Diagnosis, management and prognosis of familial hypercholesterolaemia in a UK tertiary cardiac centre

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ABSTRACT

Objective: To describe demographic characteristics, current local clinical management and outcomes for patients with familial hypercholesterolaemia (FH) managed at the Royal Brompton and Harefield NHS Foundation Trust (RBHT), a specialist UK tertiary cardiac centre.

Research design and methods: A local service evaluation of patients with FH was conducted by RBHT. Patients were identified from local FH databases and medical records based on pre-defined eligibility criteria. Descriptive statistics were performed.

Main outcome measures: Proportion of patients with cardiovascular (CV) events during the period of follow-up; per cent change in low-density lipoprotein cholesterol (LDL-C) between highest untreated and most recent measurement; description of patient characteristics and treatment pathways.

Results: The final evaluation sample included 306 patients whose first contact with the RBHT FH service was between November 1991 and February 2015. Patients were followed up until 2016 (median 4.4 years, range 1.2–24.9). Forty-three per cent (131/306) of patients had genetically confirmed FH and 56% (172/306) did not but meet a modified Simon Broome criteria. One fifth (20%, 60/306) had at least one CV event prior to their first contact with the service, mainly angioplasty (15%, 45/306) and MI (10%, 32/306). Thirty-five patients (11%) had CV events during the period of follow-up, occurring at a mean of 5.2 years after first contact. Of 269 “current” patients (i.e. patients with at least one contact with the service in the previous 3 years) 90% (241/269) were prescribed statins, with adverse events experienced by 30% (73/241). Eleven patients received lipoprotein apheresis. Only 34% (49/143) of patients had a reduction of ≥50% between the highest untreated and most recent LDL-C measurement.

Conclusions: Results highlight the challenges of diagnosing and management of this high risk patient group whilst reducing CV events. Future work should focus on characterisation of patient subgroups and optimising treatment with novel therapeutic agents.

Introduction

Familial hypercholesterolaemia (FH) is an inherited genetic defect characterised by elevated low-density lipoprotein cholesterol (LDL-C) levels from birth leading to early atherosclerotic heart disease and increased risk of premature death. Without effective treatment, the cumulative risk of a coronary event by the age of 60 is ≥50% in men and ≥30% in women [1–3]. Mutations in three genes, LDL-receptor gene (LDLR), gene coding for apolipoprotein B (apoB) and the gene encoding proprotein convertase subtilisin/kexin 9 are responsible for causing FH. In patients in whom no causative mutation can be found a polygenic cause for their raised LDL-C level is most likely. In the UK the 2008 National Institute for Health and Care Excellence (NICE) guidelines on FH [4] and the associated Quality Standard [5] recommend cascade screening for first degree relatives of all patients with FH. This results in early diagnosis for many individuals with FH and once identified, individuals will be offered healthy lifestyle advice and appropriate lipid lowering therapies. However, despite this, it is thought that FH remains widely under diagnosed and therefore often under treated [6]. Until recently, heterozygous FH prevalence in the UK was considered to be 1 in 500 and homozygous FH 1 in 1,000,000. However, recent Northern European population studies suggest that prevalence of heterozygous FH is likely to be 1 in 200 to 270 and homozygous FH 1 in 640,000 [7–10].

Lipid-lowering drug treatment includes statins with ezetimibe as an addition in those with severe hypercholesterolaemia. Furthermore, in a small group of patients with severe hypercholesterolaemia and established coronary artery disease, lipoprotein apheresis treatment is recommended. Further to this, a recent
recommendation to manage patients with FH whose LDL-C levels are not controlled despite maximal tolerated doses of lipid-lowering combinations and who are intolerant to statins will be considered for PCSK9 inhibitors [4,11,12].

Royal Brompton and Harefield National Health Service (NHS) Foundation Trust (RBHT) is a specialist, tertiary NHS centre with a comprehensive service for the screening and management of patients with FH. Dedicated nurse specialists run regular genetic screening clinics (since 2005) for patients with suspected FH and a “cascade testing” programme for systematic identification of affected relatives. Follow-up management for patients with confirmed FH, including medication management and lifestyle and dietary advice, is also provided. This single centre offers CV prevention and follow-up for both adult and paediatric patients. RBHT is one of the few Trusts in the UK to offer lipoprotein apheresis for patients whose cholesterol levels are not adequately controlled with medication alone.

RBHT has conducted an evaluation of its current FH service. Specifically, this evaluation is aimed to describe the baseline demographic and clinical characteristics of patients with FH at the date of first contact with the service; to describe the proportion of patients who experienced a CV event during follow-up; to describe FH management pathways including lipid-lowering treatments; to describe levels of lipid control achieved; and to describe the NHS resource use associated with the management of patients with FH by the service. The results will be beneficial in identifying any areas that may require improvement, helping to ensure optimal patient management and most effective use of NHS resources. We share here our key learnings for the benefit of other organisations involved in the management of patients with FH.

Materials and methods

Study design and approval

A single centre retrospective local service evaluation was conducted between November 2015 and November 2016 at RBHT. Approval by a NHS Research Ethics Committee was not sought since local service evaluations are exempt from REC review in the UK [13]. Also, there was no requirement for patient/next of kin consent because the evaluation data were collected from identifiable medical records by members of the patient’s direct care team therefore maintaining confidentiality. However, local management approval for the evaluation’s conduct and for release of pseudonymised data to pH Associates, an independent research consultancy, was obtained prior to commencement of data collection.

Patients

Figure 1 provides an overview of the study design and patient eligibility criteria. In brief, a list of potentially eligible patients who had been seen by the clinical lead of the RBHT FH service and genetically tested for FH was generated by a member of the patient’s direct care team using local FH databases and hospital patient administration systems. The medical records of these patients were obtained in descending chronological order according to the date of genetic testing with the aim to review as many as possible within the given time frame and data collection resource available. However, some eligible patients were included on the basis of convenience as their notes were available for data extraction. It was originally intended that all eligible patients would be included in this evaluation but due to data collection resources and time constraints this was not possible. 306/500 (61%) patients were included in this evaluation.

Patients were eligible for inclusion in the evaluation if they were genetically tested for FH at RBHT; had a diagnosis of FH (either genetically confirmed FH [heterozygous or homozygous] or genetic test result was inconclusive but the patient met a modified version of the Simon Broome criteria [used by Harefield Hospital for possible FH]) [14] and was receiving treatment for the condition; their routine management (following genetic testing) took place at RBHT under the FH service (i.e. one or more management [follow-up] visits); and their first contact (this could be before genetic testing was undertaken if they were under the care of the RBHT FH service) with the RBHT FH service was ≥12 months before the date of data collection. All ages were included.

Patients were excluded if FH was deemed “unlikely” based on the results of genetic testing and/or clinical presentation; their routine management (following genetic testing) was performed at another NHS Trust or another department within RBHT; their RBHT medical records were unavailable for retrospective review; or their first contact with the RBHT FH service was ≤12 months before the date of data collection.

Data collection methodology

Data including age, gender, ethnicity, prior CV events and age at occurrence, comorbidities, blood pressure, smoking status, body mass index and alcohol consumption were collected for all eligible patients at the time of first contact with the service. Data were collected from existing local FH databases, RBHT hospital medical records and electronic hospital systems, and recorded
in pseudonymised form onto a standard data collection form (DCF) designed specifically for the evaluation. The collected pseudonymised data were released to pH Associates for data management, analysis and reporting. Genetic testing results and data on CV outcomes during the period of follow-up with the service (i.e. from first contact until the date of data collection, death, lost-to-follow-up or permanent discharge) were also collected from RBHT records. CV outcomes included death from CV causes, non-fatal myocardial infarction (MI), non-fatal cerebrovascular accident (CVA), transient ischaemic attack (TIA), unstable angina, coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI). For “current” patients (those who had at least one contact with the RBHT FH service in the three years prior to data collection), data on lipid parameters (i.e. LDL-C), management pathways (i.e. drug treatment and apheresis) and resource use (i.e. outpatient appointments) for the most recent three years of management were also collected. Collected
data was entered into the study database and cleaned against a series of data validation checks. No source data verification was undertaken.

**Statistical methods**

Data was analysed using Microsoft Excel™ and Stata™. Distributions and descriptive statistics of both central tendency (medians and arithmetic or geometric means) and dispersion (standard deviation [SD], range, and interquartile range) are presented for quantitative variables. Nominal variables are described with frequencies and percentages, while ordinal variables also have medians and interquartile ranges described. No assumptions were made to account for missing data and analysis was conducted on data available. Results are presented for the evaluation sample overall and (for CV history/outcomes and LDL-C control) stratified by gender. As the natural history and treatment outcomes are likely to differ between patients with homozygous and heterozygous FH, analyses for the key evaluation outcomes were also conducted excluding the three patients with genetically confirmed homozygous FH (see Supplementary Tables 1–4). Owing to the small number of patients with homozygous FH, results for this subgroup are not presented separately.

**Results**

**Sample characteristics**

The final evaluation sample included 306 patients, who had their first contact with the RBHT FH service between November 1991 and February 2015. At the date of data collection, 65% of the patients evaluated (198/306) remained under the care of the FH service, with a median of 4.4 years (mean 6.2 years) between the date of the first contact and the date of data collection. Twenty-eight per cent of patients (85/306) had been discharged from the service (median 3.8 years from first contact to discharge) and 6% (19/306) were lost-to-follow-up (median 2.1 years from first to last contact). One patient died and for three patients their status was not recorded. Of the patients who had been permanently discharged from the FH service, the majority (80%, 68/85) were discharged to General Practice.

The 306 patients included in the evaluation were genetically tested for FH at RBHT between October 2005 and April 2016. Forty-three percent (131/306) had genetically confirmed FH (1% [3/306] confirmed homozygous, 41% [125/306] confirmed heterozygous, 1% [3/306] variant of unknown significance), 56% (172/306) were not confirmed FH and the screening outcome was not recorded for 1% (3/306). Patients that were not genetically confirmed each clinically met the modified Simon Broome criteria.

**Patient demographic and clinical characteristics**

The demographic and clinical characteristics of included patients are displayed in Table 1 (also in Supplementary Table 1, excluding the three patients with homozygous FH). A similar proportion of males and females (52% versus 48%) comprised the overall sample. The median age of patients at first contact with the service was 51.8 (range 4.9–84.9) years.

One fifth of patients overall (20%, 60/306) (14% [21/147] of female and 25% [39/159] of male patients) had at least one CV event prior to their first contact with the service, mainly PCI (15% of patients, 45/306) and MI (10%, 32/306). At presentation half of the patients (150/306) were on statins (27%, 83/306 were on high-intensity statin doses [atorvastatin 20–80 mg, rosuvastatin 10–40 mg or simvastatin 80 mg]) and 8% (26/306) were on ezetimibe. Thirty-seven per cent of patients (114/306) had recorded co-morbidities; essential hypertension was the most common (10%, 31/306), thyroid disease (6%, 19/306), diabetes mellitus (4%, 12/306). Almost 67% (118/176) of patients with recorded BMI were overweight or obese, 38% (115/ 306) were current or ex-smokers. Half of the patients (154/ 306) were current consumers of alcohol and 29% (88/306) were abstinent (data not available for 21%, 64/306).

The median LDL-C value at first presentation was 4.7 (IQR 3.3–5.6) mmol/L (n = 212) overall; 4.8 (IQR 3.6–5.7) mmol/L (n = 104) in females and 4.4 (IQR 3.3–5.4) mmol/L (n = 108) in males. The median highest untreated LDL-C value was 5.8 (IQR 5.3–6.6) mmol/L (n = 181) overall; 5.8 (IQR 5.3–6.8) mmol/L (n = 93) in females and 5.9 (IQR 5.3–6.6) mmol/L (n = 88) in males.

**CV events**

Eleven per cent (35/306) of patients in the evaluation (8% [12/147] of female and 14% [23/159] of male patients) had CV events during the period of follow-up. None of the patients with CV events had a diagnosis of homozygous FH. Overall, there were 82 events in total occurring at a mean of 5.2 years after the first contact. The most common CV events were PCI (a total of 47 events, occurring at a mean 6.5 years after the first contact), unstable angina (8 events, occurring a mean 2.9 years after the first contact), CABG (7 events, occurring a mean 2.6 years after the first contact), MI (5 events, occurring a mean 6.3 years after the first contact).
Table 1. Patient demographic and clinical characteristics (at first presentation, unless specified).

| Patient demographic and clinical characteristics | Number of patients (n = 306) | % | Mean (SD) age at occurrence (years) | Median (IQR) age at occurrence (years) |
|--------------------------------------------------|-----------------------------|---|-------------------------------------|---------------------------------------|
| **Gender**                                       |                             |   |                                    |                                       |
| Male                                             | 159                         | 52%|                                   |                                       |
| Female                                           | 147                         | 48%|                                   |                                       |
| **Age (years)**                                  |                             |   |                                    |                                       |
| Under 18                                         | 25                          | 8% |                                   |                                       |
| 18 < 30                                          | 30                          | 10%|                                   |                                       |
| 30 < 40                                          | 25                          | 8% |                                   |                                       |
| 40 < 50                                          | 56                          | 18%|                                   |                                       |
| 50 < 60                                          | 78                          | 25%|                                   |                                       |
| 60 < 70                                          | 69                          | 23%|                                   |                                       |
| ≥70                                              | 23                          | 8% |                                   |                                       |
| Median age (years) = 51.8                        |                             |   |                                    |                                       |
| Range (years) = 4.9–84.9                         |                             |   |                                    |                                       |
| **Ethnicity**                                    |                             |   |                                    |                                       |
| White (British/Irish/Other)                      | 228                         | 75%|                                   |                                       |
| Asian (British/Asian)                            | 32                          | 10%|                                   |                                       |
| Black (British/African/American/Caribbean)       | 5                           | 2% |                                   |                                       |
| Other                                            | 39                          | 13%|                                   |                                       |
| Not recorded                                     | 2                           | 1% |                                   |                                       |
| **Comorbidities**                                |                             |   |                                    |                                       |
| Hypertension                                     | 31                          | 10%|                                   |                                       |
| Diabetes mellitus                                | 12                          | 4% |                                   |                                       |
| Liver disease                                    | 0                           | 0% |                                   |                                       |
| Renal disease                                    | 0                           | 0% |                                   |                                       |
| Pancreatic disease                               | 0                           | 0% |                                   |                                       |
| Thyroid disease                                  | 19                          | 6% |                                   |                                       |
| Other                                            | 62                          | 20%|                                   |                                       |
| None                                             | 159                         | 55%|                                   |                                       |
| Not known/not recorded                           | 33                          | 11%|                                   |                                       |
| **Body Mass Index (n = 176)**                    |                             |   |                                    |                                       |
| Underweight (<18.5)                              | 6                           | 3% |                                   |                                       |
| Healthy weight (18.5–24.99)                      | 52                          | 30%|                                   |                                       |
| Overweight (25–29.99)                            | 76                          | 43%|                                   |                                       |
| Obese (30 or over)                              | 42                          | 24%|                                   |                                       |
| **Smoking status**                               |                             |   |                                    |                                       |
| Current smoker                                   | 48                          | 16%|                                   |                                       |
| Ex-smoker                                        | 67                          | 22%|                                   |                                       |
| Never smoked                                     | 168                         | 55%|                                   |                                       |
| Not recorded                                     | 23                          | 8% |                                   |                                       |
| **Alcohol consumption**                          |                             |   |                                    |                                       |
| Consumes                                         | 154                         | 50%|                                   |                                       |
| Does not consume                                 | 88                          | 29%|                                   |                                       |
| Not recorded                                     | 64                          | 21%|                                   |                                       |
| **Blood pressure**                               |                             |   |                                    |                                       |
| Low (<90/60)                                     | 1                           | 0.3%|                                  |                                       |
| Ideal (90/60–120/80)                             | 70                          | 23%|                                   |                                       |
| Pre-high (>120/80 – <140/90)                      | 89                          | 29%|                                   |                                       |
| High (≥140/90)                                   | 45                          | 15%|                                   |                                       |
| Not known/not recorded                           | 101                         | 33%|                                   |                                       |
| **Prior CV events (not mutually exclusive)**     |                             |   |                                    |                                       |
| MI                                               | 32                          | 10%| 45.8 (11.6)                       | 45.6 (38.7–54.0)                      |
| CVA                                              | 3                           | 1% | 46.9 (17.5)                       | 46.9 (40.7–53.1)                      |
| TIA                                              | 5                           | 2% | 56.7 (14.8)                       | 57.5 (48.8–65.4)                      |
| Unstable angina                                  | 15                          | 5% | 51.9 (12.4)                       | 47.2 (41.8–58.4)                      |
| CABG                                             | 17                          | 6% | 46.3 (9.0)                        | 46.0 (40.6–52.2)                      |
| PCI/PTCA                                         | 45                          | 15%| 50.7 (10.9)                       | 48.4 (43.7–58.6)                      |
| Target vessel revascularisation                  | 8                           | 3% | 56.4 (10.6)                       | 56.4 (49.5–60.5)                      |
| **Drug treatments for FH (not mutually exclusive)** |                       |   |                                    |                                       |
| **Statins (overall)**                            | 150                         | 49%|                                   |                                       |
| Atorvastatin                                     | 75                          | 25%|                                   |                                       |
| Rosuvastatin                                     | 18                          | 6% |                                   |                                       |
| Simvastatin                                      | 51                          | 17%|                                   |                                       |
| Pravastatin                                      | 4                           | 1% |                                   |                                       |
| **High intensity statin treatment**              | 83                          | 27%|                                   |                                       |
| **Ezetimibe (overall)**                          | 26                          | 8% |                                   |                                       |
| Bile acid sequestrant                            | 1                           | 0.3%|                                 |                                       |
| Fibrate                                          | 11                          | 4% |                                   |                                       |
| Nicotinic acid                                   | 1                           | 0.3%|                                 |                                       |
| Other (omega 3)                                  | 6                           | 2% |                                   |                                       |

*Not mutually exclusive

All patients on 10 mg

CABG: Coronary artery bypass graft; CV: Cardiovascular; CVA: Non-fatal cerebrovascular accident; FH: Familial hypercholesterolaemia; IQR: Interquartile range; LDL: Low density lipoprotein; MI: Non-fatal myocardial infarction; PCI/PTCA: Percutaneous coronary intervention/percutaneous transluminal coronary angioplasty; SD: Standard deviation; TIA: Transient ischaemic attack
Management pathways and resource use

These results relate to the 269 “current” patients only (i.e. those who had at least one contact with the RBHT FH service in the previous three years). The proportion of patients receiving each treatment for FH during the evaluation period is displayed in Table 2 (also in Supplementary Table 2, excluding the three patients with homozygous FH). In the most recent 3 years of management, 90% of patients in the overall sample (241/269) were prescribed statins. The proportion of patients prescribed high-intensity statin treatment was 60% (161/269). Ezetimibe was prescribed for 36% of patients (97/269) and fibrates were prescribed for 7% (18/269) of patients.

Thirty per cent (73/241) of the patients on statin therapy reported to have experienced an adverse event during the three year evaluation period. The most common adverse events were muscle ache (35 events in 12% [30/241] and muscle cramps (28 events in 8% [20/241]). Nineteen per cent (45/241) of the patients on statin therapy had at least one discontinuation or change in therapy/dose during the three year observation period that was reported to be due to adverse events.

Ninety-nine per cent (267/269) of the “current” patients had at least one outpatient visit with the service within the three year period before the date of data collection, with a mean of 3.7 (SD 1.3) visits per patient overall; 2.4 (SD 1.7) visits per patient to the coronary prevention clinic and 1.2 (SD 1.3) visits to the FH follow-up clinic. Two per cent of patients (6/269) had day-case attendances at RBHT during the evaluation period, 0.4% (1/269) had A&E attendances and 5% (14/269) had inpatient admissions. Four per cent (11/269) of patients had biweekly lipoprotein apheresis treatment. The mean number of apheresis sessions in these patients was 54.4 (SD 19.9), ranging from 20.0 to 78.0 sessions per patient.

LDL cholesterol (LDL-C) control

Details of LDL-C control during the three year observation period for the sample overall and stratified by gender are presented in Table 3 (also in Supplementary Tables 3 and 4, excluding the three patients with homozygous FH).

Of the 143 patients in the overall sample with measurements available at both time points, the median LDL-C value was 5.8 mmol/L for the highest ever untreated measurement and 3.4 mmol/L for the most recent measurement. Twenty-one per cent (30/143) had a reduction of up to 25%, 38% (54/143) had a reduction of between 25% and 50% and 34% (49/143) had a reduction of ≥50%. The median percentage change in LDL-C was –43% overall (–41% in females [n = 74] and –44% in males [n = 69]).

For 48% of patients with one or more CV event (before presentation or during follow-up; n = 52), LDL-C measurements recorded within the three year observation period were persistently higher than 3.5 mmol/L and for 75% of patients with no documented CV event (n = 199), LDL-C measurements recorded were lower than 5.0 mmol/L.

Discussion

This local service evaluation reports on the current management, clinical outcomes and resource use for patients with FH who have been genetically tested and received follow-up treatment under the FH service.

Table 2. Treatments prescribed for FH during the evaluation period.

| Treatment* | Number of patients | % (n = 269) |
|------------|--------------------|-------------|
| Statins (overall) | 241 | 90% |
| Atorvastatin | 142 | 53% |
| Rosuvastatin | 89 | 33% |
| Simvastatin | 62 | 23% |
| Pravastatin | 16 | 6% |
| High-intensity statin treatment | 161 | 60% |
| Atorvastatin 20–80 mg | 111 | 41% |
| Rosuvastatin 10–40 mg | 67 | 25% |
| Simvastatin 80 mg | 0 | 0% |
| Ezetimibe | 97 | 36% |
| Fibrates | 18 | 7% |
| Other (omega 3) | 20 | 7% |
| No drug treatments recorded/prescribed | 20 | 7% |
| Lipoprotein apheresis | 11 | 4% |

*Number of patients on each drug not mutually exclusive

Table 3. Low density lipoprotein (LDL) cholesterol – highest ever and most recent measurements during the 3-year observation period.

| LDL cholesterol (mmol/L) | Overall | Females | Males |
|--------------------------|---------|---------|-------|
| Highest ever | Most recent | Highest ever | Most recent | Highest ever | Most recent |
| Number of results | 143 | 143 | 74 | 74 | 69 | 69 |
| Mean | 6.0 | 3.6 | 6.0 | 3.8 | 6.0 | 3.5 |
| SD | 1.4 | 1.3 | 1.6 | 1.4 | 1.2 | 1.2 |
| Median | 5.8 | 3.4 | 5.8 | 3.3 | 5.8 | 3.4 |
| IQR | 5.3–6.5 | 2.8–4.1 | 5.2–6.8 | 2.8–4.2 | 5.3–6.5 | 2.7–4.1 |
| Range | 0.8–10.5 | 1.3–8.2 | 0.8–10.5 | 1.8–8.1 | 3.0–9.7 | 1.3–8.2 |

Only includes patients with paired data (i.e. measurements available at both time points).
IQR: Interquartile range; LDL: Low density lipoprotein; SD: Standard deviation
at RBHT. This is a comprehensive, integrated service offering CV prevention and management as well as specialist screening for FH, the length of patient follow-up was substantial and CV outcome data are reported. The evaluation was conducted primarily to explore and optimise the service, however, key learnings are shared to benefit other organisations involved in the management of patients with FH.

The characteristics of the evaluation sample indicate a high-risk patient group with multiple CV risk factors, as might be expected for patients with FH receiving long-term specialist management. During the period of follow-up 11% of patients overall had CV events, a rate lower than that reported in other studies from Canada, Denmark and the United States [7,15,16]. This lower rate should be interpreted with caution however as not all eligible patients from the service were included in the dataset and only CV events documented in the RBHT records were collected. The CV event rate in the present evaluation appears higher than that observed in the SAFEHEART Registry study [17], although SAFEHEART included only incident CV events.

Target recommendations for lipid control in patients with FH have been provided by a number of UK and international organisations. In the UK, NICE recommends a reduction in LDL-C concentration of >50% from baseline (i.e. before treatment [4,5]). Although considerable improvements in lipid control were observed during the period of management with the service, only 34% of patients met this target. These data are consistent with other reports in the literature from the UK [18], other European countries [19–21] and the Americas [15,16]. This highlights the challenge of managing this patient group despite multiple interventions, frequent contact and dietary/lifestyle advice. Every effort was taken to prescribe the maximally tolerated lipid lowering combination. The relatively low use of ezetimibe in this cohort, many of whom were treated prior to the final publication of the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) in 2015, is likely to be due to concerns raised about the safety of ezetimibe in an earlier (2008) study (SEAS; Simvastatin and Ezetimibe in Aortic Stenosis), which reported a possible increased risk of cancer [22]. It is anticipated that the use of ezetimibe would be higher in a more recent patient cohort. The adverse events experienced by patients on conventional therapies may have resulted in non-compliance. Tolerability of statins was a significant limiting factor in this cohort with almost a third of patients on statins experiencing adverse events. However, this should be viewed with caution as it has been suggested that many of the symptomatic adverse events that are attributed to statin therapy in routine practice may not actually be caused by it [23,24]. Also, patient choice or reluctance to use statins and compliance issues associated with the requirement for long-term treatment may have contributed to the challenge of managing lipid levels whilst also minimising lifestyle impairment and maximising quality of life in this patient group. Furthermore, as the evaluation captured only a snapshot of patients’ management over a three year period rather than complete pathways of care, data relating the degree of statin intolerance (for example the number of statins tried) or compliance with established protocols to manage these side effects [25] are not available.

In spite of best efforts of staff and patients in a specific coronary prevention clinic, the results indicate the real-world difficulty in achieving recommended targets. There is a need for more effective treatments to further improve lipid control and reduce CV risk. The PCSK9 inhibitors alirocumab and evolocumab, are both now approved by the European Medicines Agency for patients with FH who are unable to reach LDL-C goals with the maximum tolerated dose of a statin, are statin intolerant and those for whom statins are contraindicated [26,27], and are also recommended by NICE under certain conditions [11,12]. Almost half of patients (48%) with one or more CV event and a quarter of the patients (25%) with no CV event had LDL-C levels persistently above the NICE-recommended thresholds for PCSK9 inhibitor treatment (3.5 mmol/L and 5.0 mmol/L, respectively) and therefore, may potentially have been eligible to receive these treatments. These medicines were not available during the evaluation period but can be expected to have an impact on the future treatment landscape [28–32]. Indeed, since this evaluation was conducted some patients in this Trust have started treatment with PCSK9 inhibitors.

During the three-year observation period “current” patients in the evaluation sample had a mean of 3.7 outpatient visits with the FH service, indicating that they are followed up at least once every year. This is in line with the current NICE guidelines for the identification and management of FH which recommends that all people with FH should be offered a regular structured review that is carried out at least annually [4]. The vast majority of FH-related resource use during the evaluation period was for care delivered on an outpatient rather than inpatient basis. It is important to remember however, that the evaluation only collected NHS resource use at RBHT and overall resource use may have been higher still due to admissions to other hospitals that have not been captured.

Although the overall burden of inpatient hospital care was low, 11 patients (3 patients were homozygous) required lipoprotein apheresis treatment and had a very high level of resource use (a mean of 54 apheresis sessions per patient in three years). Apheresis is an
important treatment option for patients whose cholesterol levels are not adequately controlled with medication alone and is known to be associated with substantial annual resource costs [33]. Further work to characterise this patient subgroup would be of value to help guide future treatment decisions. PCSK9 inhibitors may help to reduce reliance on apheresis in the most difficult-to-manage patients with consequent impact on cost and patient experience [34].

**Limitations**

There are a number of limitations that need further consideration. This was a local service evaluation. Consequently, although the results may be of interest to clinicians and researchers outside the Trust, they may not be generalisable to the wider population of UK patients with FH.

As this was a retrospective evaluation, the data quality relied on the accuracy and completeness of information recorded in patients’ RBHT hospital medical records. The results of tests and investigations were only captured if they were undertaken as part of routine clinical practice and as a result, they were not available for every patient at every time point. Importantly, pre-treatment lipid parameters were not documented for a number of patients and it was not possible in these cases to calculate a percentage change from an untreated baseline. Also, lipoprotein(a) concentrations, known to be a potential confounder of the diagnosis of FH [35–37], were available for only a small number of patients in the evaluation sample.

It is recognised that more detailed information about certain aspects of the diagnosis of FH would be beneficial, to enable a more complete description of the patient cohort and confirm the appropriateness of genetic testing. However, it was not possible to confirm Dutch Lipid Clinical Network Scores, or the proportion of patients with probable/possible FH according to the Simon Broome criteria, using the information available retrospectively from patients’ medical records.

A breakdown of genetic diagnoses for those with genetically confirmed FH is not presented because patients were genetically tested for FH between 2005 and 2016, not all using current testing methodologies. In addition, we are unable to determine whether patients with inconclusive genetic results were due to variants in apoB or high polygenic score, as this diagnostic method was not available to our centre before May 2016.

Finally, as mentioned previously, it was originally intended that all identified eligible patients would be included in the evaluation but this was not possible within the time and data collection resource available. It is possible that the sampling strategy employed to select patients for inclusion may have biased the sample in favour of living patients and those undergoing more frequent monitoring, perhaps because of a CV event; consequently, the survival and CV outcomes reported here may not reflect those of the service as a whole. Furthermore, the planned subgroup and regression analyses of patients with CV events or high resource use were not possible due to low patient numbers. This might have been possible if all eligible patients had been included.

**Conclusions**

RBHT offers a comprehensive, integrated service for the genetic testing and long-term treatment of patients with FH. Although not generalisable to the wider UK population, the long-term favourable outcome observed in this large cohort of patients with multiple CV risk factors is likely to be of interest to clinicians and researchers.

During the evaluation period patients at RBHT were treated intensively using the available lipid-lowering therapies and were reviewed on at least an annual basis. Although considerable improvements in lipid control were observed during the period of treatment, many patients did not meet published lipid control targets, highlighting a need for more effective treatments. Nevertheless, relatively low levels of CV events were observed in the cohort; this may be due to the strong emphasis placed on risk factor modification and lifestyle factors, with a particular focus on the importance of healthy diet, smoking cessation, exercise and weight control. These factors are assessed at each consultation and revisited at least annually. The vast majority of FH-related resource use during the evaluation period was for care delivered on an outpatient basis and the overall burden of inpatient hospital care was low. However, a small number of patients required lipoprotein apheresis and had a very high level of resource use. Further work to characterise this patient subgroup would be of value, to help guide future treatment decisions.

**Note**

1. RBHT uses a modified version of the Simon Broome criteria for diagnosis of possible FH, in which “Family history of myocardial infarction: below age of 50 in second-degree relative or below age 60 in first-degree relative” is replaced with “Family history of cardiovascular disease: below age of 50 years in second-degree relative or below age 60 years in first-degree relative”.

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Contributorship

MB contributed to the conception and design of the evaluation and the interpretation of the data. JB contributed to the conception and design of the evaluation and the acquisition and interpretation of the data. EN contributed to the acquisition and interpretation of the data. LP-B and FL contributed to the acquisition and interpretation of the data. RG-M contributed to the interpretation of the data. All authors critically reviewed the manuscript and approved the final version for submission.

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