4% in 2021) compared to patients presenting with stroke (24.5% in 2010 to 26.5% in 2021), IHD (27.3% in 2010 to 25.0% in 2021) or poly-vascular disease (20.8% in 2010 to 26.6% in 2021).

Male sex and diabetes were independently associated with a greater likelihood of a prescription for HI-statin, whereas incident diagnosis of stroke or PAD (compared to IHD), respiratory disease, dementia, liver disease, and CKD were associated with a lower likelihood of HI-statin prescription according to multivariable regression analyses (see Supplementary material online, *Table S10*).

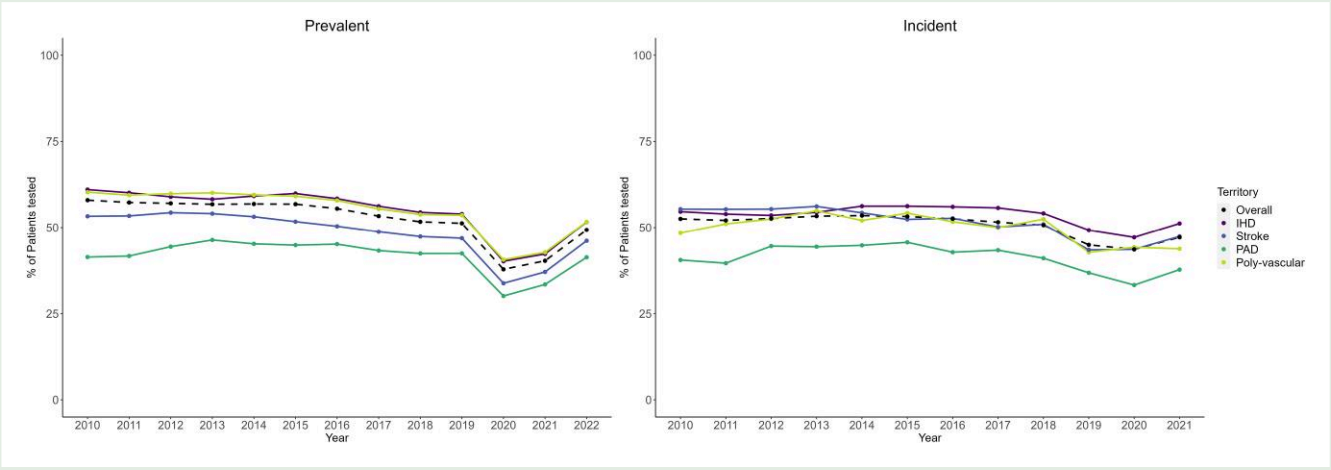


Figure 3 Proportion of prevalent and incident patients with a documented LDL-C test by vascular disease territory and year.

Lipid testing

Lipid testing in prevalent ASCVD cases

The proportion of overall prevalent cases with a documented LDL-C test between 2010 to 2016 ranged between 55.5 and 58.0%, which gradually decreased to between 51.3 and 53.3% (2017–2019), dropped further in 2020 and 2021 to 37.8 and 40.3%, respectively, and subsequently increased in 2022 to 49.3% (*Figure 3* and Supplementary material online, *Table S11*).

Lipid testing in incident cases

The proportion of incident cases with a documented LDL-C test between 2010 and 2018 ranged between 50.7 and 53.5%, decreasing in 2019 and 2020 to 45.0 and 43.6%, respectively, and slightly increasing in 2021 to 47.1%.

Documentation of LDL-C was highest for patients with IHD in both incident and prevalent groups, followed by stroke, with PAD patients least likely to have their LDL-C levels documented (*Figure 3*). Characteristics independently associated with a documented LDL-C level in the first year of diagnosis included male sex, diabetes, hypertension, and LLT prescription (compared to no prescribed LLT) (see Supplementary material online, *Table S12*). Meanwhile, a diagnosis of stroke or PAD (compared to those with an index diagnosis of IHD), dementia, and CKD were independently associated with a lower likelihood of LDL testing.

LDL-C control

The proportion of prevalent and incident patients with documented LDL-C achieving ESC/EAS LDL-C targets improved during the study period, most notably in those with IHD (*Figure 4* and Supplementary material online, *Table S13*). However, the overall proportion achieving target levels remained low, especially in those with PAD (see Supplementary *Figures 3* and *4* and Supplementary material online, *Table S18* for age-stratified achievement of LDL-C targets and age-stratified prescribed LLT).

The mean of the lowest documented LDL-C levels in the prevalent ASCVD population during 2010 was 2.3 mmol/L (SD ±0.9), modestly decreasing to 2.2 mmol/L (SD ±0.9) in 2022 (see Supplementary material online, *Table S15*). The mean lowest documented LDL-C for patients with prevalent PAD was 2.5 mmol/L (SD ±0.9) in 2010 and 2.4 mmol/L (SD ±1.0) in 2022. Patients with PAD had higher LDL-C readings than those with IHD (2.3 to 2.1 mmol/L), stroke (2.3 to 2.2 mmol/L), and poly-vascular disease (2.2 to 2.0 mmol/L).

The mean lowest documented LDL-C for the incident ASCVD cases in 2010 was 2.4 mmol/L (SD ±1.0) in 2010, decreasing to 2.1 mmol/L, (SD ±0.9) in 2021 (*Figure 4* Supplementary material online, *Table S15*). The mean lowest documented LDL-C for incident patients with PAD was 2.7 mmol/L (SD ±1.1) in 2010, decreasing to 2.5 mmol/L (SD ±1.0) in 2021, depicting levels that were consistently higher than the corresponding LDL-C results for patients with IHD (2.3 mmol/L, (SD ±0.9) in 2010 decreasing to 2.0 mmol/L (SD ±0.9) in 2021), stroke (2.4 mmol/L, (SD ±0.9) decreasing to 2.1 mmol/L (SD ±0.9) in 2021), or poly vascular disease (2.2 mmol/L, (SD ±0.9) decreasing to 2.0 mmol/L, (SD ±0.9) in 2021).

In 2010, 32.7% of the prevalent ASCVD cases with documented LDL-C levels achieved an LDL-C <1.8 mmol/L increasing to 44.0% in 2022 (*Figure 4*). Amongst the overall incident cases in 2010, 34.0% achieved an LDL-C <1.8 mmol/L increasing to 47.1% in 2021. A lower proportion of patients with PAD achieved an LDL-C <1.8 mmol/L than those with IHD, stroke, or poly-vascular disease in both prevalent and incident populations across the whole study period (*Figure 4* and Supplementary material online, *Table S13*).

Considering both prevalent and incident patients who achieved an LDL-C <1.8 mmol/L, a greater proportion were prescribed HI-statin therapy, and a lower proportion were not prescribed any LLT (within 90 days prior to the lowest documented LDL-C result) when compared to those who had LDL-C levels ≥1.8 mmol/L across each year of the study (*Figure 5*).

Characteristics independently associated with an LDL-C <1.8 mmol/L in the incident year included male sex, diabetes mellitus, and any LLT prescription, whereas a diagnosis of stroke or PAD (compared to IHD) and a history of dementia were associated with a likelihood of LDL-C levels ≥1.8 mmol/L (see Supplementary material online, *Table S16*) on multivariable logistic regression analysis.

Discussion

This study was conducted to describe trends in the incidence and prevalence of ASCVD, including its clinical subgroups, and evaluate

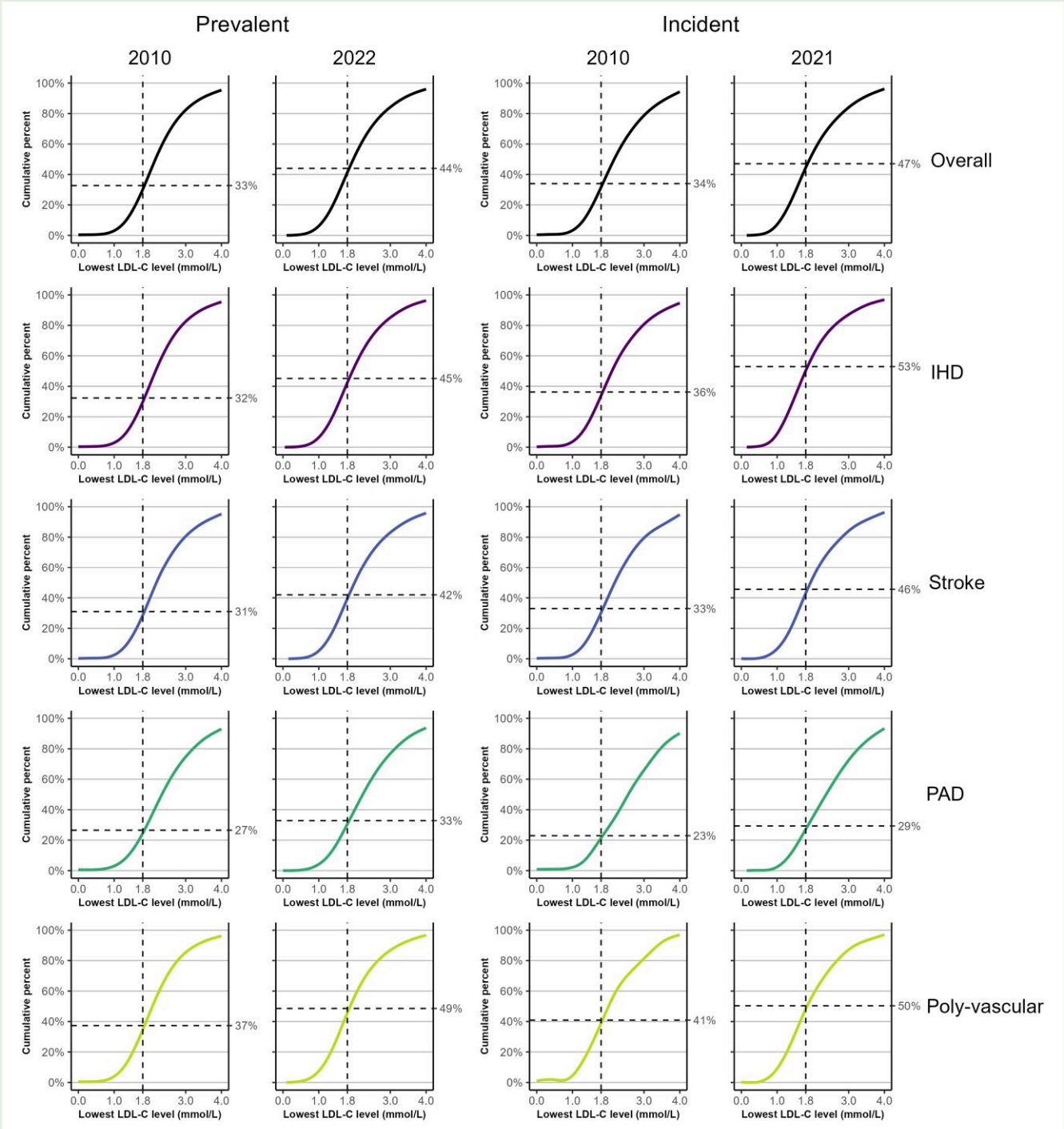


Figure 4 Lowest low-density cholesterol (LDL-C) for prevalent cases in 2010 and 2022 and incident cases in 2010 and 2021 by vascular disease territory.

the treatment, testing, and control of lipids at a population level in these patients. An increase in the prevalence of ASCVD across the study period was observed, with an increasing prescription of HI-statin therapy, especially amongst incident cases. Documentation of LDL-C levels decreased across the study period in both incident and prevalent populations, although a greater proportion of those with documented LDL-C levels achieved acceptable LDL-C control (below ESC/EAS target of 1.8 mmol/L). Notably, patients with IHD were more likely to be treated with HI-statin LLT to achieve lower LDL-C levels, including ESC/EAS targets, compared to those with stroke and PAD, with the latter being consistently the least effectively managed.

The prevalence of ASCVD increased by over 14% over the study period, while the proportion of the population with documented ASCVD

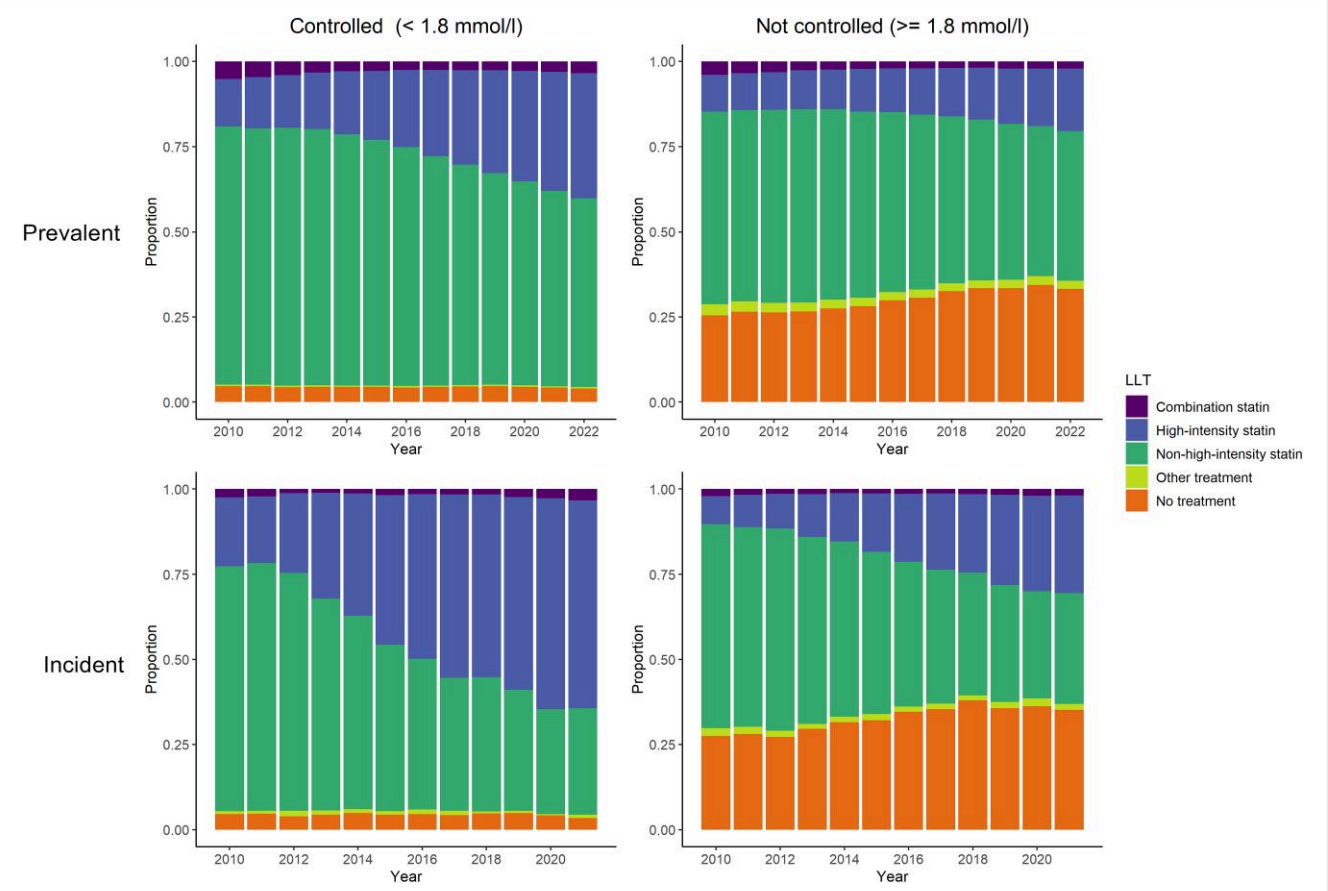


Figure 5 Prescribed lipid lowering therapy in the 90 days prior to the lowest LDL-C recorded each year for all prevalent (top) and incident ASCVD cases (bottom), where LDL-C was <1.8 mmol/L (left) and ≥1.8 mmol/L (right).

increased by 5.8%. The difference was attributed to the overall growth of the population. Despite a 2.1% increase in the absolute numbers of patients with IHD, there was a 5.8% decrease in the proportion of population with IHD. Stroke had the greatest absolute increase in prevalence over time in both individual cases and by proportion of the population. However, PAD had the largest relative increase in prevalence over time, with a 62% increase in numbers from 2010 to 2022 and a 50% relative increase in cases per 100 K of the population. The change in incidence of PAD over time was also notable with a 43% increase in the number of new presentations and a 31.2% increase in cases per 100 K of the population.

Although a decrease in the numbers of active smokers was noted, there was a substantial increase in diabetes, liver disease, and obesity, which may have contributed to the observed trends of the ASCVD presentation.

The population estimates of the prevalence of IHD, PAD, and stroke are often conflicting.[12–15] Results from global studies will be influenced over time by differences and changes in population size, age, prosperity, and healthcare infrastructure.[15] In contrast to our data, previous research conducted using primary care records in England reported a decline in the incidence of symptomatic PAD from 38.6 to 17.3 cases per 10 000 patient-years between 2000 and 2014, despite the increase of diabetes within the population.[13] Another study that also used primary care records in England between 1998 and 2008 reported a decrease in stroke incidence, but an increasing prevalence, presumably due to increasing survival.[14] Differences in methodologies, especially included data sources, classification and confirmation of disease, and/or population risk factors could explain these contradictory results. This study, which incorporates both primary care and hospital diagnostic data, may provide a more comprehensive case documentation.

An increase in the prescription of HI- and a decrease in NI-statin therapy amongst both the prevalent and incident cohorts was observed. These data suggest that statin intensification in the treated population accounts for most of the observed improvements in LDL-C control, particularly in the IHD subgroup, rather than a wider LLT coverage at a population level, with over one in four patients in both prevalent and incident groups not prescribed any LLT in the final years of the study. Only a small proportion of the incident cases who were not prescribed HI-satin therapy had previously been prescribed HI-statin therapy in primary care, suggesting that (HI-)statin intolerance cannot fully explain its suboptimal use during the study period. The increase in the prescription of HI-statin therapy over time amongst incident cases vs. prevalent cases suggests that better care of newly presenting patients is a major driver of improved control in the wider ASCVD population, although remaining underutilised in these patients.

Amongst the incident group, there was only a slight variation in the overall proportion of patients with a documented LDL-C level between 2010 and 2018. The marked decrease in the LDL-C documentation observed amongst incident cases during 2019–20 is most likely to be

explained by the Coronavirus 9 (COVID-19) pandemic, given the slight rebound in testing seen in 2021.

Amongst the prevalent cases, a similar decrease in testing was observed during 2020–21, with a recovery in 2022, again likely to be explained by restrictions and changes in healthcare provision during the COVID-19 pandemic. Prior to this, amongst the prevalent population, a small downward trend in LDL-C testing from 2016 onwards was noted, coinciding with the relaxing of the Quality outcome Framework (QoF) (a payment for performance scheme) for GPs in Wales, which previously included incentives for lipid testing and the prescription of LLT in patients with PAD, stroke, and IHD. Other studies observing the withdrawal of QoF (in Scotland) also reported a reduction in the recorded quality of care for performance indicators.[16]

Numerous studies have explored the impact of the COVID-19 pandemic on CVD diagnosis, risk management, and outcomes. Studies that have included the dispensing of LLT, as well as antihypertensives and antidiabetic agents, as a proxy for the CVD population risk showed a decrease in the dispensing of these drugs during the COVID-19 pandemic, with model estimates of the associated increase in CVD events.[17] Although this study was not designed to assess the interactions between ASCVD diagnosis, risk management, and outcomes or the impact of COVID-19 on these factors, the data in this study show a drop in both the documented incidence of ASCVD and the testing of lipids amongst those with an established ASCVD diagnosis during the height of the pandemic period. While this observed change during the pandemic is of concern, data from this study highlights the gap in the provision of evidence-based, prognostically beneficial, and guideline-approved medication and risk factor management across the entire study period beyond the COVID-19 pandemic.

The low achievement of guideline-directed LDL-C targets and the underutilisation of LLT had been previously reported.[18–23] These studies had been undertaken in high- or very high-risk ASCVD patients and reported higher use of LLT compared to our study. The EUROSPIRE-V study included patients hospitalised for recent ACS, reporting that 84% were prescribed LLT (range 75–98% between 27 countries), half of whom were prescribed HI-statin therapy.[21] The DYSIS-II study included patients attending a scheduled physician visit for stable coronary heart disease (CHD) and patients hospitalised due to an acute coronary syndrome (ACS), reporting that over 90% of both stable CHD and ACS patients were prescribed LLT.[19]

A previous study examining trends in the prevalence and incidence of symptomatic PAD in English GPs from 2012 to 2014 reported that two-thirds were prescribed statins, which was slightly higher than the overall prescription of LLT observed amongst those patients with PAD in this study.[13]

A Danish population study showed that patients with critical limb-threatening ischaemia (CLTI) were less likely to fill a prescription for LLT, as well as other evidence-based therapies, compared to those with myocardial infarction (MI).[24] The investigators also found that patients with CLTI with a history of MI were more likely to fill prescriptions than those with CLTI alone, similar to observations in this study where patients with PAD and IHD were more likely to be prescribed LLT compared to those with PAD alone.

An increase in the prescription of HI-statin and achievement of the target amongst those with documented LDL-C across the overall ASCVD population were observed over the course of this study. However, patients with PAD were not only the least likely to be prescribed HI-statin therapy, they were also the least likely to have LDL-C documented or achieve target LDL-C levels. Although the precise role of lipids in the pathophysiology and epidemiological relationships may differ between IHD, PAD, and stroke, professional clinical guidelines support intensive LLT for patients with each of these ASCVD conditions.[4,5] Although the reasons for the observed differences in lipid testing, treatment, and control between disease subgroups cannot be determined, the differences in treatment pathways and clinician priorities between the particular specialist care services may be highly relevant and provide a potential target for preventive pathway optimisation.

Strengths and limitations

To the best of the study team's knowledge, this is the first study to describe contemporaneous national trends in the incidence and prevalence of ASCVD across the three vascular territories. Using linked longitudinal primary and secondary care data sources enabled the investigation of a population cohort over multiple years across multiple data sources, providing a comprehensive picture of disease patterns in a developed nation.

The criteria for the identification of ASCVD included major clinical events, such as MI, stroke, or peripheral vascular intervention, as well as symptoms of disease, such as angina or intermittent claudication, and diagnostic codes that reported the presence of atherosclerotic disease in the cerebrovascular, cardiac, and peripheral vascular systems that may have not resulted in major clinical events. The study team believes that taking this comprehensive approach to classification of disease from routinely held data would provide a more accurate picture of the trends in incidence and prevalence of ASCVD and effectiveness of lipid management in the population.

The design of this study allowed the identification of incident cases from 2010 onwards, providing a sufficient period to describe changing trends in the presentation of ASCVD, the prescription of LLT, and LDL-C control. Patients with diagnoses of ASCVD prior to this period were entered as prevalent cases, limiting the misidentification of patients with existing ASCVD diagnoses as incident cases, where diagnostic codes may have been re-entered in the primary and/or secondary care data sources.

The ESC/EAS clinical guidelines recommend that patients with clinical ASCVD are prescribed LLT and treated to target LDL-C level according to a consistent approach, regardless of the vascular territory/territories involved. In this study, an ESC/EAS LDL-C target of 1.8 mmol/L for high/very high-risk patients with ASCVD was used in line with the guideline recommendation for most of the observation period (2011–19).[7,25] In 2019, a more stringent target of 1.4 mmol/L was recommended. A lower proportion of patients would have achieved this target (13.6% in 2010 to 22.6% of the overall prevalent cohort in 2022) compared to a target of 1.8 mmol/L (32.7 to 44.0% over the same period) (Supplementary *Tables 13* and *14*). It is acknowledged that the ESC/EAS guidelines have also recommended a reduction of LDL-C of >50% from the baseline. However, it could not be confidently determined whether (or indeed which of) the LDL-C results entered in the primary care record were true 'pre-treatment' levels from which to ascertain a reduction. Nevertheless, it is likely that having this additional information would have identified an even greater proportion of patients not achieving the LDL-C target.

The LDL-C levels documented in the primary care data were recorded to evaluate the effectiveness of lipid management in the setting where the majority of long-term CVD risk management is delivered in the UK. Within each year of the study, the documentation of LDL-C was slightly more frequent amongst the prevalent cases than the incident cases, contrary to expectation. It is possible that amongst those patients where the initial diagnosis of ASCVD was made in secondary

care, the initial assessment of lipids may have also been undertaken in secondary care. While this information would be available to clinicians in primary care via shared pathology records, primary care clinicians may not always have documented these lipid levels in their GP data, which may, at least in part, account for the less frequent documentation of LDL-C in the year following incident diagnosis.

No patients prescribed the proprotein convertase subtillsin/kexin type 9 (PCSK9) monoclonal antibodies (MAb) evolocumab or alirocumab were identified. These agents were approved for use within the UK National Health Service in 2016.[26,27] Similarly, no patients prescribed bempedoic acid or inclisiran (approved for use in NHS Wales in 2020 and 2021, respectively) were identified.[28,29] Although the prescription of all these treatments has mainly been through specialist hospital outpatient services, with their data not available for this study, the uptake of these agents has been low. Therefore, it is unlikely that the absence of data on the prescription of these therapies would have had any meaningful impact on the wider implications of our results.

In this study, we took a liberal approach to reporting whether patients were prescribed LLT, with only a single prescription required to be classified as receiving LLT. It was not possible to account for compliance or adherence to therapy, which has frequently been reported to be low. Therefore, our results represent the best-case scenario, with the real-world use of LLT likely to be lower than that reported here.[30,31]

As with all real-world observational studies using anonymised, routinely collected data, it is not possible to account for the accuracy or validity of observations and events that were entered (or not) into the respective datasets. We have only been able to evaluate lipid results and LLT documented in the primary care record. Whilst this may not provide a fully comprehensive record of testing and control, most long-term lipid management is undertaken in primary care in Wales and almost all prescriptions for LLT. As such, we believe that our data provide a comprehensive overview of care for the vast majority of the general secondary prevention population. Changes in diagnostic processes and criteria may account for changes in the documentation of ASCVD. Although it was not a major objective of our study, we did note an increasing proportion of new diagnoses of ASCVD being made in the secondary care setting over time (see Supplementary material online, table *S17*).

The nature of using real-world data does not allow us to explore why so few of this very high-risk cohort were prescribed LLT, had lipids assessed, or achieved the target. However, we offer several suggestions. Differences in speciality training and clinical focus may explain some of the observed differences between those with stroke or PAD compared to those presenting with IHD. Patients with ASCVD often have care directed by both secondary and primary care. The responsibility for risk factor management often falls between these clinical settings; with the lack of time available to clinicians, or robust systems/pathways to support patient care, or reimbursement/investment for implementing treatment guidelines opportunities to optimise risk factor management is often missed, as these data demonstrate.

Conclusions

This study has described the changing trends in the presentation of ASCVD across multiple vascular territories, highlighting the low rate of LLT prescription and low achievement of the guideline-recommended target lipid levels across a very high-risk patient population. Study data suggest that to realise the full benefit from the implementation of lipid lowering interventions proven in randomised trials and recommended by the national and international guidelines, a more robust implementation strategy will be required, particularly in those with stroke and PAD.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Disclosures

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Declarations

DH, DK, AA, MG, and JH were responsible for data curation, methodology, and formal analysis. DH, DK, AA, MG, JH, and CW contributed to the interpretation of the data, draft writing, editing, and preparation of the final manuscript. JH, CH, and LP were responsible for funding acquisition. All authors were responsible for the final manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Access to data and ethical approval

The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure the proper and appropriate use of SAIL data. When access has been approved, it is gained through a privacy-protecting trusted research environment (TRE). SAIL has established an application process to be followed by anyone who would like to access data via https://saildatabank.com/data/apply-to-work-with-the-data. This project was approved by the IGRP (SAIL project number 1483). Participant consent was not required by the IGRP as all data were anonymised prior to the study.

Conflict of interest: None declared.

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