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Original Research

Lipid-lowering optimisation for secondary prevention vascular and diabetic foot patients in a pharmacist-led clinic



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KEYWORDS

Low density lipoprotein cholesterol;
Lipid-lowering;
Pharmacists;
Prevention;
Atherosclerotic cardiovascular disease

BACKGROUND AND AIMS: Patients attending vascular or diabetic foot clinics commonly have atherosclerotic disease, are at increased risk of cardiovascular disease (CVD), merit high-intensity lipid-modifying therapy to maintain secondary prevention targets and are often sub optimally treated in primary care. We set out to assess the impact of a pharmacist led lipid optimisation clinic in these patients in an area with high levels of social deprivation.

METHODS: We performed a clinical cohort study to assess the effectiveness of a pharmacist led clinic to optimise lipid lowering therapy by optimising of statin therapy and commencing additional lipid lowering therapy if applicable with monitoring of blood lipid profiles.

Results: Of the 216 patients (166 [77%] on statins) triaged by the pharmacist, 175 (81%) had non-high-density lipoprotein (non-HDL) cholesterol levels above the target value of 97 mg/dL (2.5 mmol/L) with a mean non-HDL cholesterol level of 135.73 mg/dL (3.51 mmol/L). Pre optimisation by the prescribing clinical pharmacist 41/216 (19%) patients were at target with a mean non-HDL cholesterol of 135.5 mg/dL improving to 92/137 (67%) patients achieving the target non-HDL cholesterol level with a mean post optimisation non-HDL cholesterol of 94.35 mg/dL (2.44 mmol/L), odds ratio (OR) for being at target 8.67 (95% CI 5.30–14.20). The calculated low-density lipoprotein cholesterol levels (Friedewald) demonstrated a mean reduction of 35.19 (95% CI 29.23–41.38) mg/dL (0.91 [95% CI 0.76–1.07] mmol/L). Proportion on high intensity statin increased from 65 out of 166 (39%) to 129 of 170 (76%) at follow up (OR 4.89 [3.06–7.82]), equivalent to an number needed to treat = 3.

CONCLUSIONS: A pharmacist led service in undertreated and clinically challenging vascular and diabetic foot patients in an area of high social deprivation produced significant improvements in utilization of high intensity statin and other lipid lowering therapies and attainment of lipid goals.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death accounting for a quarter of all deaths in the UK and more than 100,000 hospital admissions.¹ Stroke causes 38,000 deaths and 100,000 admissions in the UK annually.² Associated healthcare costs are estimated to be £9 billion every year with an overall CVD burden of approximately £19 billion annually.³

CVD death rates vary with age, gender, time of the year (an excess of winter deaths), and also by socioeconomic status, with deaths from CVD being three times higher among people in the most deprived communities. Geographic location also influences CVD rates within England.⁴

The National Health Service (NHS) long term plan published in 2019 recognises that CVD is the single biggest opportunity to save lives and sets a specific ambition to prevent 150,000 heart attacks, strokes and dementia by treating atrial fibrillation (A), high blood pressure (B) and raised cholesterol (C).⁵

In the UK up to 28 % of CVD deaths are due to elevated cholesterol.⁶ Multiple clinical trials and meta-analyses have shown that the primary determinant in atherosclerotic cardiovascular disease risk reduction is the absolute reduction in low density lipoprotein cholesterol low-density lipoprotein (LDL) cholesterol. Every 39 mg/dL (1 mmol/L) in LDL cholesterol is associated with a 23% relative risk reduction in major atherosclerotic cardiovascular disease events.⁷ Standard lipid-lowering therapy such as statins, ezetimibe and injectable lipid-lowering therapy are effective and can significantly reduce the incidence of coronary heart disease and other major vascular events in a wide range of individuals.⁸ This is reflected in standard treatment guidance in both USA⁹ and Europe.¹⁰ Despite knowledge of effectiveness many patients remain undertreated.^{8,11}

Patients attending vascular or diabetic foot clinics commonly have atherosclerotic disease, are at increased risk and merit high-intensity lipid-modifying therapy to maintain secondary prevention targets. Adults with diabetes are 2–3 times more likely to develop heart or circulatory diseases and are nearly twice as likely to die from heart disease or stroke. A third of UK adults with diabetes die from heart or circulatory disease.¹²

Previous research has shown that pharmacist led interventions are effective in these patients. A recent systematic and meta-analysis showed that pharmacist intervention significantly reduced LDL cholesterol compared with usual care. Across 26 described interventions in secondary prevention the pooled reduction in LDL cholesterol was -7.9 mg/dL, increasing to -13.73 mg/dL when the intervention focused solely on lipid medication.¹³ In the UK similar interventions have been described in the context of evaluation for initiation of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.¹⁴ In patients with peripheral artery disease (PAD), using maximal lipid lowering therapies and treating to target, a reduction in major adverse cardiovascular and limb events can be achieved.¹⁵

In this study we set out to assess the impact of a pharmacist led lipid optimisation clinic for secondary prevention patients by measuring the impact of the interventions on lipid profiles in a clinically challenging PAD and diabetes population in an area with high levels of social deprivation.

Methods

The setting for the study was at the Freeman Hospital which is a tertiary referral vascular centre offering a full range of vascular services and which works closely with colleagues in cardiology and cardiothoracic surgery. It provides vascular services for patients in Northumberland, North Tyne-side, Newcastle and Gateshead and tertiary services for the wider North East region. The large geographical area with a diverse patient population (1.2 million) has one of the highest rates of socioeconomic deprivation ensuring a challenging patient cohort.

An approach was developed to deliver a pharmacist led secondary prevention service. This was a new innovative role funded by the Academic Health Science Network for a time limited period of two years. Suitability for implementing the intervention was confirmed by a baseline audit of 100 consecutive patients who attended the vascular clinics of whom 62 % of patients were eligible for lipid optimisation. A vascular clinical pharmacist (MH) who was an independent prescriber was seconded to the lipid clinic for six months to gain experience with deployment of lipid modifying therapy. At the end of this period, he returned to the vascular surgery department but maintained attendance at the multidisciplinary lipid meeting. In collaboration with the lipid clinic, pre-defined standards for inclusion and exclusion were developed for triaging patients so that high-risk patients with a need for lipid optimisation could be identified as shown in Fig. 1. A non-high-density lipoprotein (non-HDL) cholesterol target of 97 mg/dL was chosen as opposed to LDL cholesterol target of 70 mg/dL as some patients attended phlebotomy appointments non-fasted.

Two virtual clinics were conducted each week delivered by the trained clinical pharmacist (MH) who was able to prescribe the full range of National Institute for Health Care and Excellence (NICE) approved secondary prevention lipid lowering therapies. Management followed current national and regional guidelines.^{16,17} Patients were prioritised according to their CVD risk. The service covered the vascular outpatient clinics including direct referral from the vascular team and the weekly regional diabetic foot multidisciplinary team meetings. The service was staffed solely by one pharmacist for 15 h per week (two working days). All patient contact was in the form of telephone consultations initiated by the pharmacist. Medication history, lipid profiles and a full discussion of secondary prevention targets, intended benefits and potential harms was undertaken. Changes to prescribed lipid lowering therapies were decided in consultation with the patients and any necessary prescriptions actioned by

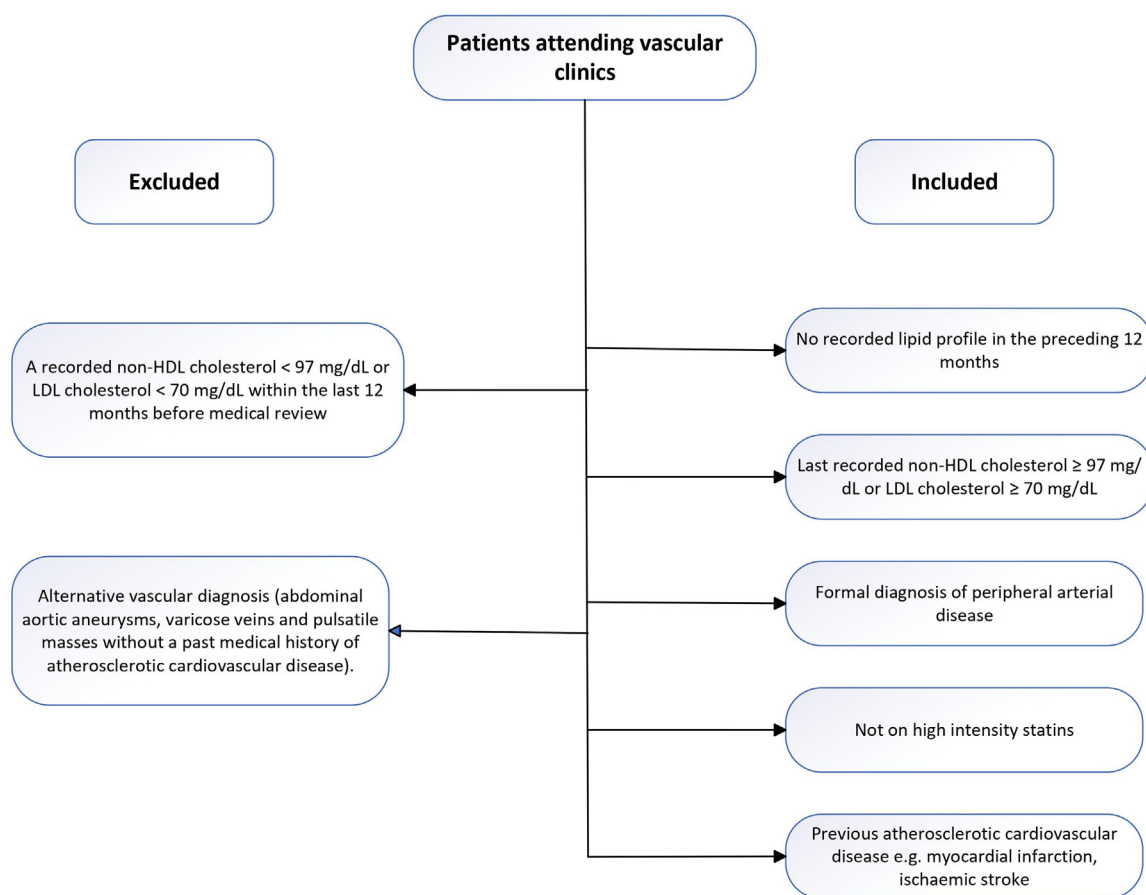


Figure 1 Inclusion and exclusion flow chart.

Abbreviations: LDL, low-density lipoprotein; non-HDL, non-high-density lipoprotein.

the prescribing pharmacist as a request made by letter to the responsible primary care team. All consultations outcomes were documented on electronic patient records.

Patients eligible for optimisation were offered review in the virtual clinics and post-intervention monitoring. Relevant information to confirm eligibility was captured using an Excel spreadsheet. Information gathered included demographics such as postcode which was used to obtain index of multiple deprivation (IMD) decile, lipid modifying therapy, previous lipid measurements, documented medication intolerance and comorbidities.

All follow up was in the form of telephone consultations by the prescribing clinical pharmacist at 3 monthly intervals. At follow up prescribed lipid lowering therapies were reviewed for compliance (though no formal measures of compliance were taken), adverse effects and efficacy in relation to an updated blood lipid profile. At each visit progress was evaluated in relation to secondary prevention targets of non-HDL cholesterol < 97 mg/dL (< 2.5 mmol/L). Where these were not met further medication changes were introduced in accordance with current guidelines^{16,17} and patient agreement. For these patient's additional information was recorded as shown in Fig. 2.

Data were analysed using JASP 0.17.1. Within subject differences between scale variables were analysed using paired

t-tests and ANOVA as appropriate. Changes in proportions of patients at target were analysed using McNemar's test. An alpha level of 0.05 for significance was used throughout.

Results

A total of 216 individuals (161 seen in the peripheral vascular disease clinic and 55 in the diabetic foot clinic) were evaluated by the pharmacist (44 were directly referred by the team and 172 as a result of pharmacist triage). The demographics and initial blood lipid measurements of the entire sample are displayed in Table 1. There were no significant differences in age, gender breakdown, IMD decile, proportion on treatment or baseline blood lipid levels between referral source (all $p > 0.4$). Across all patients reviewed the modal IMD decile was 1 (most deprived) with the distribution of deprivation strongly skewed towards the lower end with 100 (47%) patients being in the lowest three deciles. At pharmacist review 166 (77%) were already on lipid lowering treatment with total cholesterol and non-HDL cholesterol being significantly lower in the treated group however 188 patients (87%) including 139 (84%) of those on treatment were still above the target non-HDL cholesterol level of 97 mg/dL (2.5 mmol/L).

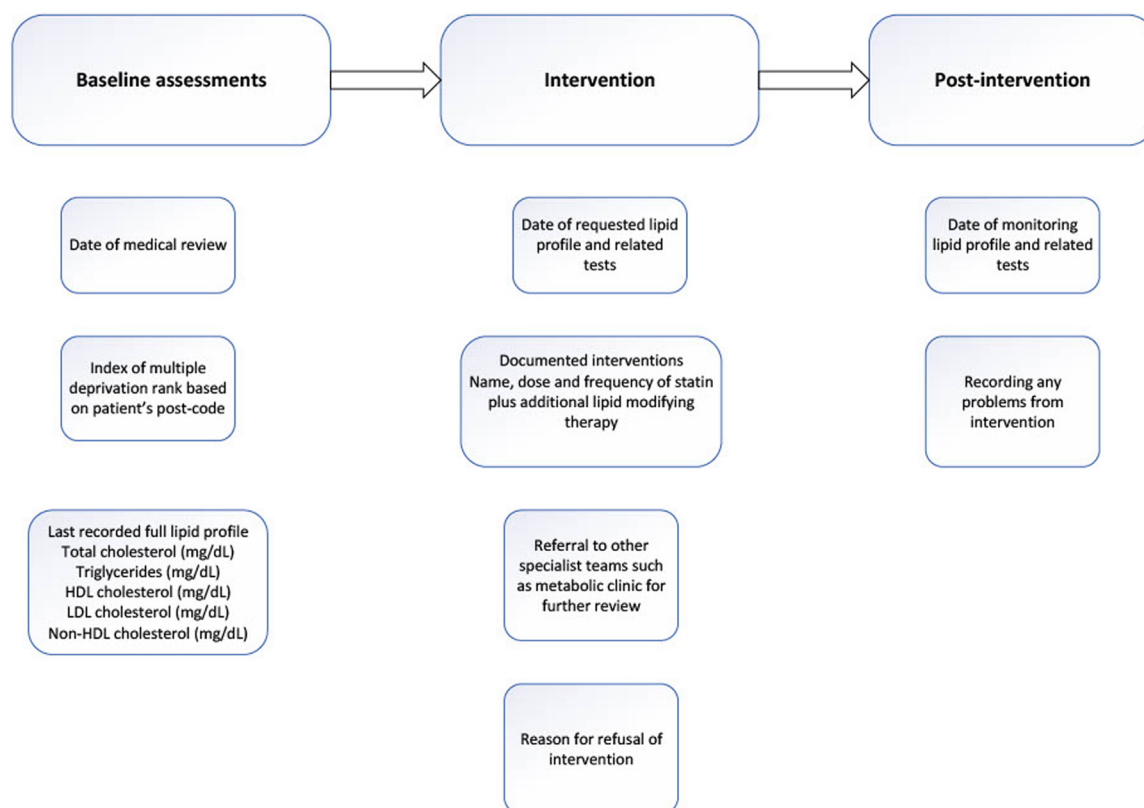


Figure 2 Patient flow in the lipid optimisation clinic.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; non-HDL, non-high-density lipoprotein.

Table 1 Demographics and baseline characteristics at triage.

	Total sample <i>n</i> = 216	On treatment at baseline <i>n</i> = 166 (77%)	Not on treatment at baseline <i>n</i> = 50 (23%)
Sex	M 144 (67%) F 72 (33%)	M 111 (67%) F 55 (33%)	M 33 (66%) F 17 (34%)
Age (SD) years	69.7 (10.6) 68.6 (11.6)	M 69.7 (10.1) F 67.9 (11.6)	M 69.6 (12.3) F 71.1 (11.5)
IMD decile	Mode 1 Median 4	Mode 1 Median 4	Mode 2 Median 4
Mean (SD) Total Cholesterol (mg/dL)	186.00 (51.43)	178.27 (49.11)	213.46 (50.66)
Mean (SD) Triglycerides (mg/dL)	202.83 (210.80)	204.60 (236.74)	198.40 (142.60)
Mean (SD) HDL-C (mg/dL)	49.50 (15.08)	48.72 (15.47)	51.82 (14.69)
Mean (SD) non-HDL-C (mg/dL)	135.35 (46.02)	127.61 (41.76)	162.41 (49.88)
Mean (SD) LDL-C (mg/dL)	96.95 (43.85)	89.80 (40.99)	121.93 (44.74)
Number (%) at target	41 (19%)	40 (24%)	1 (2%)
Mean (SD) distance of non-HDL-C from target (mg/dL)	35.19 (48.72)	26.30 (41.76)	66.13 (58.78)
Number (%) on high dose statin	N/A	65 (39%)	N/A

Abbreviations: F, female; HDL-C, high-density lipoprotein cholesterol; IMD, index of multiple deprivation; LDL-C, low-density lipoprotein cholesterol; M, male; N/A, not applicable; non-HDL-C, non-high-density lipoprotein cholesterol.

Post-intervention by the pharmacist, 137 patients had follow up blood tests (118 vascular surgery and 19 in diabetic foot clinic) and all of these have had lipid optimisation recommendations followed. There were significantly more at target than pre-intervention - a change from 41 out

of 216 (18.9%) to 92 out of 137 (67.2%) being at target with mean distance from target post intervention being 1.55 (SD 36.74) mg/dL below. This is a significant change in the proportion at target (McNemar's test, $p < 0.001$, odds ratio for being at target 8.67 [95% confidence interval {CI}

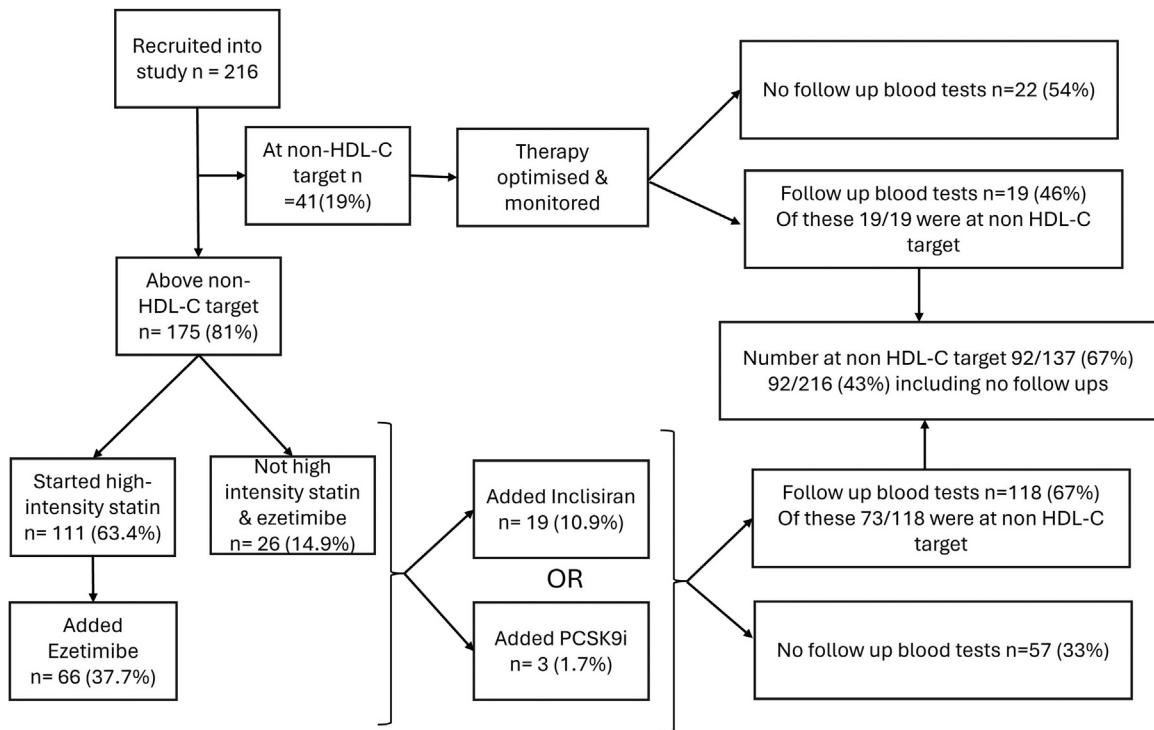


Figure 3 Subject disposition and lipid optimisation flow chart.

Abbreviations: non-HDL-C, non-high-density lipoprotein cholesterol and PCSK9i, proprotein convertase subtilisin kexin type 9 inhibitor.

Table 2 Comparison data from pre to post review in clinic of lipid profiles.

	Pre (M (SD))	Post (M (SD))	p	Effect Size d [95% CI]
Total cholesterol	184.84 (49.88)	153.52 (39.06)	<0.001	0.99 [0.78 – 1.21]
Triglycerides	185.11 (102.74)	152.34 (104.51)	<0.001	0.39 [0.21 – 0.57]
HDL cholesterol	49.11 (14.31)	49.11 (15.85)	.922	<0.01 [–0.18 – 0.17]
Non-HDL cholesterol	136.12 (46.02)	94.35 (35.19)	<0.001	1.06 [0.84 – 1.28]
LDL cholesterol	99.00 (40.60)	63.42 (38.67)	<0.001	1.03 [0.81 – 1.25]

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, mean; non-HDL, non-high-density lipoprotein.

5.30–14.20)). Patient flow through the service and treatments prescribed are shown in Fig. 3. Initially introduction of maximum intensity statin was attempted with ezetimibe introduced for patient's intolerant of or not at target on maximum intensity statin. Further addition of inclisiran or PCSK9 inhibitor was used in accordance with guidelines.^{16,17}

Full pre- and post-intervention blood tests were available on 125 patients and in these LDL cholesterol was calculated using the Friedewald equation as shown in Table 2. There was a significant reduction in non-HDL cholesterol, calculated LDL cholesterol, total cholesterol and triglycerides but no notable change in HDL cholesterol. There was a mean reduction in LDL cholesterol of 35.58 (95% CI 11.21–59.94) mg/dL for those new to treatment and of 19.72 (95% CI 11.6–27.84) mg/dL for those already treated yielding a mean reduction across the cohort of 22.82 (95% CI 15.08–34.42) mg/dL.

Prior to intervention 65 of 166 (39%) on treatment were on a high intensity statin which increased to 129 of 170 (76%) at follow up (odds ratio 4.89 [3.06–7.82], $p < 0.001$ equivalent to a number needed to treat =). Other lipid lowering treatments at baseline were bezafibrate (2), fenofibrate (1), ezetimibe (11) and one patient on both Fenofibrate and Ezetimibe. Additional drugs started by the clinical pharmacist for patients achieving target non-HDL cholesterol as detailed in Fig. 3 resulted in 31 patients being on one, 40 patients on two and two patients on three lipid lowering therapies.

Factorial ANOVA revealed that the pattern of fall was similar for previously treated and untreated participants in the cohort as shown in Fig. 4 and did not differ between referral sources though the previously untreated had larger initial reductions in blood lipid measurements as shown below for the change in non-HDL cholesterol (mean reduction of 44.32 [95% CI 19.74–68.90] mg/dL in untreated vs. 35.01 [95% CI 27.18–42.85] mg/dL in treated, $p = 0.002$).

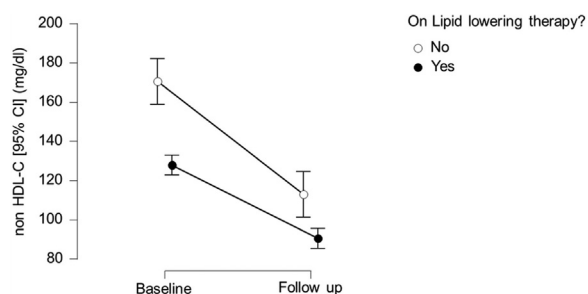


Figure 4 Mean (95% CI) non-high-density lipoprotein cholesterol (mg/dL) pre and post intervention for patients who were/were not on treatment at baseline.

Discussion

We developed a pharmacist-led lipid optimisation service with pathways based on the national guideline (The Accelerated Access Collaborative)¹⁶ and the regional guideline (The Northern England Evaluation and Lipid Intensification Clinical Guideline).¹⁷ By applying pre-specified criteria to identify patients who are at the highest risk of CVD, high-risk patients were reviewed in a virtual clinic at the earliest opportunity for lipid optimisation and offered intervention by an appropriately trained pharmacist with access to electronic general practitioner (GP) records. Patients were prescribed tailored combination treatment plans. The intervention was successful with most patients being started on high intensity statins and meeting secondary prevention targets.

A major finding was that most patients were undertreated even at referral to secondary care. This mirrors two large European studies (DAVINCI¹¹ and SANTORINI⁸) which have shown that high and very risk CVD patients rarely achieve treatment targets primarily because of risk underestimation and underutilisation of combination treatment. Under prescribing of statins in PAD compared to comparator groups with coronary or cerebral atherosclerosis has been recently described.¹⁵

Overall, the results show a positive effect of the intervention. The magnitude of the LDL cholesterol reduction is larger than that reported in a recent meta-analysis¹³ which could reflect the fact that all patients in the current study had symptomatic PAD or were being treated for diabetic foot problems. Clarity of communication of secondary prevention targets and collaborative goal setting with patients may have also contributed. The LDL cholesterol reductions achieved for vascular outpatients and diabetic foot multidisciplinary team patients would if maintained correspond to relative risk reductions in major vascular events of >19% and >31% respectively. Current findings reflect similar outcomes in previously described UK studies.¹⁴

One limitation of the study was that not all patients had a baseline lipid profile recorded therefore we were unable to calculate the reduction in LDL cholesterol from pre- to post-intervention for all patients reviewed in the clinic. Another limitation was that some patients were unable to be contacted via telephone. A letter was sent to their GPs with recom-

mended lipid optimisation interventions. Some interventions were unfortunately not actioned by the GP, or if they did, the appropriate follow-up lipid profiles for some patients were not obtained. There is little evidence that unmonitored patients derived lipid optimisation benefits and further work in this area would be valuable.

Further work is needed to confirm the durability of the lipid control achieved by the pharmacist-led interventions. Repeat lipid profiles at annual reviews may provide this data. Ultimately a comparison of the recurrence of vascular events with historical data would confirm the true benefit of this service. In addition, the nature of the patient population at a tertiary referral centre probably contributes to the relative success of the project and it may be harder to replicate in a non-symptomatic patient cohort.

Conclusions

We have demonstrated that a pharmacist led service in undertreated and clinically challenging vascular and diabetic foot patients in an area of high social deprivation produced significant improvements in utilization of high intensity statin therapy and attainment of lipid goals. The service resulted in significant reductions in LDL cholesterol, non-HDL cholesterol, total cholesterol and triglycerides. Overall, a pharmacist led lipid optimisation service, as an adjunct to existing clinical services, is highly effective and has the potential for long term gains if embedded.

Declarations of competing interest

None

CRedit authorship contribution statement

Matthew Hart: Writing – original draft. **Jon Rees:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Julia L Newton:** Writing – review & editing, Supervision, Conceptualization. **Gerard Stansby:** Writing – review & editing, Supervision. **Kate Mackay:** Writing – review & editing, Supervision. **Ahai Luvai:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Use of AI and AI-assisted technologies statement

AI or AI-assisted technologies have not been used.

Data statement

Upon reasonable request, it can be expected that specific anonymous data will be shared to a qualified researcher.

Ethical approval

Ethical approval was not required due to this being an innovation arising out of a baseline audit that showed low utilisation of lipid treatments.

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