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Lipoprotein apheresis efficacy, challenges and outcomes: A descriptive analysis from the UK Lipoprotein Apheresis Registry, 1989–2017

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HIGHLIGHTS

- The UK Lipoprotein Apheresis (LA) Registry was established in 2011.
- Between 2011 and 2017 data was entered retrospectively and prospectively by seven LA centres in the UK for 151 patients.
- The mean reduction in interval mean LDL-C from the pre-procedure baseline was 43.14% and 37.95% for Lp(a).
- There was a 62.5% reduction in major adverse cardiovascular events (MACE) following introduction of LA.

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ABSTRACT

Background and aims: In 2008, the National Institute of Health and Care Excellence in the UK recommended that patients undergoing lipoprotein apheresis (LA) should be included in an anonymised registry. The UK Lipoprotein Apheresis Registry was subsequently established in 2011.

Methods: Between 2011 and 2017, data was entered retrospectively and prospectively by seven LA centres in the UK for 151 patients. Twenty-two patients were involved in a research study and were therefore excluded from the analysis. Observational data was analysed for the remaining 129 patients.

Results: Most patients had heterozygous familial hypercholesterolaemia (HeFH) (45.0%); 23.3% had homozygous FH (HoFH); 7.8% had hyper-lipoproteinaemia (a) (Lp(a)) and 24.0% had other forms of dyslipidaemia. Detailed treatment data is available for 63 patients relating to 348 years of LA treatment. The number of years of treatment per patient ranged from 1 to 15. The mean reduction in interval mean LDL-C from the pre-procedure baseline was 43.14%. The mean reduction in interval mean Lp(a) from baseline was 37.95%. The registry data also shows a 62.5% reduction in major adverse cardiovascular events (MACE) between the 2 years prior to, and the first 2 years following introduction of LA.

Conclusions: The data generated by the UK Lipoprotein Apheresis Registry demonstrates that LA is a very efficient method of reducing LDL-C and Lp(a) and lowers the incidence rate of MACE. LA is an important tool in the management of selected patients with HoFH and drug-resistant dyslipidaemias.

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1. Introduction

Lipoprotein apheresis (LA) is a well-established extracorporeal technique, which removes apolipoprotein B containing particles from the circulation [1]. Patients with homozygous familial hypercholesterolaemia (HoFH), severe heterozygous familial hypercholesterolaemia (HeFH) with progressive cardiovascular disease and some patients with hyper-lipoproteinaemia (a) (hyper Lp(a)) benefit from this procedure through lowering of low-density lipoprotein cholesterol (LDL-C) and Lp (a) and the consequent reduction in cardiovascular events [2–5]. Registry data, together with more recent prospective data, support the value of LA for radical modification of atherogenic lipoproteins by providing a record of lipid levels and cardiovascular events [6,7]. In the UK, the National Institute for Health and Care Excellence (NICE) requires patients to be included in an anonymised register [8]. The Hyperlipidaemia Education and Atherosclerosis Research Trust United Kingdom (HEART UK, the cholesterol charity) provides guidance on eligibility of patients for LA in the UK [9]. Its current recommendations are that LA should be the treatment of choice for: (1) all HoFH from the age of seven onwards, unless their serum cholesterol can be reduced by > 50% and/or decreased to ≤9 mmol/l by drug therapy; (2) individual patients with either HeFH or a significant family history of premature cardiac death whose coronary disease progresses and where LDL cholesterol remains > 5.0 mmol/l or is decreased by < 40% with maximal drug therapy. LA may also occasionally be indicated on a case-by-case basis for patients with lower levels of LDL cholesterol. (3) LA should also be considered for patients with aggressive progressing coronary disease and Lp(a) > 600 mg/l whose LDL cholesterol remains > 3.2 mmol/l despite maximal drug therapy. These recommendations are currently under review, to take account of newer pharmacological therapies and the much lower target levels of LDL cholesterol proposed by the European Atherosclerosis Society [10]. However, LA remains an important therapeutic option for the management of HoFH in the United Kingdom (UK), in whom treatment needs to ideally start in childhood [11]. The newer LDL-C lowering agents are not currently licensed for use in children.

2. Materials and methods

The UK lipoprotein apheresis register was established in 2011 under the auspices of the HEART UK Lipoprotein Apheresis Working Group. The registry was developed by Net Solving Ltd, is managed by HEART UK and its website, initially hosted by the Royal College of Physicians and subsequently by Net Solving Ltd. Funding for the development of the registry was provided by the manufacturers of the apheresis equipment used in the UK. Retrospective data were collected and are presented herein. Data are inputted by each apheresis centre in the UK and currently 7 units contribute data to the registry. These are located at Harefield Hospital - London, Hammersmith Hospital - London, Llandough Hospital – Cardiff, Queen Elizabeth II Hospital - Birmingham, Manchester Royal Infirmary and NHS Blood transfusion services in Leeds and Bristol (Supplementary Fig. A). The majority of units only treat adult patients (over the age of 16 years), however, the Hammersmith Hospital and Birmingham Children's Hospital have treated younger patients with HoFH. The only unit performing lipoprotein apheresis, which has not contributed data, is a paediatric renal unit which treats 1 child with HoFH.

Informed consent is obtained from each patient before adding their data to the registry. Data are password protected and each centre has a designated person to input the data. Individual units can see only their own data and only designated HEART UK personnel are able to see the data in its entirety. Anonymised data is exported from the registry by HEART UK and has been analysed by an independent analyst to provide data for this paper. Data were extracted on February 12, 2017.

2.1. Statistical analysis

The raw data were extracted directly from the database into an Excel spreadsheet (Excel 2016) and then analysed by an independent analyst. Data are presented as means for continuous variables, or as medians and interquartile ranges for variables with skewed distributions and as frequencies or percentages for categorical variables.

2.2. Baseline data collected

Baseline demographic and clinical data were collected for each patient including gender, ethnicity, age at diagnosis and the main indication for LA. Baseline medical conditions and cardiovascular disease (CVD) risk factors together with investigations previously performed and lipid-modifying drugs administered were also recorded. Specific data relating to LA included the system used, date LA treatment was commenced and vascular access method employed. Serum lipid levels were analysed before commencement of LA and then immediately pre- and post each LA and interval means calculated as previously described [12]. The volume of plasma or whole blood treated was also recorded. The data fields are shown in Supplementary Table A.

Baseline data for 151 individual patients were entered into the registry. Twenty-two of the patients were involved in a research study investigating the impact of LA in patients with refractory angina and raised Lp(a) and have therefore been excluded from the analysis [13]. Data from 129 patients have been analysed.

The CVD data were obtained for all 129 patients in the registry from the individual units. Information was requested on all major adverse cardiovascular events (MACE) that had occurred prior to commencement of, and since undergoing LA therapy, together with the dates of the events. Data were collected for the following events: myocardial infarction (MI), percutaneous coronary intervention (PCI), cerebrovascular accident – CVA/transient ischaemic attack (TIA), transcatheter aortic valve implantation (TAVI), coronary artery bypass grafting (CABG), carotid surgery, new diagnosis of aortic stenosis (AS)/aortic valve replacement (AVR) or surgery for supravalvular-aortic stenosis, orthotropic cardiac transplantation (OCT).

2.3. Annual averages data

In addition to the baseline data entered in the registry, centres are required to enter annual average data for each patient undergoing lipoprotein apheresis. This includes the number of treatments each year, average volume of blood/plasma treated per procedure over the year and average levels of TC, LDL-C, High density lipoprotein cholesterol (HDL-C), and Lp(a) both pre- and post-treatment. (Supplementary Table B).

The annual averages data was downloaded on January 18, 2018 and was submitted by four of the LA centres – Harefield, Llandough, Hammersmith and Bristol. These data were extracted after the baseline data to allow additional time for data entry and therefore provide more data for analysis.

3. Results

3.1. Patient demographics

Most patients 58, (45.0%) had HeFH, 30 (23.3%) had HoFH, 10 (7.8%) had hyper Lp(a), and 31 (24.0%) had other forms of dyslipidaemia. The latter group included patients with polygenic dyslipidaemia and mixed dyslipidaemia and are identified as 'non-FH'. Patients with hyper Lp(a) are those with isolated an raised Lp(a) of > 300 mg/L, undergoing LA purely for this indication and this group does not include those patients with HoFH, HeFH or non-FH who may also have raised Lp(a). Unsurprisingly, the patients with HoFH were

Table 1
Patient demographics.

Factor	Homogygotes [n = 30]		Heterozygotes [n = 58]		Hyper Lp(a) [n = 10]		Non-FH [n = 31]	
Gender								
Male	14	(18.4%)	31	(40.8%)	8	(10.5%)	23	(30.3%)
Female	16	(30.2%)	27	(50.9%)	2	(3.8%)	8	(15.1%)
Ethnicity								
White	10	(33.3%)	55	(94.8%)	6	(60.0%)	28	(90.3%)
Asian Indian	5	(16.7%)	2	(3.4%)	1	(8.3%)	1	(3.1%)
Asian Pakistani	7	(23.3%)	0	(0.0%)	1	(8.3%)	1	(3.1%)
Black African	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.1%)
Other	8	(26.7%)	1	(1.7%)	2	(16.7%)	0	(0.0%)
Age at diagnosis								
Median (range)	14.8	(1–57)	40.0	(12–68)	51.0	40–70	47.5	17–64
Age apheresis commenced								
Median (range)	26.3	(5 – 60)	51.0	(14–76)	53.7	(44–72)	53.2	(28–76)
Genetic testing								
Positive	30	100.0%	43	91.5%	0	0	0	0
Not confirmed	0	0.0%	4	8.5%	9	100.0%	20	100.0%
Total	30	100.0%	47	100.0%	9	100.0%	20	100.0%

diagnosed at a younger age, median 14.8 years, whereas most patients with HeFH, hyper Lp(a) and non-FH presented between the ages of 30 and 70 (median 40.0, 51.0 and 47.5 respectively) (Table 1), often following a cardiovascular event. The majority of patients with HeFH, hyper Lp(a) and non-FH were white, whereas those with HoFH came from a variety of ethnic backgrounds including the Philippines, Indian subcontinent, Middle-east, Sardinia and Portugal (Table 1). There was an even gender distribution for both HoFH and HeFH patients however most patients with hyper Lp(a) and non-FH were male. 106 of the patients had undergone genetic testing for FH (82.2%). All the HoFH patients had a confirmed genetic diagnosis as did the majority (81.0%) of the HeFH patients (Table 1).

3.2. Risk factors for cardiovascular disease (CVD)

The majority of patients in all groups were either non-smokers (60.5%) or ex-smokers (29.5%). Some patients continued to smoke, the highest percentage of whom had HeFH or non-FH (4.7% and 3.9% respectively) (Supplementary Table C).

The most frequent non-lipid risk factor for CVD was hypertension which occurred in 37.9%, 50.0% and 67.7% of the HeFH, hyper Lp(a) and non-FH patients respectively. 10.0% of the HoFH patients were hypertensive (Supplementary Table A). None of the HoFH or hyper Lp (a) patients were known to have diabetes. Type 1 diabetes was found in 12.9% of non-FH patients. Type 2 diabetes occurred most frequently in the HeFH and non-FH patients, 12.1% and 16.1% respectively (Supplementary Table C).

Most patients had clinical evidence of premature atherosclerotic cardiovascular disease (ASCVD) at entry to the register. The mean age of first MI, CABG or PCI was less than 55 years in all groups. MI and CABG occurred earlier in those with HeFH compared to patients with hyper Lp(a) or non-FH (43.1 years vs 44.9 and 48.3 respectively (MI) and 42.2 years vs 45.0 and 50.1 respectively (CABG)) [14] but PCI occurred at a younger age in patients with hyper Lp(a) (44.9 years vs 48.2 HeFH and 50.2 non-FH). Patients with HoFH present at a younger age than other patients treated with LA (< 36 years), and were the only group requiring AVR (13.3%), as expected (Table 2) [15].

3.3. Apheresis treatment

The number of patients treated by each centre varied between 2 (Leeds) and 58 (Harefield) (Supplementary Table D). The number of patients who commenced LA each year is shown in Supplementary Fig. B. The most frequently used LA technique was Dextran Sulphate adsorption of whole blood (DSA-B), used in 36.4% of patients. The DALI system was the next most used system, employed in 25.6% of patients. Double filtration plasmapheresis (DFPP) was used in 27.1%, Dextran Sulfate adsorption of plasma (DSA-P) in 7.0%, plasma exchange in 2.3% and HELP (heparin extracorporeal LDL precipitation) in 1.6% (Supplementary Table D).

There was significant variation in the age at which LA was commenced. As expected, treatment started earlier in the HoFH patients (mean age 26.3 years) than in the other groups, although there were 4 patients with HoFH who did not start LA treatment until over the age of 50, one of whom was initially treated with plasma exchange from the age of 28 and switched to LA age 56 (Table 1).

The mean volume of blood treated each time was 7.60 L (range 4.00–12.00 L) and the mean volume of plasma treated was 3.19 L (range 1.10–4.80 L). Vascular access was obtained via peripheral veins in 58.1% of patients, arterio-venous (AV) fistula in 36.4% and via permanent central venous access in 5.4% (Supplementary Table D).

78 (60.5%) patients were still undergoing LA at the time of the data download and 51 (39.5%) were no longer on treatment. The commonest reason for discontinuation of LA, apart from death of the patient, which occurred in 35.3%, was the introduction of a proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody as an alternative therapy (31.4%). These agents were approved for use in the UK by the National Institute for Health and Care Excellence in 2016. The reason for discontinuation of LA was not recorded by all centres. 81 patients were taking a statin on initiation of LA (62.8%). A significant number of patients were documented as being intolerant to statin therapy (41.1%), however some of these (34.0%) were still taking a statin but at a low dose. 14.7% were taking no lipid lowering therapy (Supplementary Table E).

The distance travelled by patients to and from an LA centre was significant, with 22.5% of patients travelling greater than 100 miles (160 km) roundtrip. The longest roundtrip was 318 miles (511 km), travelled by one of the patients with HoFH. In the UK, transport may be provided by a hospital, at no charge to the hospital if this is clinically required and social circumstances mandate it; this was applicable in 24.0% of patients (Supplementary Table F).

3.4. Lipid data

As expected, the total cholesterol (TC) and LDL cholesterol levels were highest in the HoFH patients before starting LA (median TC 13.1 mmol/l; median LDL 10.4 mmol/l). Patients with HeFH and non-FH had the next highest levels (median TC 8.5 mmol/l; median LDL 6.3 mmol/l and TC 8.5 mmol/l; LDL 5.0 mmol/l respectively). TC and LDL-C levels were lowest in the Lp(a) patients (median TC 4.5 mmol/l:

Table 2
Baseline cardiovascular disease status.

Factor:	Homozygotes		Heterozygotes		Hyper Lp(a)		Non-FH	
	No.	% of total	No.	% of total	No.	% of total	No.	% of total
Angina	10	33.3%	42	72.4%	8	80.0%	24	77.4%
Previous MI	4	13.3%	31	53.4%	7	70.0%	19	61.3%
Average age (range)	33.3 (23–46)	–	43.1 (29–65)	–	44.9 (38–52)	–	48.3 (35–66)	–
Previous CABG	5	16.7%	27	46.6%	7	70.0%	8	25.8%
Average age (range)	33.0 (21–42)	–	42.2 (21–68)	–	45.0 (39–54)	–	50.1 (37–71)	–
Previous PCI	7	23.3%	39	67.2%	8	80.0%	18	58.1%
Average age (range)	35.5 (23–46)	–	48.2 (21–72)	–	44.9 (38–65)	–	50.2 (35–64)	–
Cardiac transplant	0	0.0%	1	1.7%	1	10.0%	2	6.5%
Average age (range)	N/a	–	55.0 (55)	–	60.0 (60)	–	46.5 (41–52)	–
AVR	4	13.3%	0	0.0%	0	0.0%	0	0.0%
PVD	0	0.0%	14	24.1%	1	10.0%	6	19.4%
Carotid disease	5	16.7%	10	17.2%	1	10.0%	3	9.7%

MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; AVR, aortic valve replacement; PVD, peripheral vascular disease.

Table 3
Lipid data prior to commencing lipoprotein apheresis.

Factor	Homogygotes [n = 30]		Heterozygotes [n = 58]		Hyper Lp(a) [n = 10]		Non-FH [n = 31]	
	mmol/l	Range	mmol/l	Range	mmol/l	Range	mmol/l	Range
TC (median and range)								
Pre-apheresis	13.1	(4.5–24.7)	8.5	(4.3–14.6)	4.5	(2.3–8.0)	8.5	(3.0–16.5)
LDL-C (median and range)								
Pre-apheresis	10.4	(2.7–22.2)	6.3	(1.9–12.3)	2.3	(1.2–5.2)	5.0	(1.1–8.2)
Lp(a) (median and range)								
Pre-apheresis, mg/l	999.5	(75–2480)	858.6	(20–2370)	898.7	(471–1570)	458.5	(20–2089)
Non-HDL-C (median and range)								
Pre-apheresis	11.9	(3.7–23.8)	7.3	(3.2–13.3)	3.2	(1.7–7.0)	7.1	(1.9–15.1)

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); HDL-C, high-density lipoprotein cholesterol.

median LDL 2.3 mmol/l). Lp(a) levels were highest in the HoFH patients followed by the Lp(a) cohort (999.5 mg/l and 898.7 mg/l, respectively). The HeFH patients also had significantly raised levels of Lp (a) (858.6 mg/l), reflecting that many HoFH and HeFH patients have combined dyslipidaemias (Table 3).

3.5. Annual averages data

Data are available for a total of 63 patients (48.8%) and amounted to 348 years of LA treatment. The number of years of treatment per patient ranged from 1 to 15. The average number of treatments per year and the average volumes of blood/plasma treated are shown in Supplementary Table G. The overall average volumes of blood and plasma treated were 6.85 L and 4.07 L respectively.

The annual average data are presented in Table 4. The lipid concentration (C) prior to the apheresis procedure is termed the baseline value (c-Baseline), the immediate post apheresis level is the minimum value (c-Min), the level at the start of the subsequent apheresis is the maximum value (c-Max_x) and the average value between the sequential procedures is the interval mean (c-Mean) [12]. Baseline and maximum values become equal after 2–4 cycles of apheresis [11].

The overall mean baseline TC pre-apheresis was 8.1 mmol/l (range 3.4–16.9 mmol/l) and the c-Mean TC was 6.4 mmol/l (range 1.13–13.03 mmol/l). The overall mean baseline LDL cholesterol was 6.9 mmol/l (range 1.34–14.37 mmol/l) and the c-Mean was 4.68 mmol/l (range 1.00–11.02 mmol/l). The mean acute reduction in TC in all the patients was 52.6%, for LDL cholesterol it was 60.2% and for Lp(a) it was 60.0%.

The mean reduction in interval mean LDL-C from baseline was 43.14%. The mean reduction in interval mean Lp(a) from baseline was 37.95%.

Lp(a) levels were raised in all patients and were highest in the HeFH group when compared to the HoFH, hyper Lp(a) and Non-FH patients (1275.4 mg/l; 1001.9 mg/l; 1160.0 mg/l and 878.3 mg/l respectively).

3.6. CV data

In addition to the annual averages data, each centre was asked to provide data on the number of CV events suffered by their patients both before and since commencing LA. This is presented in Fig. 1 and shows a significantly higher rate of events just prior to starting LA. There was a 62.5% reduction in MACE between the 2 years prior to LA and the first 2 years of treatment. In the year prior to starting treatment, there were a total of 40 CV events, compared to the 2, 3, 4 and 5 years before LA when the event rates were 16, 19, 10 and 9 respectively. The event rate gradually decreases as the number of years of treatment increases, however, this takes time to occur. There were 14 CV events in the first year of LA, and 7, 19 and 18 in years 2, 3 and 4 respectively. After 10 years of LA, the event rate had fallen to 4. CVD events occurred most frequently before and after commencement of LA in patients who required a central line for access with an average of 3.71 events per patient pre LA and 1.0 events post LA. In patients who required an AV fistula there were 1.76 events per patient pre, and 0.98 post and in those whose native veins were used for the treatment the rate was 1.48 pre and 0.93 after starting LA.

Table 4
Annual lipid parameters data.

Factor	Homogygotes [n = 15]	Heterozygotes [n = 25]	Hyper Lp(a) [n = 5]	Non-FH [n = 18]
TC				
C baseline - mmol/l	10.54 [n = 15]	7.72 [n = 25]	5.45 [n = 5]	7.02 [n = 18]
% ↓C baseline *vs* TC off treatment	47.54	27.20	19.74	18.20
C mean - mmol/l	8.27	6.36	4.60	5.31
% ↓C interval mean *vs* baseline TC	56.67	31.77	24.49	33.01
Acute % reduction (range)	62.27 (38.7–81.2)	52.87 (40.1–77.4)	51.29 (46.1–61.0)	43.90 (32.0–58.8)
LDL-C				
C baseline - mmol/l	8.61 [n = 15]	5.51 [n = 23]	3.42 [n = 5]	7.84 [n = 17]
% ↓C baseline *vs* LDL off treatment	50.44	34.57	34.36	24.58
C mean - mmol/l (range)	6.57 (1.90–11.02)	4.36 (1.79–8.22)	2.70 (1.05–4.05)	3.66 (1.70–8.47)
% ↓C interval mean *vs* baseline LDL	63.17	37.93	34.83	30.09
Acute % reduction (range)	69.22 (40.3–88.5)	60.22 (43.0–60.2)	65.34 (51.4–78.3)	49.15 (25.0–68.7)
Lp(a)				
Baseline – mg/l	1001.9 [n = 11]	1275.4 [n = 12]	1166.0 [n = 5]	878.3 [n = 4]
% ↓C baseline *vs* Lp(a) off treatment	23.07	25.50	No data	31.65
C mean – mg/l (range)	745.7 (166.0–1472.0)	978.6 (97.0–1892.7)	853.85 (606.4–1097.3)	550.7 (13.0–960.5)
% ↓C interval mean *vs* baseline Lp(a)	34.60	34.16	No data	66.06
Acute % reduction (range)	71.95 (43.8–89.1)	60.72 (35.5–82.5)	64.68 (57.2–75.0)	60.95 (51.5–61.0)
HDL-C				
C baseline - mmol/l	1.27 [n = 15]	1.23 [n = 25]	0.90 [n = 5]	0.93 [n = 18]
% ↓C baseline *vs* HDL off treatment	29.30	15.99	9.69	16.50
Acute % reduction (range)	35.01 (12.7–79.7)	22.42 (12.5–22.4)	22.44 (12.1–38.9)	16.88 (5.8–35.0)

C baseline, lipid concentration prior to apheresis; C mean, interval mean between sequential treatments; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); HDL-C, high-density lipoprotein cholesterol.

4. Discussion

This is the first presentation of registry data illustrating the UK experience of LA. Only two of the four UK nations have LA services. Access to treatment remains a challenge due to the limited number of centres providing LA, lack of understanding of its benefits by clinicians and commissioners, and the expense and invasive nature of the intervention. Although the diagnosis and treatment of familial hypercholesterolaemia (FH) has attracted an increased profile in recent years [16], Lp(a) is not routinely measured in UK clinical practice, other than in specialist lipid clinics and treatment of hyper Lp(a) is rarely considered. In the UK, 8 units provide LA. These are geographically located in the south of the UK (Supplementary Fig. A), such that LA is rarely offered to patients who do not reside near a unit. Three of these units are dedicated LA centres, two are in renal dialysis units, two are run by the Blood Transfusion Service and one is a paediatric renal unit. If a physician considers LA as a suitable intervention for a patient, they will need to make a case to the relevant commissioning body to fund

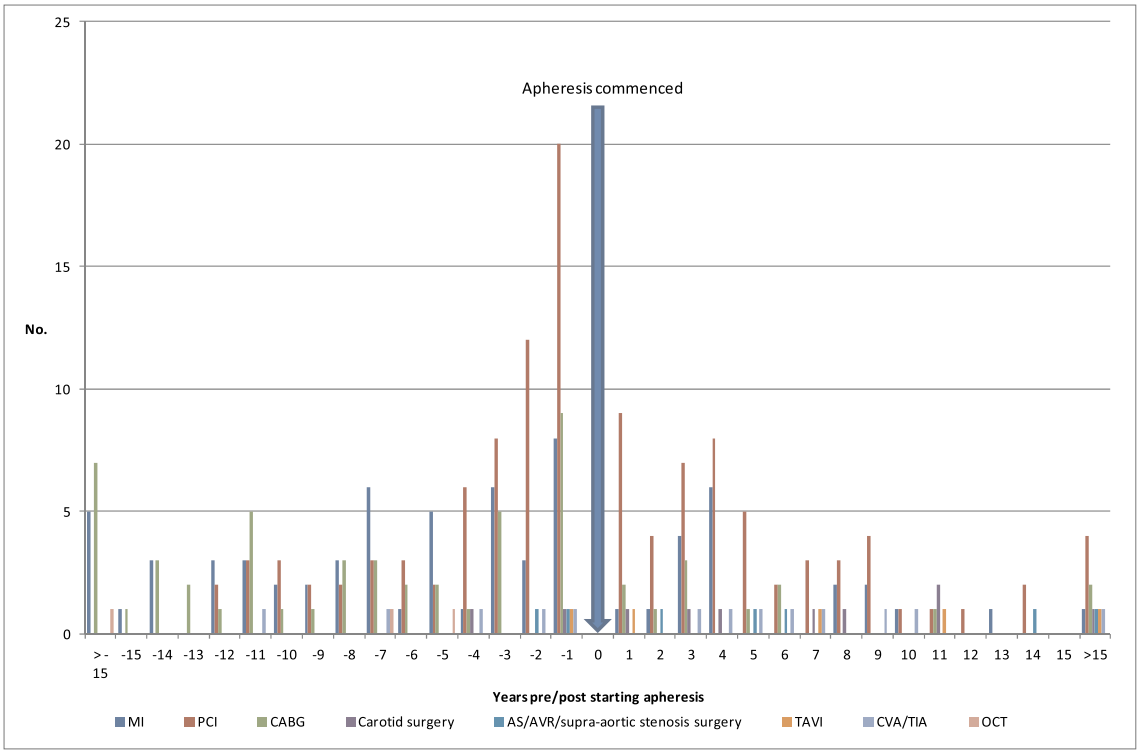

Fig. 1. Cardiovascular events prior and subsequent to commencing lipoprotein apheresis.

treatment. This process is not always straightforward and patients who might benefit from LA may not have the treatment funded.

It is apparent that access to this important intervention remains difficult in the UK, with significantly less patients accessing treatment compared to other developed countries [9]. Recent registry data from Germany presented data from 1435 patients in 71 centres over 4 years [6]. In Turkey there is a national registry for HoFH patients which, in 2018, included 88 patients undergoing regular LA in 19 specialised centres [17]. None of these patients had genetic confirmation of HoFH and the diagnosis is based on clinical criteria alone. There is no registry data for other patients undergoing LA. At present, there is no central registry of HoFH in the UK, although the development of this is being explored. It is not clear if all patients with HoFH in the UK currently have access to LA, as they should in accordance with international and UK guidance [11,18,19]. Hyper Lp(a) as an indication for LA is well-established in some countries [6,20], but nearly all patients in the UK treated for this indication are from one centre, where a clinical trial which explored the utility of LA in reducing Lp(a) in the context of refractory angina was recently completed [13]. Registry data from Italy includes all patients undergoing any form of therapeutic apheresis and has identified a total of 21 patients undergoing LA for FH and a further 10 for hyper Lp(a) [21]. Access to LA, for this and other indications remains sub-optimal in the UK, mainly in relation to commissioning constraints. Increasing the profile of LA as an important treatment intervention has been recognised as a significant issue and HEART UK continues to address this with clinicians and commissioners.

The LA technique utilised by centres does vary. This is related to local expertise and in some cases due to contractual arrangements between centres and companies which provide the equipment and consumables. It is recognised that access to multiple LA modalities is advantageous [22], but this is often not possible in small centres. Dextran Sulphate adsorption of whole blood (DSA-B) which employs negatively charged Dextran Sulphate to directly bind with the positively charged surface of apoprotein B containing lipoproteins, was the most commonly used system followed by the DALI system (direct adsorption of lipoproteins), using polyacrylate-coated polyacrylamide beads which selectively adsorb LDL and Lp(a) from whole blood. The number of different systems used by each centre ranged from 1 (Bristol and Leeds) to 5 (Llandough).

Most patients achieved vascular access using native veins alone, in contrast to the recommendation within NICE guidance [8]. Many centres have found this to be safe, effective and well tolerated for patients across several different treatment modalities. This is now the vascular access route of choice in most centres. Some LA centres are co-located with renal dialysis units and in those there is a preference for use of an arterio-venous (AV) fistula. However, the high flow rates needed for haemodialysis that they provide are not needed for LA and AV fistulas can give rise to problems such as strictures at the anastomosis [23]. Infection, aneurysm, vascular steal and thrombosis are well-described in the context of AV fistulas used for haemodialysis [24].

PCSK9 monoclonal antibodies have emerged as an alternative to LA in some patients with HeFH, polygenic and combined dyslipidaemias, which is reflected in our experience. This is now a common reason for discontinuation of LA and is likely to be both safe and effective, unless if the patient is known to be LDL receptor negative [25–27]. It seems likely that LA will remain an important intervention in HoFH and in patients with hyper Lp(a), although anti apo(a) antisense therapy, which is undergoing clinical trials may influence the latter, if proven to be effective.

Although intolerance to statin therapy is not a specific indication for LA, in patients who have significant dyslipidaemia, usually in the presence of ASCVD, it might be considered an option. Our experience indicates that this can be an effective treatment in this patient group. However, due to funding constraints in the UK, this is in a small number of patients, who will often have progressive ASCVD.

Geographical distance from a LA unit is a significant challenge for patients and due to the location of current units (Supplementary Fig. 1), LA is not a practicable option for many patients within the UK. Many patients travel more than 50 miles to access treatment. The impact of travel should not be underestimated, as it may also influence treatment adherence. Distance to a unit may also affect treatment acceptance and referral.

German registry data shows an impressive 78.0% reduction in MACE in the first 2 years on LA when compared to the 2 years prior to treatment [6]. The UK data shows a trend to fewer MACE after initiation of LA, although this is less marked than in Germany. This may in part be due to patients being referred later for LA in the UK than in Germany and often not until several MACE have occurred. This is evidenced by the high rate of PCI carried out in the patients in the registry in the 2 years prior to initiation of LA, 32 versus 13 in the 2 years following commencement of LA. It is likely that this event rate highlighted the need for more aggressive therapy and drove the referral for LA treatment. Although incidence of MACE is included in the UK registry, this data had not been completed by some of the centres, however, the MACE data presented here, regarding 63 patients in four of the LA centres, was obtained by individual contact with each of the LA centres which increases the accuracy of this data. The German registry contains data on a significantly larger number of patients and treatments, 1435 patients undergoing 19,800 treatments [6]. Italian registry data from 2015 describes improvements in patients' health status rather than MACE events. LA was reported as showing an improvement in health status in 50.0% of patients but prevented worsening cardiovascular condition in 92.0% of cases [21].

Since the initiation of this registry in 2011 three major developments have occurred. Firstly, it has been shown unequivocally that total and CV mortality and the incidence of MACE in HoFH are all determined by on-treatment levels of total and LDL-C [7]. Patients with a total cholesterol > 15.1 mmol/l had a hazard ratio for death that was more than tenfold higher than better treated patients with a total cholesterol < 8.1 mmol/l. Secondly, there has been increased availability and proof of efficacy of the novel LDL-C lowering drugs, lomitapide [28] and evolocumab [27]. And thirdly, consequent upon these advances, the target levels of LDL-C for effective treatment of HoFH have now been set much lower than hitherto [11,29], at 1.8 and 2.5 mmol/l for adults with and without CV disease, rendering previous recommendations obsolete [11,13]. Hence for a homozygote with a baseline LDL-C off all treatment of 20.0 mmol/l an overall mean reduction of 90% is required if the 1.8 mmol/l target is to be met. Similar LDL-C targets are applicable to patients with HeFH and progressive CV disease despite maximal drug therapy [28]. The registry results indicate that these objectives are not being met.

Regarding hyper-Lp(a), a recent study suggests that the CV risk associated with an Lp(a) > 80th percentile is markedly attenuated in a primary prevention setting if the LDL cholesterol is < 2.5 mmol/l [30]. Another analysis based on Mendelian randomisation proposed that reductions in Lp(a) of 100 mg/dl are required to achieve a reduction in CV risk comparable to lowering LDL cholesterol by 1.0 mmol/l [31]. Reductions in Lp(a) of that magnitude are impossible to achieve with existing therapies which raises the question of whether it might not be more profitable in future to focus on reducing LDL-C to < 2.5 mmol/l in hyper Lp(a) patients with CV disease, accepting that this means basing a secondary prevention policy on primary prevention data.

In comparison to the data from the German registry [6], the UK patients achieved similar overall acute reductions in LDL-C, 60.2% in the UK registry patients and 68.6% in the German registry patients. Although the overall reduction in the UK patients was similar, this was not seen in all patients undergoing LA, as the reduction in the non-FH patients was seen to be far less, only 49.15%. The German registry data only differentiates between patients with raised LDL-C and hyper Lp(a), therefore the number of patients with HoFH, HeFH or non-FH is unknown. This variation in acute reduction in the UK may be a reflection on the fact that funding for treatment in the UK is not dependant on

specific reductions in lipids as it is in Germany. The German registry patients achieved an overall superior acute reduction in Lp(a) compared to the UK patients; 70.4% versus 60.0%. The proportion of patients in the two registries undergoing LA for hyper Lp(a) differs which probably reflects the contrasting emphasis in the two countries on treatment of hyper Lp(a). In Germany it is 50.8% and in the UK, it is only 7.75%. An acute reduction in any lipid fraction of less than 50% with LA is usually felt to be a suboptimal treatment. It is important that these data are used to review the current treatment strategies in the UK and change practice so that patients receive optimum treatment and therefore gain the most benefit.

It is important to recognise that interval mean levels of LDL and Lp (a) reflect both the volume of plasma or blood treated and the frequency of apheresis. Ideally this should be two plasma or blood volumes per procedure (acute reduction > 80%) at weekly intervals. HoFH patients in the Turkish registry achieved a mean acute reduction in LDL of 68.2% in the last four sessions of LA [17] which is similar to the 69.22% reduction seen in the HoFH patients in the UK registry. Data from a Norwegian study of seven patients with HoFH showed comparable results with an average acute reduction in LDL of 62.71%. Two of the Norwegian patients also had significantly raised Lp(a) levels and these were acutely reduced by an average of 65.68%, which is similar to the UK patients [32]. Lipid results are not collected in the Italian registry.

4.1. Limitations

There are some limitations to this report. This is registry data rather than randomised controlled trial data however it would be difficult to carry out a randomised study on the benefits of LA for many of the patients included in the registry for ethical reasons. There is limited information in the registry, some of which was entered several years ago and it would be beneficial to include some additional fields such as length of each LA treatment and adverse effects to provide a more comprehensive report. LA is generally felt to be a safe treatment with a low incidence of adverse events [17]. Adverse events are currently not collected in the apheresis registry and therefore it is unknown if the incidence in the UK is comparable with other centres around the world. There is a plan to add this to the data collected when the registry is updated.

Not all the patients undergoing LA in the UK have been recorded in the registry. Participation in the registry is voluntary although each centre is requested to contribute data. In addition, the annual averages data which provided the important information about efficacy of LA, is lacking for many patients. It is important that all centres carrying out LA enter complete data for all their patients to ensure it is representative of LA in the UK.

There is incomplete data on lipid levels at diagnosis, especially in the hyper Lp(a) group, reflecting the infrequent measurement of this lipoprotein in the UK. This is due to several factors; some of the patients were born outside the UK and there is limited access to blood results from other countries. This information is also not available for some patients who were diagnosed at a young age. Some data on levels at the start of apheresis is also lacking, particularly in patients who started LA prior to 2011 when the registry was created. The age at which LA was started was not recorded uniformly by all centres. Some recorded the date treatment started at their centre whereas others recorded that date that any LA commenced. This particularly relates to some of the HoFH patients who received treatment as children in one centre (Hammersmith) and then moved to another UK centre and others who started their treatment in another country.

There is a lack of follow-up data for the patients who have stopped LA which would be useful to compare outcomes without treatment or with alternative treatment. The long-term CVD data is encouraging but is limited as most of the patients have only been receiving LA for a few years.

4.2. Conclusion

Lipoprotein apheresis remains an important therapy for patients with resistant forms of dyslipidaemia, particularly those with HoFH. The establishment of the UK registry has enabled collection of clinical outcome data relating to the treatment and its effects. In contrast to some other countries in Europe, provision of this treatment continues to be poor in the UK. The introduction of novel pharmacological agents such as PCSK9 inhibitors and lomitapide is likely to reduce the number of patients requiring LA. However, data from the UK registry demonstrates the efficacy of the treatment in reducing both LDL-C and Lp(a) and its positive impact on the incidence of CV events. This underlines the therapeutic benefit of LA for patients with HoFH and those who do not respond to, or are intolerant of drug therapy, especially those with progressive CVD.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

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