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RAPID COMMUNICATION
CVD risk factors

Treatment and control of low-density lipoprotein cholesterol in patients in Wales: impact of depression

Carla White[1], Richard Summers[1], Ann John[1], David P.J. Osborn[2], Keith Lloyd[1], Ashley Akbari [1], Michael B. Gravenor[1], Julian P. Halcox[1], and Elizabeth A. Ellins [1]*

[1]Faculty of Medicine, Health and Life Science, Swansea University Medical School, Swansea University, Singleton Park, Swansea SA2 8PP, UK; and [2]Division of Psychiatry, University College London, Maple House, Wing A Floor 6 Tottenham Court Road, London W1T 7NF, UK

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Optimal lipid management is a core component of atherosclerotic cardiovascular disease (ASCVD) prevention. However, the effectiveness of lipid management in patients with depression in the wider ASCVD population is unknown. Our study explored relationships between guideline-recommended lipid-lowering therapy (LLT) prescribing and achievement of guideline-recommended low-density lipoprotein cholesterol (LDL-C) targets following ASCVD diagnosis in patients with/without depression.

We conducted a retrospective observational cohort study (2010–19) using individual-level linked anonymized routinely collected electronic health record data sources held in the Secure Anonymized Information Linkage (SAIL) Databank trusted research environment.[1,2] Patients 18 years or over, with/without depression (identified using Read codes in General Practice data)[3] and without documentation of an ASCVD diagnosis (coronary artery, peripheral artery or cerebrovascular disease) at baseline were included (see Ellins *et al.* and https://github.com/carlalwhite/ASCVD_lipids_additional_information).[3] ASCVD diagnoses were identified during the study period, as was depression pre- and post-ASCVD documentation. Prescriptions within primary care for LLT, including statins (high and normal intensity), ezetimibe, fibrates, and prescription-grade *n*-3 supplements were identified. LLT initiation was taken as the date of the first prescription. Patients prescribed LLT before their ASCVD diagnosis were excluded.

The lowest LDL-C, within the year following ASCVD diagnosis, was recorded. The number (and proportion) of patients achieving the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) 2016 lipid guidelines targets for LDL-C of <1.8 mmol/L were identified.[4]

Outcome variables were any LLT prescription within 6 months of first ASCVD diagnosis and documented LDL-C levels <1.8 mmol/L within 1 year of diagnosis. Logistic regression analysis explored associations between depression and outcome variables, adjusting for the variables in *Figure 1C*. R version 2024.24.0 was used for analyses.

The cohort consisted of 56 463 ASCVD patients, of whom 1937 (3.4%) had depression documented pre-ASCVD diagnosis, 879 (1.6%) developed depression post-ASCVD diagnosis, and 53 647 (95%) were non-depressed. Depression pre-ASCVD patients [57.3 (SD 17.4) years] were 11.5 years younger at ASCVD diagnosis than non-depressed [68.8 (SD 14.7) years] and included a greater proportion of females [pre-ASCVD 956 (49.4%), post-ASCVD 388 (44.1%), and non-depressed 21 900 (40.8%)].

Only 17 166 (32.0%) were prescribed LLT within 6 months of first ASCVD diagnosis, with non-depressed patients less likely to be prescribed LLT than the depressed (30.2% non-depressed vs. 39.8% depression pre-ASCVD and 56.2% depression post-ASCVD, $P < 0.001$). LLT was initiated earlier post-ASCVD diagnosis in depressed patients compared with the non-depressed group (*Figure 1A*).

In the multivariable analysis (*Figure 1C*), depression was associated with LLT prescription within 6 months of ASCVD diagnosis (a stronger association was noted in the depression post- vs. depression pre-ASCVD group), and females were prescribed LLT less frequently than males.

Only 16 115 (28.5%) patients had a LDL-C level documented during the first year post-ASCVD diagnosis. A higher proportion of patients prescribed LLT had LDL-C assessment (57.0% tested vs. 43.0% not tested), as did depressed patients (28.1% non-depressed, 33.8% depression pre-ASCVD, and 43.1% depression post-ASCVD).

Of the 28.5% patients with a documented LDL-C level within 1 year post-ASCVD diagnosis, those with depression pre-ASCVD were less likely to achieve the <1.8 mmol/L target (31.5% depression pre-ASCVD vs. 35.1% non-depressed and 35.6% depression post-ASCVD).

Unsurprisingly, patients prescribed LLT were more likely to achieve lower LDL-C levels than those not on LLT (*Figure 1B*), but among those prescribed LLT, those with depression pre-ASCVD were least likely to have documented LDL-C < 1.8 mmol/L post-ASCVD diagnosis. However, differences in proportions achieving an LDL-C < 1.8 mmol/L

* Corresponding author. Tel: +44 1792 295092, Email: e.a.ellins@swansea.ac.uk

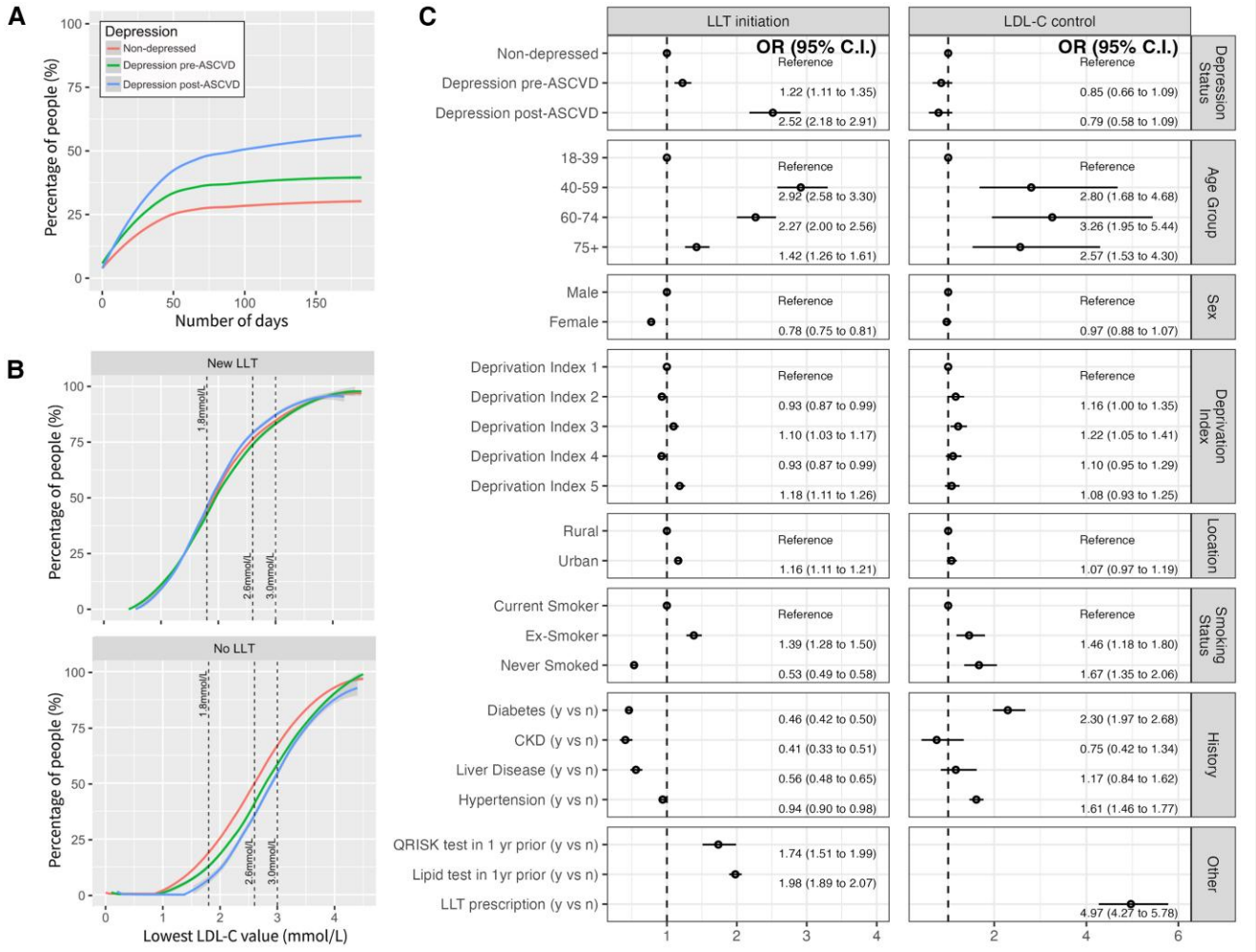

Figure 1 (*A*) Time in days from diagnosis of atherosclerotic cardiovascular disease to prescription of lipid-lowering therapy by depression group. (*B*) Minimum low-density lipoprotein level within 1 year of atherosclerotic cardiovascular disease diagnosis in those with documented results by lipid-lowering therapy status [number tested post-atherosclerotic cardiovascular disease diagnosis = 16 115 (28.5%) of cohort]. (*C*) Multivariable analysis of lipid-lowering therapy prescription within 6 months of atherosclerotic cardiovascular disease diagnosis and achievement of European Society of Cardiology guideline target of low-density lipoprotein <1.8 mmol/L within 1 year of atherosclerotic cardiovascular disease diagnosis. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; Deprivation, Welsh Index of Multiple Deprivation, 1 most deprived—5 least deprived; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

between the depression groups were much smaller for those prescribed LLT than for those who were not.

LLT prescription and age (up to 75+ years) were associated with documentation of LDL-C < 1.8 mmol/L within 1 year post-ASCVD diagnosis, but depression status and sex were not following multivariable analysis (*Figure 1C*).

Fewer than 1 in 3 patients developing ASCVD during the study were prescribed LLT within six months of ASCVD diagnosis, although those with depression (both pre- and post-diagnosis) were somewhat more likely to be prescribed LLT than those without. Furthermore, lipid testing rates were very low, and achievement of LDL-C target <1.8 mmol/L was also low within the first year post-ASCVD diagnosis, but similar in those with and without depression.

Notably and concerningly, those with prior depression were diagnosed with ASCVD at a much younger age than those without, despite their lower prevalence of diabetes and hypertension. This may reflect an accelerated rate of accumulation of cardiometabolic dysfunction, unhealthy lifestyle, and physical conditions in those with depression.[5,6] Remarkably, patients with depression were no more likely to achieve ESC/EAS guideline targets despite greater prescribing of LLT and more frequent LDL-C monitoring, suggesting a more intensive management strategy may be required. This may include greater attention to adherence to LLT and behavioural and physiological factors, all of which are known to occur in patients with depression.[7–9] The 2016 ESC/EAS guideline targets were used for these analyses as they were similar to previous versions of the guidelines and covered the period of the study.[4] The 2019 guideline with a lower LDL-C target was not in place for the period of study and was not achieved by most patients, indicating an incremental therapeutic gap.

In general, LLT prescribing was very low (32% of ASCVD), with fewer patients prescribed LLT than not, irrespective of depression status, despite a class 1A guideline-recommended indication for LLT. We

cannot identify all underlying reasons in a study of this design without direct access to patients and practitioners. Possible explanations include patient reluctance due to concern regarding side effects and choosing lifestyle changes, as well as clinician inertia.

As with many studies using routinely collected observational data, the information was not originally gathered for research purposes, and some inaccuracies of data entry and data omission may have occurred, but importantly do represent real-world care delivery. We are unable to investigate the impact of adherence to LLT on lipid control as dispensing and pill consumption data are not routinely available within the SAIL Databank.

In conclusion, whilst ASCVD patients with depression were more likely to be prescribed LLT, this did not translate into better LDL-C control, which was similar to non-depressed patients. Major efforts are required to improve suboptimal lipid management in ASCVD patients.

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Author contributions

J.P.H. and E.A.E. contributed to the conception of the work. E.A.E., R.S., C.W., A.J., D.O., K.L., M.B.G., and J.P.H. contributed to the study design and analysis plan. E.A.E., C.W., M.B.G., and J.P.H. undertook the analysis and interpretation of data for the work, which was reviewed by A.A., A.J., D.O., and K.L. C.W. and E.A.E. drafted the manuscript. R.S., A.A., A.J., D.O., K.L., M.B.G., and J.P.H. critically revised the manuscript for important intellectual content. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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Conflict of interest: J.P.H., A.A., and M.B.G. are investigators on an unrestricted research grant from Amgen Inc., related to cardiovascular risk management in clinical practice, which is investigating related issues but does not overlap in scope with the current work. J.P.H. has received honoraria from Amgen. K.L has received consultancy fees from Health Technology Wales.

Data availability

The data used in this study are available within the national trusted research environment for Wales, the SAIL Databank at Swansea University, Swansea, UK. Due to the sensitive nature of these data, all proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). SAIL has an established application process for all projects and users who want to access data https://www.saildatabank.com/application-process. This project was approved by the IGRP at Swansea University (SAIL project number 0800).

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