A multi-methods study of the factors influencing the adoption of proprotein convertase subtilisin/kexin-type 9 (PCSK9) inhibitors

by

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Declaration

I declare that the work contained in this thesis is my own with cited material explicitly referenced. I have not submitted this thesis for any other personal qualification or degree within Keele University or any other institution.

Abstract

Introduction

A new class of lipid lowering agent Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors (PCSK9) was launched in 2015 for the treatment of heterozygous familial hypercholesterolemia (HeFH) in combination with statin therapy. There appeared to be a relatively slow uptake of PCSK9 inhibitors. The first aim of the study was to examine clinical attributes associated with reduction in low-density lipoproteins cholesterol (LDLC) among HeFH patients, while the second aim was to explore the factors influencing the use of PCSK9 inhibitors in clinical practice.

Methods

The quantitative phase of the study used logistic regression to investigate HeFH clinical attributes from the Clinical Practice Research Datalink (CPRD) database (n=5134) in relation to a final LDLC level of 5 mmol/l; which is the threshold for PCSK9 inhibitor eligibility for HeFH. The qualitative phase of the project involved 17 in-depth semi-structured interviews to explore stakeholder perceptions of the factors influencing the use of PCSK9 inhibitors.

Results

LDLC levels featured prominently in the results of both phases of the study. Quantitative analysis showed that 18% of HeFH patients did not meet the 5mmol/l threshold for PCSK9 inhibitor eligibility even though they did not achieve the guideline recommended treatment target of 50% LDLC reduction with statin therapy. Lipid consultants perceived the eligibility threshold as an inhibitor of prescription in these cases. There was also an issue with LDLC levels not being recorded; 48% of HeFH patients in the CPRD dataset did not have a record of LDLC. In the clinical

setting, this had the effect of delaying PCSK9 inhibitor prescription when evidence of multiple LDLC readings meeting the prescription threshold was required. In primary care, GPs suggested that nurses could increase the recording of LDLC records because they had first contact with patients while performing health checks. Overall, low awareness of HeFH was associated with low rates of referral to secondary care for PCSK9 inhibitor consideration. Facilitators of PCSK9 inhibitor use included support from pharmaceutical companies who provided educational material for PCSK9 inhibitor use. Patients were also perceived to engage with treatment when they understood that HeFH could cause cardiac events.

Conclusions

This study found that LDLC records were critical to the prescription of PCSK9 inhibitors. In the quantitative analysis the clinical attributes of maximum LDLC on record, age and lipid medication use were statistically associated to LDLC achievement. It was however not possible to predict PCSK9 inhibitor eligibility; further work would involve the addition of clinical attributes such as lipoprotein (a) to the model analysis. PCSK9 inhibitor prescription was perceived to be hindered by inadequate recording of LDLC records. Consultants also reported that the LDLC thresholds for eligibility were restrictive in some cases. LDLC is an important determiner of PCSK9 inhibitor use; improved LDLC recording and evaluation of LDLC thresholds may be necessary in efforts to optimise PCSK9 inhibitor use.

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Chapter 1 Introduction

Heterozygous familial hypercholesterolemia (HeFH) is a genetic disorder that is characterised by elevated levels of serum low density lipoprotein cholesterol (LDLC) from birth. According to Nordestgaard et al. (2013), less than 1% of heterozygous familial hypercholesterolemia (HeFH) patients have been diagnosed in most countries, and a majority of identified patients do not meet recommended treatment targets.

A new class of lipid lowering medication, Proprotein Convertase Subtilisin/ Kexin-Type 9 (PCSK9) inhibitors has been launched for the treatment of HeFH. These medicines effectively reduce LDLC levels in HeFH and present a potential opportunity to improve the therapeutic management of the disease.

However, multiple factors have been identified to influence the adoption of new medicines (Jones et al. 2001; Garjón et al. 2012; Stevenson et al. 1999; Prosser, Almond and Walley, 2003). Prosser, Almond and Walley (2003) categorise these factors into; influence from the pharmaceutical industry, colleagues, patient contexts, educational written information and biomedical/ pharmacological factors. The existence of these factors could result in potential delays in the adoption of PCSK9 inhibitors.

The aim of the present thesis is to explore the potential factors influencing the adoption of PCSK9 inhibitors. In order to achieve this, the objectives of the data collection phases of the study were; to examine clinical attributes associated with

reduction in low-density lipoprotein cholesterol (LDLC) among HeFH patients, and to explore the factors influencing the use of PCSK9 inhibitors in clinical practice.

The current chapter provides a background for this thesis, it discusses;

- HeFH and identifies potential challenges to its management that could influence PCSK9 inhibitor use.
- The role of PCSK9 inhibitors in the treatment of HeFH.
- The rationale for studying the barriers and facilitators to the adoption of PCSK9 inhibitors.

1.1 Heterozygous familial hypercholesterolemia

1.1.1 Definition of familial hypercholesterolemia

HeFH is an autosomal dominant genetic condition caused by one of several gene mutations that affect the metabolism of low density lipoprotein (LDL) cholesterol; the resultant clinical effect is a marked increase in serum cholesterol levels (Hopkins et al., 2011) (Goldberg et al., 2011).

1.1.2 Molecular pathology

The HeFH phenotype is expressed by a mutation(s) on the low density lipoprotein receptor (LDLR) alleles causing a loss of function in the clearance of LDL cholesterol from the blood stream (Soutar and Naoumova, 2007). Civeira (2004) reported that more than 800 mutations had been located on the gene; however, this currently stands at more than 1600 (http://www.ucl.ac.uk/fh). These mutations account for about 85-90% of FH cases (Goldberg et al., 2011). Defects in specific loci have been identified to cause similar variations of FH; these include apolipoprotein b-100 (apoB – the ligand for the receptor), PCSK-9 (an enzyme that down regulates LDLR) and a mutation in LDLRAP1 which causes a rare autosomal recessive form of FH (Austin et

al., 2004).The clinical management of these variations of FH does not differ (Civeira, 2004).

Due to the autosomal dominant nature of familial hypercholesterolemia, HeFH is observed when mutations occur on a single copy of the low density lipoprotein receptor (LDLR) allele (Raal and Santos, 2012) (Hopkins et al., 2011). There is therefore a 50% chance that HeFH is inherited by a child in the case that one parent is affected by the disease (Civeira, 2004). The resultant effect is that 50% of LDL receptors are dysfunctional, increasing plasma LDL cholesterol levels to the range of 5 – 12 mmol/L (Watts et al., 2012).

1.1.3 Pathophysiology

Cholesterol is a lipid that forms part of the structural component of cell membranes; it is also involved in the synthesis of steroid hormones, vitamin D and bile acids. Cholesterol is mainly transported in the circulatory system as low density lipoprotein (LDL) secreted by the liver. Watts et al. (2012) described the clearance of the LDL from the blood as:

“Circulating LDL-cholesterol is pre-dominantly cleared via the liver by a tightly regulated LDL receptor pathway that involves particle binding and internalisation, endosome formation, cholesterol release to the cell and recycling of the receptor back to the cell surface.”

Uncontrolled serum cholesterol leads to increased deposition in tissues causing tendinous xanthomata, accelerated atherosclerosis and increased risk of premature coronary heart disease (CHD) (Austin et al., 2004). The degree of serum LDLC elevation is determined by the extent of the fault on hepatic metabolism of LDLC; which in turn is affected by the graveness of genetic mutation.

Cholesterol lowering forms the basis of HeFH management. When the disease is untreated, 1 in 2 male and 1 in 6 female patients suffer from CHD by the age of 40 (Watts et al., 2012), translating to a 24 fold increase in CHD (Robinson, J. and Goldberg, 2011) compared to a healthy individual.

1.1.4 Cardiovascular pathology

Heart disease is the main cause of death in the UK, approximately 25% of disease related mortality is attributed to CVD by the Office for National Statistics (2012). Coronary heart disease and stroke cause 75% of these deaths. The contributive effect of FH in the causation of irregular serum cholesterol levels that lead to premature deaths due to CVD is well documented. The exact cost implication of FH to the NHS is however unclear due to a high incidence of undiagnosed cases.

Coronary heart disease (CHD) is a multifactorial disorder with contributory effects from environmental and genetic factors. Age, lifestyle factors including smoking, lack of exercise and unhealthy diet form key components of environmental determinants of CHD; the mechanism of action of these factors are due in part to the accumulation of LDL cholesterol and the depletion of high density lipoprotein (HDL) cholesterol (Castelli et al., 1987) (Austin et al., 2004). The association between genetics and CHD is drawn from a consistent relationship between CHD patients and their family histories (Kardia et al., 2003); this relationship, however, does not account for the cumulative effects from the environment.

The clinical manifestations of CHD are caused by the deposition of excess LDL cholesterol in blood vessel walls. LDL cholesterol enters the wall endothelium through small damaged segments; the LDL particles are then oxidized and monocytes aggregate in these cuts absorbing the LDL cholesterol in the process. In fully functional vessel walls; there is a re-uptake of these monocytes into the blood

stream followed by a healing process, excessive serum LDL cholesterol overwhelms the natural healing process causing continuous deposition (Watts et al., 2012) (Austin et al., 2004). Healthy vessels are responsible for maintaining blood pressure and vascular tone; dysfunctional vasculature, arteries in particular, leads to atherosclerosis and an increase in cardiovascular events (Watts et al., 2012).

1.1.5 Summary of heterozygous familial hypercholesterolemia

HeFH is a genetic disorder with an autosomal dominant inheritance pattern. This means that a child would have a 50% chance of contracting the disease given that one parent carries the defective gene. HeFH renders cholesterol clearance pathways defective; this causes an accumulation of LDLC in the blood. Elevated serum LDLC damages blood vessels and the cardiovascular system in general, resulting in an increased rate of CVD morbidity and mortality in HeFH patients.

1.2 Prevalence and screening of HeFH

1.2.1 Prevalence of familial hypercholesterolemia

Patient identification remains an important challenge in the management of HeFH. The prevalence rate of the heterozygous form of FH is often quoted as 1/500 (0.2%) as documented in Goldstein et al. (1973) in USA. This was confirmed in different countries as follows; the UK by Slack (1979) and Patterson and Slack (1972), Japan by Mabuchi et al., (1977) among other studies.

However, more recent studies have reported higher prevalence rates. These include Nordestgaard et al. (2013), Marks et al., (2003) and Watts et al., (2012) that report prevalence rates of 1/200 (0.5%), consider the prevalence rates reported earlier to be underestimates basing their arguments on the actual number of myocardial infarction deaths associated with impaired lipid metabolism world-wide, and more recent epidemiological studies. Similar results include Neil et al. (2000), which found that only 25% of predicted HeFH patients were diagnosed. An audit for the Royal College

of Physicians estimated that ~15% of the predicted 120,000 cases in the UK were diagnosed (Pedersen et al., 2010). Civeira (2004) estimates that only 10% of 10,000,000 people with FH world-wide are diagnosed and less than 25% are on lipid lowering therapies.

Screening of HeFH patients and their family members is recommended by the National Institute for Health and Care Excellence (NICE) clinical guidance 71(CG71) to improve patient identification. This is discussed in section 1.2.3.5 below.

1.2.2 Signs and symptoms

Prior to the advanced stages of the disease, HeFH is largely asymptomatic. This lack of symptoms constitutes a potential problem in the diagnosis of the disease. The onset of clinical symptoms is associated with a high rate of CVD mortality and morbidity and warrants aggressive lipid reduction. This is because the disease progresses during the asymptomatic phase as several studies have shown. For example, Cabellero et al. (2012), using non-invasive methods (ultrasounds, MRI and blood tests), showed the development of aortic (94%) and lipid (33%) plaques in asymptomatic FH patients signifying the increase in CHD risk. Although the sample size for this study was small, several other researchers have reported similar findings; of note is the paper by Neefjes et al. (2011) which found accelerated development of subclinical CHD in patients who were receiving intensive lipid lowering therapies. The extent of CHD was related on gender and the level of LDLC attained during treatment.

The Cardiac Society of Australia and New Zealand in a review carried out by Sullivan et al. (2013) outlined the clinical features of HeFH as shown below;

"…

Premature coronary heart disease (CHD)

Premature cardiovascular disease (CVD)

Aortic stenosis

Tendon xanthomas (11%)

Corneal arcus (27%)

Xanthelasmas (12%) ".

Similar to the cardiovascular pathology of the disease (discussed in section 1.1.4), the signs and symptoms of HeFH are caused by the deposition of LDL cholesterol in bodily tissues (Watts et al., 2012). Xanthomas are caused by the accumulation of lipids in the skin, xanthelasmas by the accumulation of lipids around the eyes while corneal arcus are formed by the deposition of lipids in the cornea. Xanthomas are not associated with any further symptoms; however, corneal arcus have been linked to increased intraocular pressure and decreased central corneal thickness (Hovingh et al., 2013).

1.2.3 Diagnosis and screening

The diagnosis of HeFH is categorized into three criteria that separate the clinical, biochemical and genetic aspects of the disease (Marks et al., 2003). A clinical diagnosis of HeFH is usually made in primary care and is based on the physical symptoms of the disease; this is usually supported by biochemical tests that mainly assess LDLC levels. A definite diagnosis of HeFH is based on genetic testing.

1.2.3.1 Clinical testing

An understanding of clinical signs and symptoms form an integral part of the initial diagnosis of HeFH. Civeira (2004) lists these signs and symptoms as high plasma cholesterol levels, family history of hyperlipidemia especially in children, xanthomas,

xanthelasmas and arcus cornealis. Some of these symptoms are not specific to HeFH; therefore, secondary causes (obesity, diabetes, smoking, hypothyroidism, corticosteroids, nephrotic syndrome) have to be excluded before postulating the existence of HeFH (Hopkins et al., 2011) (Watts et al., 2012).

1.2.3.2 Biochemical testing

Biochemical diagnosis, the measurement of LDLC levels, is necessary for the confirmation of HeFH (Marks et al., 2003). However, the range of total serum cholesterol levels in HeFH patients overlaps with that of non-genetic hypercholesterolemia. This could produce false positive or negative results of between 8-18% in suspected HeFH cases (Kwiterovich et al., 1974). Although diagnosis based on the clinical and biochemical elements of HeFH ensure that lipid lowering agents are initiated in a timely manner; genetic testing remains the best method for HeFH diagnosis.

1.2.3.3 Genetic testing

NICE UK (CG71) recommends the use of genetic testing to confirm clinical/ biochemical test results and to produce a definitive diagnosis of HeFH. A deterrent in the use of this method is the cost (Marks et al., 2003) (Pears et al., 2014); from a cascade screening perspective however, there is a reduction in the cost once causative mutations are identified and family members are tested.

The multifactorial genetic nature of HeFH means that several causative mutations can affect the LDL receptor; additionally, new mutations continue to be discovered for this gene as discussed in section 1.1.2 (Molecular pathology). This presents a potential limitation in the use of genetic testing for HeFH. In populations with a high number of genetic mutations causing FH, this testing process is elongated and may be less accurate (Heath et al., 1999). Marks et al. (2003) accredits the limitations of genetic testing to insensitivity, failure to test all LDLR or apoB genes and inaccurate

diagnosis from clinical and biochemical testing. Genetic testing is nonetheless an important method of finding a conclusive diagnosis for HeFH due to inaccuracies in biochemical testing, and lack of or insufficient family/ personal histories and lack of clinical symptoms (Watts et al. 2012). Furthermore, it has been shown that the benefit gained from correctly identifying patients outweighed the procedural difficulties experienced (Austin et al., 2004). This is because definitive diagnosis of HeFH allows for cascade screening of family members and early identification of the condition.

1.2.3.4 Diagnostic criteria

Diagnostic criteria are tools that are developed to aid patient identification and diagnosis. Austin et al. (2004) discusses diagnostic criteria developed by three groups for HeFH. These include the US MedPed (Utah Make Early Diagnosis to Prevent Early Deaths) Program, the Simon Broome Register Group in the United Kingdom, and the Dutch Lipid Clinic Network (DLCN). These criteria take into account key factors that reduce the efficiency of the clinical and biochemical diagnostic methods discussed above, and have been statistically and genetically validated (Hovingh et al., 2013). The three systems are shown in table 1.1 below. The MedPed criteria use only lipid levels, while the Simon Broome Register Group criteria and DLCN use physical signs, family and personal history in addition to cholesterol levels (Fahed and Nemer, 2011).

MEDPED Criteria (USA)					
	Total Cholesterol (LDL-C) levels in mg/dL				Comments
Age	1st Degree relative	2nd Degree relative	3rd Degree relative	General population	
<18	220 (155)	230 (165)	240 (170)	270 (200)	98% specificity 87% sensitivity
20	240 (170)	250 (180)	260 (185)	290 (220)	
30	270 (190)	280 (200)	290 (210)	340 (240)	
40 +	290 (205)	300 (215)	310 (225)	360 (260)	
Simon Broome Criteria (UK)					
Total Cholesterol (LDL-C) in mg/dL 290 (190) in adults, or 260 (155) in pediatrics	AND	DNA mutation			Definite FH
		Tendon xanthomas in the patient or in a 1st or 2nd degree relative			Propable FH
		Family history of MI at age <50 in 2nd degree relative or at age <60 in 1st degree relative OR Family history of total cholesterol >290 mg/dL in 1st or 2nd degree relative			Possible FH
Dutch Criteria (The Netherlands)					
1 point	1st degree relative with premature cardiovascular disease or LDL-C >95th percentile, or Personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 and 189 mg/dL				Definite FH (= or > 8 points
2 points	1st degree relative with tendinous xanthoma or corneal arcus, or 1st degree relative child (<18 yrs) with LDL-C > 95th percentile, or Personal history of coronary artery disease				
3 points	LDL-C between 190 and 249 mg/dL				Probable FH (6-7 points)
4 points	Presence of corneal arcus in patient less than 45 yrs old				
5 points	LDL-C between 250 and 329 mg/dL				Possible FH (3-5 points)
6 points	Presence of a tendon xanthoma				
8 points	LDL-C above 330 mg/dL, or Functional mutation in the LDLR gene				

Table 1.1 The most commonly used criteria for the clinical diagnosis of FH, obtained from Fahed and Nemer (2011).

1.2.3.5 Screening

Despite the tools available for HeFH case detection, diagnosing an index case of the disease remains an opportunistic matter (Neil et al., 2000). Pedersen et al (2010) attributed the low rates of diagnosis to the lack of comprehensive national screening programs in the UK.

NICE CG71 recommends that the screening process is initiated when cholesterol levels of >7.5 mmol/l are recorded in a patient. This should be followed by the use of diagnostic criteria to assess the likelihood of HeFH. In the UK, the Simon Broome Criteria are commonly used; these provide HeFH likelihood as a ‘definite’ or ‘possible’ score. Cascade screening of family members should follow this finding using both genetic and biochemical (LDLC) tests. Whenever there is a negative

result from the genetic testing of a hypercholesteraemic patient, cascade screening of family members is still recommended using LDLC measurements.

National cascade screening services have been initiated in several countries including Netherlands (Umans-Eckenhausen et al., 2001), Norway (Leren et al., 2004), Spain (Pocovi et al., 2004), Scotland and Wales (Finnie, 2010) and England. The service in England is however limited as evaluated by Pedersen et al. (2010); Pears et al. (2014) attributed the mixed results of the national FH screening service to costs and a general laxity of commissioning groups to adopt the service due to current spending commitments, pressure to increase savings and disruption of existing models of care.

Similarities between national screening services include the use of family-based methods as opposed to the 'universal' approach or population screening. Nevertheless, varying rates of effectiveness have been achieved across countries as discussed by Fahed and Nemer (2011). This could be explained by the difference between the systems in using both patient screening (opportunistic or targeted screening) and cascade testing; Iceland, in particular, uses a novel system where the ancestors of index cases are traced and the oldest in each lineage screened as opposed to testing only first and second degree relations. Netherlands, Spain and Wales use a community approach that involves home visits (Hovingh et al., 2013).

1.2.4 Summary of prevalence and screening of HeFH

Despite the measures put in place for diagnosis and screening of HeFH patients, the identification of patients is limited. Evidence shows that HeFH is managed more efficiently in countries that have set up screening, and cascade screening services. NHS hospitals continue to implement the screening services; however, more work is still required (Pears et al., 2014). Inadequate identification of patients has the

potential of reducing the number of patients that receive medication. For a new medicine, such as PCSK9 inhibitors, inadequate diagnosis could lead to low usage. It may therefore be important to assess the patient journey from the perspective of the stakeholders involved. This could potentially serve to improve the process, and explore the potential effect that the patient identification process could have on PCSK9 inhibitor usage.

1.3 Therapeutic agents for HeFH

The treatment of HeFH is based on statin therapy. Statins are recommended as first line therapy by NICE UK (CG71) in both adults and children of 10 years or older (it is however advised that children and young people should be referred for specialist treatment); ezetimibe can be used in place of statins due to intolerance or contraindications. The treatment objective is to reduce LDL cholesterol levels by 50% from baseline using the maximally accepted doses of high intensity treatment if required. Bile acid sequestrants (resins), nicotinic acid and fibrates are alternative treatment options available from specialists when statins and ezetimibe are not appropriate or as additional therapies.

1.3.1 Statins

HMG-CoA reductase inhibitors or statins antagonise the effect of the enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase); a component of the cholesterol synthesis process in the liver. The result is a decrease in serum cholesterol levels (Patel, 2014). The safety and efficacy of statins, in lowering blood cholesterol and preventing cardiovascular disease, have been demonstrated in several placebo controlled clinical trials. Watts et al. (2012) asserts that statins are powerful agents in the control of blood lipids, a statement that is reflected in the recommendation of statins as the first line medication for the treatment of

hypercholesterolemia by NICE UK. The effectiveness of statins in reducing mortality rates due to heart disease was shown in the Scandinavian simvastatin survival study (SCANDINAVIANSIMVASTATINSURVIVAL, 1994). This result was reaffirmed by many studies thereafter Sacks et al. (1996), Baigent et al. (2005), Ebrahim et al. (1999). As part of the National Health Service (NHS) health technology assessment program, Ward et al. (2007) reviewed 49 randomized controlled trials and 5 major clinical trials on statins and reported an average reduction of coronary heart disease of 27%. In an assessment of lipid management using statin therapy, Waters et al. (2009) studied 9955 patients across 9 countries with the primary end point of a successful reduction of LDLC levels. The success rate was found to be between 47%-84% with patients with a higher CVD risk profile having a significantly lower possibility of achieving normal cholesterol levels. In a meta-analysis of seven randomised controlled trials; Thavendiranathan et al. (2006) estimated that there was a 29.2% reduction in relative risk of major coronary events with statins compared to placebo. The reduction effect on overall mortality and coronary heart disease mortality was found to be an 8% and 22.6 % respectively. There is general agreement on the benefit of statins in the reduction CVD event rates in secondary care; however, studies in primary care have produced dissonant results (Thavendiranathan et al., 2006) (Ward et al., 2007) (Mills et al., 2008). The effect of statins on FH has not been studied; Robinson and Goldberg (2011) attribute this to the ethical issues arising from denying patients an effective form of treatment for the purposes of research. Statins are effective lipid lowering agents; rosuvastatin is presently the only branded statin in the market (NICE UK TA132); it has been shown to produce reduction in LDLC of between 40.6-58.1% according to Civeira et al. (2004); the paper notes that this result is significantly greater compared to other statins.

The benefit of statins in children and adolescents with HeFH is recognized although the precise age at which the agents are safe for use is currently a matter of clinical judgement and consideration of other risk factors in a given situation (Watts et al., 2012). Statins are contraindicated during pregnancy and breast feeding (Kusters et al., 2010). Page et al. (2015) discusses the reduced effectiveness of statins in LDL receptor-negative hyperlipidaemia. Intolerance to statins remains a key problem under investigation; Williams and Mishra (2015) reported an adverse event rate of 18.2%.

1.3.2 Ezetimibe

Ezetimibe inhibits the absorption of cholesterol by impeding the function of Niemann Pick C1-like 1 protein (Hovingh et al., 2013); the effect is a reduction in the amount of cholesterol crossing the intestinal wall. As monotherapy, ezetimibe reduces LDLC levels by 17.3% while as an adjuvant to statin therapy (at a dose of 10mg) a decrease of 14-25% compared to placebo has been recorded (Civeira et al., 2004). Although ezetimibe is recommended as an alternative or add-on to statins in specific cases for many international guidelines (NICE UK included), there is a general agreement that it lacks a robust evidence base of its safety and effectiveness profiles (Battaggia et al., 2015) (Califf et al., 2010). Battaggia et al. (2015), a meta-analysis of multiple clinical trials on ezetimibe, documented the disparities in results between subgroups of the ENHANCE trial (Kastelein et al., 2008) and concern about causation of cancer in the SEAS trials (Rossebø et al., 2008) among several other trials with similarly discordant results.

1.3.3 Alternative therapies; bile acid sequestrants, nicotinic acid and fibrates and novel therapies

Bile acid sequestrants bind to bile in the small intestines inhibiting its reabsorption to the liver. This causes a reduction on serum cholesterol using a dual mechanism.

Firstly, cholesterol is the lone precursor in the formation of bile; a reduction of cholesterol causes an incremental function of the hepatic enzyme cholesterol 7-α-hydroxylase, resulting in the conversion of cholesterol to bile acids. Secondly, there is an up-regulation of LDL receptors leading to increased absorption of cholesterol from the blood system (Hovingh et al., 2013).

The action of nicotinic acid, a water soluble vitamin B agent, on LDL cholesterol, triglycerides and lipoprotein (a) has led to its use in clinical practice for ~50 years (Drexel, 2007). Nicotinic acid is recognized to increase HDL cholesterol levels more effectively than other lipid lowering agents; for this reason, it is used in clinical practise in combination with statins in low HDLC cases (Sando and Knight, 2015). The resultant effect of lipid reduction has been investigated in relation to FH and cardiovascular risk reduction (Carlson 1963; 1990). The mode of action of nicotinic acid is currently unclear (Hovingh et al., 2013); some research has shown a multifactorial system initiated by the inhibition of liver DGAT2 (diacyl-glycerol acyltranferase-2) and NADPH (Ganji, Kashyap and Kamanna, 2015). The safety of nicotinic acid is established; ‘flushing’ as a side-effect has been the cause of many withdrawals from the medication. Multiple research projects have studied better methods of managing this side-effect including Guyton and Bays (2007).

Fibrates are metabolised to fenofibric acid which activates peroxisome proliferator-activated receptor-alpha (PPAR-α); several genes involved in the management of lipid in the body are affected by these receptor (Hovingh et al., 2013). Multiple factors have been highlighted to contribute to the function of fibrates. These include; an increase in beta oxidation of fatty acids hence reduced LDL and VLDL cholesterol, a reduction in the manufacture and increase in the elimination of triglycerides and a decrease in Apo C proteins which are known to delay triglyceride metabolism.

Fibrates are estimated to reduce serum triglyceride levels by 20-50%, increasing HDLC levels by 10-50% and reduces LDLC by 5-20% (Milionis et al., 2010).

1.3.4 Efficacy of conventional lipid lowering agents in HeFH

Studies on the long term effects of pharmacotherapy have shown that the CHD risk of HeFH patients can be reduced to that of the general population with proper identification and management of cases (Watts et al., 2012). However, many HeFH patients do not achieve the treatment target recommended by NICE UK using conventional lipid lowering therapies (i.e. 50% LDLC reduction from baseline): (Morales et al., 2018), (Razek et al., 2018), (Hartgers et al., 2018), (Page et al., 2015), (Nordestgaard et al., 2013). Pijlman et al. (2010) found that 47% of HeFH patients attained NICE therapeutic target, similar to values recorded by Morales et al. (2018). If inadequately treated, HeFH patients retain a high risk of CVD.

Several studies have documented variability in LDLC reduction following statin use. The reasons for these variations are reported to either be genetic or phenotypical in nature. For example, mutations in apolipoprotein E have been linked to LDLC response variability Pedro-Botet et al. (2001). Similarly, differences in the ADME process can also affect statin metabolism and vary clinical response Karlson et al. (2016).

Other studies have focused on the effect of decision making and prescribing practices in influencing statin efficacy. Morales et al. (2018) attributed this mainly to patient non-adherence, the effects of the medication and clinical inertia. Pijlman et al. (2010) found that many patients who were not adequately treated were not using the maximum lipid lowering treatment stipulated by guidelines. The reasons for this included patient-physician satisfaction with achieved results, adverse reactions to medication and patient reluctance. Among those that did not meet therapeutic

guidelines 27% of the patients were receiving maximum regimens of conventional lipid lowering treatments.

Nevertheless, studies conducted in more controlled settings have confirmed that on average approximately 50% of HeFH patients achieved therapeutic targets following the use of statins and conventional lipid lowering agents. For example, Robinson and Goldberg (2011) reported the results of a Dutch study involving two academic and three regional settings (n=1249); it was found that 53% of patients receiving treatment did not reach the therapeutic target in spite of maximal doses being used.

The implication is that both medication efficacy and stakeholder decision making are important in the successful treatment of HeFH. Whereas decision making processes can be assessed and changes implemented, the unavailability of effective lipid lowering agents for HeFH remained a major problem. Patients who did not achieve LDLC targets would receive additive medication while registering minimal changes. Furthermore, patients who were intolerant to statins had to take low doses of the medication, or use the less effective alternative medication available. The introduction of PCSK9 inhibitors, therefore presented an opportunity to potentially fill the gaps in the therapeutic management of HeFH.

1.3.5 PCSK9 inhibitors

PCSK9 inhibitors prevent the degradation of LDL receptors by exerting an inhibitory effect of the PCSK9 component of the LDLR gene (Okere and Serra, 2015). An increase in the recycling of LDL receptors produces a corresponding increase in LDLC absorption. PCSK9 inhibitors have been shown to reduce serum cholesterol levels consistently by up to 50% as monotherapy (Navarese et al., 2015) and up to 60% in combinative therapy with statins (Hassan, 2015). In a study comprising three phase two trials, Okere and Serra (2015) reported that the most common adverse

reactions were injection site reactions, diarrhoea, fatigue and headaches. NICE approved two PCSK9 inhibitors with marketing authorisations in the UK; alirocumab (case number ID779 with NICE) and evolocumab (case number ID765).

The guidelines for these lipid lowering agents have also been published and include LDLC thresholds for primary and secondary treatment of HeFH (NICE technology appraisals 393 and 394). For the management of primary HeFH, NICE UK recommends the use of these new medicines when LDLC levels are consistently > 3.5 mmol/ l despite maximal tolerated lipid lowering therapy for secondary prevention treatment; and an LDLC > 5mmol/l in primary prevention treatment. Maximum lipid lowering therapy involves the use of statins, ezetimibe and alternative therapies prior to consideration of PCSK9 inhibitors.

1.3.6 Summary of therapeutic agents for HeFH

Following successful treatment of serum LDLC levels with statins and alternative lipid lowering agents, HeFH patients can attain CVD risk equal to that of a healthy individual. However, successful treatment is hindered by decision making practices among stakeholders and the efficacy of available medication. Currently, the use of conventional lipid lowering medication is effective in approximately 50% of HeFH patients. There is therefore a potential need for PCSK9 inhibitors in treating HeFH patients following statin therapy as guidelines recommend.

1.4 Rationale for studying barriers and facilitators to the use of PCSK9 inhibitors

The rationale for studying the barriers to PCSK9 inhibitor use can be categorised into two groups. Firstly, the general challenges in the management of HeFH, such as low patient identification and inadequate recording of clinical attributes, could potentially affect medication use. Secondly, new medicines are usually costly and their use is often limited to reduce expenditure. With these in mind, this section discusses the

general effect of stakeholder decision making that could potentially affect PCSK9 inhibitor usage.

1.4.1 Stakeholder roles in the management of HeFH

The knowledge, attitudes and experiences of stakeholders (patients, consultants, nurses, GPs etc.) in the care of HeFH has previously been studied in order to explore the practice related reasons for inefficiency in the management of disease. Past research has shown that various factors influence the decision of stakeholders to engage in the HeFH care pathway. These include; feelings of guilt associated with the dietary and lifestyle elements of disease management (Frich, Malterud and Fugelli, 2007), screening services (Green et al., 2015), and the use of statins (Ågård et al., 2005).

Research projects have focused on individual stakeholders; discussed their roles and the potential improvements that can be made to improve provision of care for HeFH. Novel approaches of improving the identification of HeFH patients continue to be developed and critiqued at various levels Weng et al., (2015), Green et al., (2015), Qureshi et al., (2016), Dhiman et al., (2014). Patients' views and opinions have also been studied to assess the reasons behind non-compliance, disease knowledge, attendance of HeFH screening and testing (Claassen et al., 2010) (Weiner and Durrington, 2008) (Hollman, Olsson and Ek, 2006)(Knowles, 2016)(Green et al., 2015) (Frich, Malterud and Fugelli, 2007) (Gidding et al., 2015) (Claassen et al., 2010) (Mortensen et al, 2016). Of interest to this study is the assertion by Watts et al. (2016) that patients' opinions on the controllability of the disease and the efficacy of current pharmacological therapies could be a potential influencing factor towards their willingness to participate in the health system. This provides an opportunity to evaluate the potential of a more effective treatment (PCSK9 inhibitors) in influencing HeFH patients' decisions.

Research focusing on healthcare providers include: factors that influence the decision to prescribe medications (Proser et al., 2003), bias in using certain medications and overprescribing (Green et al., (2007) (Wu et al. 2013) (Mohammed et al., 2012), and the level of knowledge that healthcare practitioners possess on HeFH. Rangarajan et al. (2016) identified a deficit in the knowledge and awareness of GPs based on the HeFH screening, diagnosis and treatment in Tamil Nadu.

In the management of HeFH in the NHS, patients are generally identified in primary care by general practitioners (GPs) and nurses. Patients with severe HeFH or those who are inadequately treated are referred to secondary care where they are attended to by consultant lipid specialists. The immediate stakeholders in the care for HeFH are therefore patients, specialist consultants, GPs and nurses. Specific roles of nurses in the care of HeFH are not explicitly outlined (Krass, Walker and Watts, 2012). Key roles that have been suggested include the monitoring and improvement of patient compliance, the provision of education on disease management and the facilitation of services that require patient participation. (Marks et al. (2003) (Simoens et al., 2005) (Yamada et al., 2005) (Bates,Connaughton and Watts, 2009). (Allen et al., 2014) (Watkins, 2008)(Muir,George and Whitehead, 2012). Research on HeFH (Allen et al., 2002) has shown that nurses have the potential to increase patient engagement with screening and treatment of patients: while Green et al. (2015) utilised an FH audit tool and nurse-led follow up to facilitate the identification of HeFH patients in the Medway CCG. Similarly, the potential for healthcare professionals to increase patient participation through educational campaigns has been shown by Simoens et al. (2005). While Yamada et al. (2005) found that long term interventions by healthcare professionals to facilitate adherence and compliance improved the outcomes of LDLC lowering therapies. An audit of the state of familial

hypercholesterolemia management in the UK (Pedersen et al., 2010) suggested the development of multidisciplinary teams in an effort to improve care provision for HeFH; including the payer's decision to avail a certain medicine.

The evidence suggested that a multidisciplinary approach can potentially increase patient participation, adherence and compliance. Furthermore, different stakeholders have been shown in various projects to be able to positively impact the care for HeFH. However, no research has been carried out on the roles of different stakeholders in the care of HeFH and how their interactions affect the effective delivery of treatment. Research of this nature would also allow for a study of the views and opinions of stakeholders on PCSK9 inhibitors; what they perceive their potential role to be, and issues that may hinder or facilitate the medication's use.

Finally, the prescription of PCSK9 inhibitors are mainly based on the initial use of statins and other conventional lipid lowering therapies as outlined by NICE guidelines (NICE technology appraisals 393 and 394). Considering the potential influences to stakeholder decision making, especially agreement between physician and patients in LDLC targets and external influences to prescription practices, it may be useful to assess the population of HeFH patients that would require PCSK9 inhibitors following statin use in addition to the views and opinions of stakeholders.

1.5 Conclusion

The current knowledge in the field of HeFH indicates that the disease is currently under-diagnosed and under-treated. Most HeFH patients do not achieve the treatment target of 50% reduction in LDLC levels as stipulated by NICE guidelines following the use of statins, and conventional lipid lowering agents. This presents a therapeutic gap that PCSK9 inhibitors could potentially fill.

The use of a medicine is however influenced by factors that revolve around stakeholder decision making practices and organisational policies for prescription. In the case of PCSK9 inhibitors, it is expected that prescription restrictions will be placed on the medication because of their high cost. Additionally, PCSK9 inhibitors are indicated following the inadequate control of LDLC levels using conventional lipid lowering pharmacological therapies. This may suggest the need to assess patient medical records to determine their utility in guiding PCSK9 inhibitor prescription.

The current literature did not include much research on the potential factors influencing the use of PCSK9 inhibitors. The overall implication is that there is scope to increase knowledge on these factors with the aim of facilitating the adoption of PCSK9 inhibitors into current practice; thereby improving HeFH management.

Chapter 2 A review of literature

The current thesis aims at assessing the potential factors influencing the use of proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors in the management of for the heterozygous familial hypercholesterolemia (HeFH). As discussed in chapter one, the current state of knowledge on heterozygous familial hypercholesterolemia (HeFH) includes multiple research studies on the methods adopted to improve quality of care. However, PCSK9 inhibitors were not studied to the same extent, especially as pertains to their use in clinical practice.

This chapter consists of a systematic search and narrative synthesis of studies specifically focusing on PCSK9 inhibitor use in clinical practice and the associated barriers and facilitators to their use. The overall aim of this chapter is to;

- To identify gaps in literature on the barriers and facilitators to PCSK9 inhibitor use.
- Formulate a research question(s) for the current thesis.

2.1 Type of review

The advent of evidence based practices led to a growth of the significance of literature reviews in the 1990s (Grant and Booth, 2009). Broadly speaking, a literature review is an evaluation of 'all', research within a topic area with the intention of summarizing the best quality information for various purposes. These include the synthesis of knowledge for; the guidance of health policy, the assessment of the effectiveness of interventions, or the identification of gaps in literature (Moule et al., 2017). For these purposes, systematic reviews are considered the gold standard (Boland, 2017). A systematic review is a protocol-driven literature search aimed at evaluating all the evidence within a narrow research area. The resulting literature is assessed for quality and bias followed by a synthesis of the information. The key

difference between a systematic and a traditional review lies in the comprehensiveness, transparency and objectivity conveyed in a systematic review (Grant and Booth, 2009).

In some cases however, systematic reviews are either not feasible or unsuitable (Popay et al, 2007). The present study found that literature on the factors affecting PCSK9 inhibitor use encompassed a variety of research designs. From a review perspective, these did not offer sufficient similarity to allow for meta-analysis, and from a synthesis perspective different methods were deemed necessary to synthesise the data. In such a situation, Snilstveit et al. (2012 proposed the use of different types of systematic reviews and methods of synthesis to accommodate the information that did not immediately conform to the systematic review formula (Petticrew and Rogers, 2006); effectively maintaining the advantages offered by systematic methods.

Current systematic reviews on PCSK9 inhibitors focus on clinical efficacy of medication i.e. the low density lipoprotein cholesterol (LDLC) lowering action of the medicine and its effect in improving cardiovascular outcomes. On the contrary, questions regarding the factors affecting the use of PCSK9 inhibitors have rarely been addressed in literature. A systematic search of literature was therefore conducted to ensure that all studies assessing barriers to PCSK9 inhibitor use were identified. A narrative review and synthesis then followed allowing for an exploratory account of the research area.

The main aim of this literature review was therefore for scoping purposes. The intention was to map out all available literature on the barriers to PCSK9 inhibitor use, identify potential gaps in the evidence base, and situate the present study. Due to the exploratory nature of the review, and the expectation of a small number of

studies, the quality assessment process was not considered to be necessary. In place of the process, the study only included peer reviewed publications. The assumption of course, was that the perceived quality established from a peer reviewed article was sufficient to meet this review's aim of identifying literature in the topic area.

The study adopted the framework developed by Kable at al. (2012) to document the search strategy in a systematic manner (Table 2.1). Additionally, some elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol were applied to the study. This was in the form of the PRISMA-P obtained from http://www.prisma-statement.org/Extensions/Protocols.aspx. Finally, the narrative synthesis was guided by a protocol developed by the Economic and Social Research Council (ESRC) – Popay et al. (2006).A thematic approach was applied to the narrative synthesis as described by Barnett-Page and Thomas (2009) in order to categorise the potential barriers to and facilitators of PCSK9 inhibitors.

Step	**Process**
1	Purpose statement
2	Databases and search engines
3	Search limits
4	Inclusion and Exclusion criteria
5	Search terms
6	Database searches and results
7	Relevance of retrieved literature

8	Table reporting of literature in the review
9	Final number of search results
10	Review
11	Complete reference list

Table 2.1 Literature review framework (Adapted from Kable et al., 2012)

2.2 Methods

2.2.1 Purpose statement

This literature review was composed of a systematic review of literature and a narrative synthesis (Saks and Allsop, 2013). The main aim of the review was to identify the evidence available in the research area, to describe the types of studies conducted and to locate the current study in the literature base. This chapter therefore aimed to evaluate the body of evidence on the factors influencing the use of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors. The key focus points of the evaluation were:

1. What are the potential factors affecting the use of PCSK9 inhibitors?
2. What are the effects of stakeholder perceptions and opinions on the use of PCSK9 inhibitors

2.2.2 Databases and search engines

An electronic search was conducted using the EBSCO database. EBSCO provides access to academic journals and e-books across a range of databases simultaneously; these include AMED (Alternative & Complementary Medicine), CINAHLPlus, EconLit, MEDLINE, PsycINFO among others. Further studies/ papers were handpicked from reference lists of the papers identified from the search ("footnote chasing" – (Booth, 2008)).

2.2.3 Search limits

Search limits help to maintain relevance in the search process (Kable et al., 2012). It was expected that there would be a limited number of studies addressing the use of PCSK9 inhibitors because of their relative novelty. Searches were therefore only limited to peer-reviewed articles that were written in English.

2.2.4 Search terms

Search terms were created using the provisional title of the project 'barriers and incentives to the uptake of PCSK9 inhibitors'. The PICO (Population, Intervention, Comparison, and Outcome) tool was used to ensure comprehensiveness of search terms as described by Aveyard, Payne and Preston (2016).

The population of interest was HeFH and associated terms. These terms included the two variations in the spelling of hypercholesterolemia (hypercholesterolaemia). The term 'familial hypercholesterolemia' and associated abbreviations were also included. Finally, the heterozygous form of the disease was specified. PCSK9 inhibitors have currently been approved (NICE UK) for use in HeFH. The homozygous form of the disease is treated different and falls outside the scope of the current study.

Similarly, the intervention section was comprised of terms associated with PCSK9 inhibitors. These included the name of the new class of medication in full, abbreviations of the name, and the generic and brand names of the two agents currently available in the class.

The outcome section focused on the terms that were commonly used in studies that depicted potential barriers to PCSK9 inhibitor use. A wildcard (represented by the asterisk - *) was used to represent different variations that the terms could take. For example, titles of applicable studies could include the word 'determine' in different

forms as follows; ‘factors that determine PCSK9 inhibitor use’, ‘factors determining PCSK9 inhibitor use’ or ‘determinants of PCSK9 inhibitor use’ et cetera. The addition of a wildcard would include all these variations of the term ‘determine’ in the search results. Similarly, the term ‘detect*’ would identify studies that had PCSK9 inhibitors and any variation of the word ‘detect’ in its title or body. The context of such studies could be; how HeFH patient detection affects PCSK9 inhibitor use, detecting eligible patients for PCSK9 inhibitor use and so on.

The resulting terms could be roughly grouped as follows;

- Terms that directly referred to the assessment of potential barriers in PCSK9 inhibitor use e.g. ‘barriers’, ‘factors’, ‘opinions’, ‘perceptions’.

- Terms that referred to clinical outcomes in PCSK9 inhibitor use that could act as potential barriers e.g. views on LDLC and cardiovascular outcomes reduction could potentially influence medication use.

- Terms that are associated with the management of HeFH that could affect PCSK9 inhibitor use as discussed in chapter 1 e.g. guidelines, screening, patient identification etc.

In general, the terms were found to revolve around common issues affecting HeFH use with potential impact on PCSK9 inhibitor use; terms that defined stakeholder opinions and perceptions on the medication were also included.

Finally, a preliminary search was conducted on Google Scholar to identify terms/ words that were commonly used in the research area. Synonyms of the words were added to ensure completeness. The complete list of search terms and the resulting search groups are shown in table 2.2 below.

Population	**Intervention**	**Outcome**	
familial hypercholesterolaemia	PCSK9 inhibitors	perception*	high cholesterol
FH	proprotein convertase subtilisin kexin	detect*	low density lipoprotein cholesterol
heterozygous familial hypercholesterolemia	alirocumab	opinion*	LDL*
heFH	evolocumab	determin*	high density lipoprotein cholesterol
familial hypercholesterolemia	kexin 9 inhibitors	screen*	HDL*
	proprotein convertase subtilisin/kexin	identif*	cardiovascular
	PCSK9'	affect*	cholesterol
	praluent	influen*	
	repatha	factor*	
		policy*	

		barrier*	
		guideline*	

Table 2.2 List of search terms

2.2.5 Inclusion and Exclusion criteria

The PRISMA-P checklist was used to outline eligibility criteria for the selection of relevant literature. This checklist adopts the PICO structure which describes the population or participants and conditions of interest, the intervention under study, comparison/ control groups, expected outcomes, the setting for the studies and the study designs expected. Although all these parameters were not relevant in our study the template provided a structure that ensured a rigorous set of eligibility criteria was adopted. Table 2.3 below presents a summary of the completed checklist.

Population of interest	Patients with heterozygous familial hypercholesterolemia (HeFH) Healthcare providers in the management of HeFH (consultants, general practitioners, nurses)
Primary intervention	Proprotein Convertase Subtilisin Kexin/Type 9 (PCSK9) inhibitors
Comparison group	Not relevant to the present review as the study is solely focused on PCSK9 inhibitor research.
Outcomes	The opinions and perceptions of stakeholders on the use of PCSK9 inhibitors and stakeholder perceptions on

	barriers and facilitators. Quantitative analyses that could serve to inform the discussion of barriers and facilitators to PCSK9 inhibitor use e.g. usage or uptake analyses.

Table 2.3 PICO formula of inclusion of studies

Outcomes were considered to be the opinions and perceptions of stakeholders on the use of PCSK9 inhibitors. Stakeholder views on barriers and facilitators to PCSK9 inhibitor use were also assessed.

The final list of inclusion criteria is shown below:

- Written in English
- Peer-reviewed publications
- Population of interest was HeFH patients and healthcare providers involved in the use of PCSK9 inhibitors
- The primary intervention was PCSK9 inhibitors
- Outcomes included; qualitative views and opinions of stakeholders on the barriers and facilitators to PCSK9 inhibitor use, quantitative analyses that could inform the topic of interest

The final list of exclusion criteria included:

- Studies on HeFH and related factors (e.g. cascade screening) that did not focus on PCSK9 inhibitors
- Studies that focused on the development process of PCSK9 inhibitors e.g. novel genetic research
- Studies focusing solely on efficacy of PCSK9 inhibitors or cost-effectiveness
- Studies focusing solely on the description of the initial prescription patterns of PCSK9 inhibitor usage following launch e.g. patient clinical characteristics

- The paper was a general review on PCSK9 inhibitors
- Papers focused on the discussion of clinical guidelines with no assessment of their effect on prescription

2.3 Results

2.3.1 Database searches and results

The search terms in for each group were combined in a search using the 'OR' function and saved. For example, the terms in the population group were searched as shown below;

'Familial hypercholesterolemia' OR 'heterozygous familial hypercholesterolemia' OR 'homozygous familial hypercholesterolemia' OR 'heFH' OR 'hoFH'

This combined group was named S1. This ensured that each time a search was conducted using 'S1', the search engine searched for all included variations of 'HeFH'. This process was repeated for all the groups.

The ensuing groups (S1-S4) were then combined in several searches with each term from the comparison and outcome groups using the 'AND' function. For example;

S1 (Population) AND S2 (Intervention)

S1 (Population) AND S2 (Intervention) AND S3 (Comparison)

The process was repeated until all the search terms were included.

The Search was conducted in EBSCOhost, for papers published from 1993 to 2020. The date of the search was 24/03/20, and the search covered; all text (TX), author (AU), title (TI), subject terms (SU), source (SO), abstract (AB), ISSN (IS) and ISBN (IB). A summary of the process is shown in table 2.4 below.

#	Searches	Results
1	familial hypercholesterolaemia or FH or heterozygous familial hyperchoelsterolemia or heFH or familial hypercholesterolemia	64,634
2	PCSK9 inhibitors or proprotein convertase subtilisin kexin or alirocumab or evolocumab or kexin 9 inhbitors or proprotein convertase subtilisin/kexin or 'PCSK9'	5,043
3	perception* or detect* or opinion* or determin* or screen* or identif* or affect* or influen* or factor* or policy* or barrier* or guideline*	19,896,501
4	high cholesterol or low density lipoprotein choelsterol or LDL* or high density lipoprotein cholesterol or HDL* or cardiovascular or cholesterol	1,383,282
5	1 AND 2	1,224
6	2 AND 3	2,962
7	2 AND 4	4,330
8	1 AND 2 AND 3	818
9	1 AND 2 AND 3 AND 4	810
10	27 records excluded as they were not in English	783
11	4 papers were not published in peer-reviewed journals	779

12	Exact duplicates of 140 papers removed from the results.	639

Table 2.4 Search process

2.3.2 Selection of papers for inclusion in the review

The completed search generated 810 papers (MEDLINE, n=648; CINAHL Plus n=152; SPORTDiscus, n=9; APA PsycInfo, n=1). 27 records were excluded as they were not written in English. 4 articles were not published in peer-reviewed journals and were therefore removed. 140 duplicates were also excluded leaving 639 papers. The inclusion and exclusion criteria described in section 2.2.5 were then applied to filter the results. The assessment of study titles led to the exclusion of 513. Excluded titles included studies purely on HeFH, cascade screening and the development of PCSK9i (n=22), efficacy of medication and novel genetic research (n=35), topics unrelated to the research focus (n=108), studies on PCSK9i genetics and biochemistry (n=348).The abstracts of the remaining 126 papers were reviewed based on the inclusion and exclusion criteria as specified below. 45 articles were removed; although these articles covered PCSK9 inhibitors they were mainly theoretical articles, commentaries or study protocols. Finally, a full text review of 81 articles produced 18 papers that were deemed to relevant to the literature review question. The flow-diagram below (Figure 2.1) shows the selection process described.

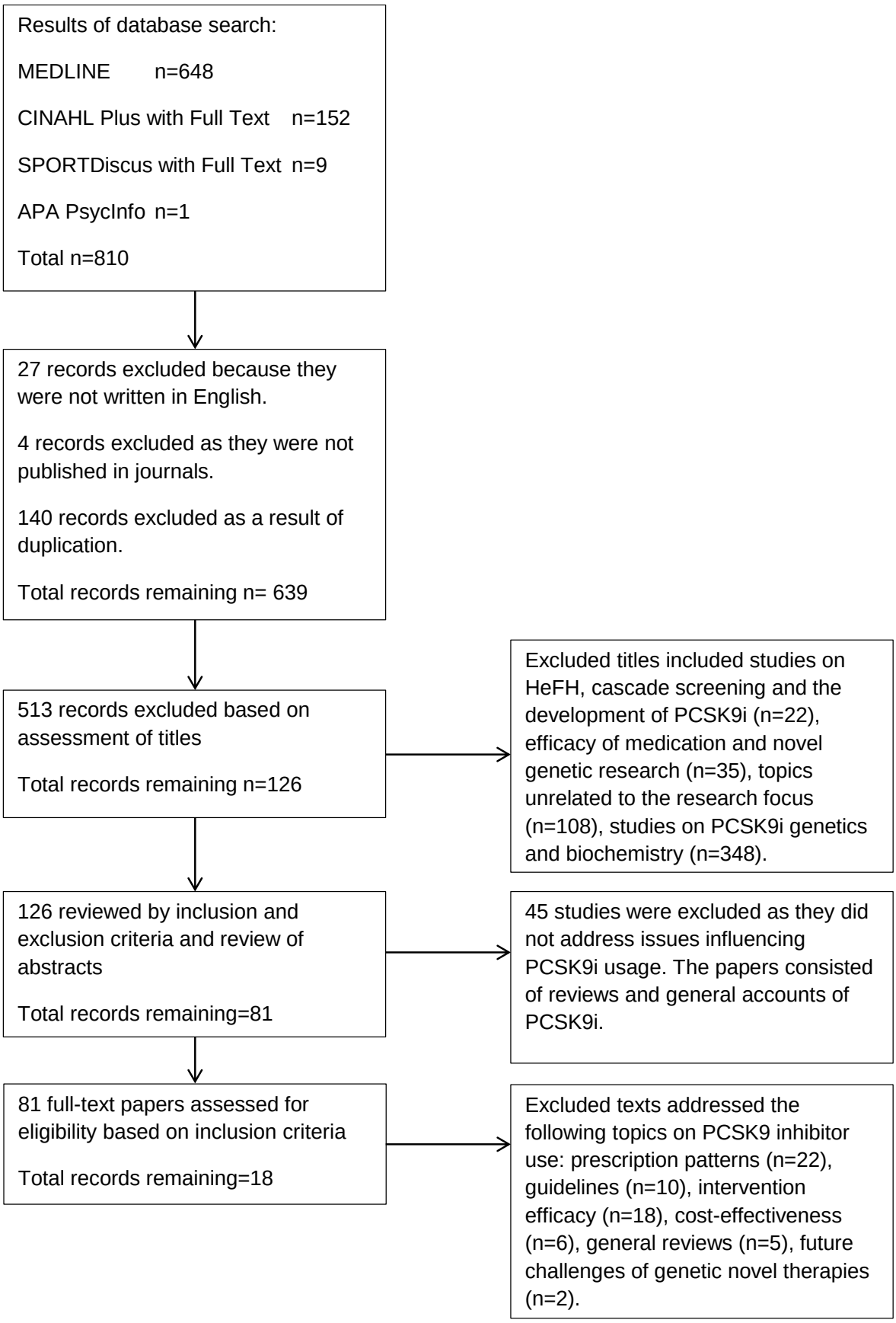

Figure 2.1 Flow diagram of selection process

2.3.3 Relevance of retrieved literature

The final evaluation of relevance was conducted by reviewing the full text of 81 articles on PCSK9 inhibitors based on the inclusion and exclusion criteria. 25 papers (31%) addressed stakeholder perceptions and barriers to PCSK9 inhibitor use directly. Excluded texts addressed the following topics on PCSK9 inhibitor use: prescription patterns (n=22), guidelines (n=10), intervention efficacy (n=18), cost-effectiveness (n=6), general reviews (n=5), future challenges of genetic novel therapies (n=2). A summary of the themes that covered PCSK9 inhibitor use are shown in figure 2.2 below. Although these texts were excluded, they were reviewed in full because the research topics had the potential of influencing PCSK9 inhibitor use. For example, cost of medication is not explicitly identified as a barrier in most studies; however, it is a consideration in the development of prescription systems for PCSK9 inhibitors. The 18 selected studies directly addressed either the barriers to PCSK9 inhibitor use (n=13), or assessed stakeholder views or experiences concerning PCSK9 inhibitors (n=5).

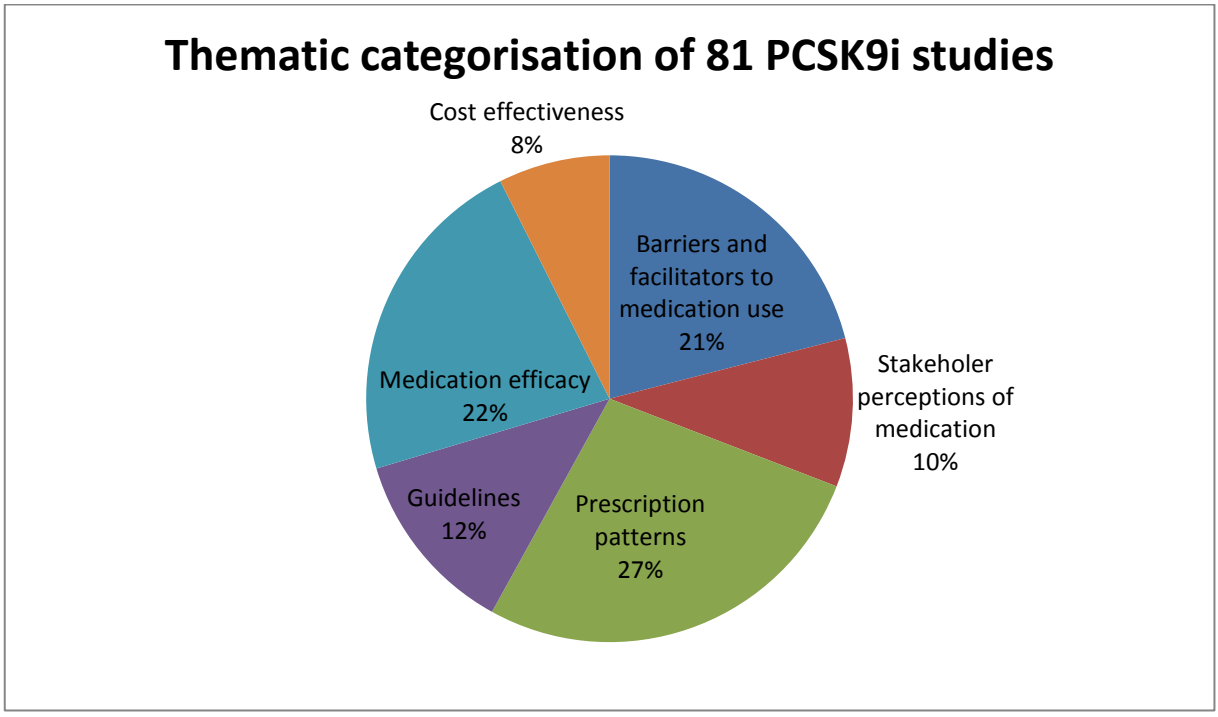

Figure 2.2 Categorisation of 81 PCSK9i studies

2.3.4 Table reporting of literature in the review

The final list of relevant studies (n=18) span 30 countries (Hong Kong, Australia, Bosnia and Herzegovina, Brazil, China, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, New Zealand, Philippines, Russia, Saudi Arabia, Serbia, Slovakia, South Africa, Spain, Taiwan, UK, Ukraine, US, Uzbekistan, Vietnam). It is worth noting, however, that 8 of these papers were based in the US (44%). This was followed by European countries (n=6, 33.3%), Asian countries (n=2, 11.1%) and Australia (n=2, 11.1%). Three studies were conducted across multiple countries and evaluated HeFH care that involved the use of PCSK9 inhibitors – Roth et al. (2015), Pang et al. (2019), Ceska et al. (2019).

2.3.4.1 Study characteristics

5 reviews were included in the final selection as they presented expert summaries of potential issues affecting PCSK9 inhibitor use. The methodologies adopted in the 10 primary studies were varied. In total, 6 studies applied quantitative analysis of patient or prescription data. However, Cheng, Gaudette & Goldman (2017) determined future cost-effectiveness of PCSK9 inhibitors by analysis of data simulations using the Future Elderly Model (FEM), while Hess et al. (2017) conducted a retrospective descriptive cohort study of HeFH prescription data to address barriers in PCSK9 inhibitor provision. 3 studies applied observational approaches; Batais et al. (2017) adopted a cross-sectional survey, a prospective observational study was chosen in Rallidis et al. (2018), and Knickelbine et al. (2019) conducted a practice evaluation involved the prescription of PCSK9 inhibitors. Cohen et al. (2017) used online survey of healthcare professionals. The remaining three studies adopted a combination of qualitative interviews and quantitative methods with Mühlbacher et al., (2018) using a DCE to started stakeholder preferences.

89% of the studies involved the assessment of either patients or prescribers of PCSK9 inhibitors; 11% involved the assessment of payers or payer approval data. Knickelbine et al. (2019) and Pang et al. (2019) assessed the influence of different healthcare providers in the management of HeFH and use of PCSK9 inhibitors. The stakeholders involved lipid specialists (such as lipidologists, endocrinologists, and cardiologists), nurses and nurse practitioners, and a physician assistant.

The study settings were mainly hospitals and lipid clinics (n= 7, 39%). However, Ceska et al. (2019), Roth et al. (2015) and Pang et al. (2019) conducted multinational studies. The remaining studies conducted analysis of prescription or patient data, of course, with the exception of the 5 included reviews. Sample sizes (across both qualitative and quantitative studies) ranged from 133 (Zafrir and Jubran, 2018) to 51,422 (Hess et al., 2017 – a retrospective cohort study using HeFH patient data in the US).

Data were extracted from the studies to allow for synthesis of the findings. These include:

- Study reference/ year of publication
- Location
- Type of research
- Participant (stakeholders) involved
- Perceived barriers and facilitators
- Study setting

Table 2.5 below presents a summary of the extracted data.

This table shows the data extracted from the identified studies. Review papers did not have a study setting and sample size but highlighted key issues regarding barriers to PCSK9 inhibitor use.

Table 2.5 Data extraction table

No.	Study reference	Location	Type of research	Participant (stakeholders) involved	Study setting	Sample size	Perceived barriers and facilitators	Conclusions
1	Alonso et al., (2020)	Spain	Review	Physicians, patients, policymakers	–	–	Cost and access for medication, long-term adherence to lipid lowering therapy and lifestyle changes, familiarity of FH and awareness of clinical	The use of detection strategies and models of care that address barriers in the management of HeFH can improve quality of care

							guidance by general practitioners, low perception of high cardiovascular risk	provided.
2	Arca, (2017)	Italy	Review	Patients, policymakers, healthcare providers	–	–	Knowledge and awareness of HeFH, detection and therapeutic management of disease	Barriers to PCSK9 inhibitor use were described as cost, and the lack of data on reduction of long term cardiovascular outcome and disease mortality (the review was publishing during

								the trials).
3	Batais et al., (2017)	Saudi Arabia	Cross-sectional study (survey)	Healthcare providers	Hospitals	294	The awareness, knowledge, practice, and detection of FH among physicians	Training may be required for many healthcare providers in the care for HeFH.
4	Baum et al., (2017)	US	Review	Patients, payers, healthcare providers	—	—	Formulary restrictions, burdensome paperwork, step-therapy and laborious appeals processes	—Barriers to PCSK9 inhibitor use were related to formulary restriction systems set up to reduce the use of costly medication.

								Uncertainties in guidelines such as the lack of a comprehensive list of CVD that warranted PCSK9 inhibitor usage allowed organisations to further restrict medication usage.

5	Ceska et al., (2019)	Czech Republic, Bosnia and Herzegovina, Lithuania, Latvia, Hungary, Russia, Serbia, Slovakia, Uzbekistan, and Ukraine.	Quantitative analysis	Patients	Country level data (in 10 countries)	9,065	Identification of HeFH patients	Development of a network for HeFH data sharing improved identification and management of the disease.

6	Cheng, Gaudette & Goldman, (2017)	US	Quantitative simulations using the Future Elderly Model (FEM)	Payers	Simulation for lifetime outcomes	–	Cost	Projections showed that PCSK9i use was cost-effective.
7	Cohen et al., (2017)	US	Online survey	Healthcare providers	Online survey	434	Insurer processes, provider documentation (inadequate documentation of maximally tolerated statin dose,	–Barriers to PCSK9 inhibitor use were related to cost, and usage restrictions imposed by payers.

							diagnostic criteria for FH, number of statins failed if statin intolerant and most recent low-density lipoprotein cholesterol), and administrative burden (time, staff, paperwork, and appeals)	

8	Doshi et al., (2018)	US	Quantitative analysis	Payers	–	–	Prior authorisation criteria(requirements for medical record submission, reauthorization requirements) and clinical/diagnostic PA criteria (required laboratories or other tests, required concomitant therapy, step therapy requirements,	Potential for excessive bureaucracy in the prescription process for PCSK9i may be a barrier to use.

							continuation criteria)	
9	Hess et al., (2017)	US	Retrospective descriptive cohort study	Payers, patients	Database analysis of nationwide patient records	51,422	Paperwork requirements for prescriptions	Variables such as age, prescriber (specialist or non-specialist), statin intolerance, payer and the duration that other LLT was used were found to be associated with successful prescription.

10	Hopkins, (2010)	US	Review	Patients, health care providers, government agencies	–	–	Insufficient data on HeFH, screening processes	The paper recommended cascade screening as a cost-effective method of screening; however, screening of cerrtain age-groups or at-risk groups was also viable.
11	Knickelbine et al., (2019)	US	Practice evaluation	3 senior staff cardiologists, 1 nurse practitioner, 1	In-house hospital pharmacy	196	Comprehensive paperwork requirements for PCSK9i prescription,	The paper identified modified barriers to the prescription of PCSK9i.

				physician assistant, 1 care coordinator, 1 pharmacist, and 1 pharmacy technician.			step-therapy, finance assessment	
12	Lan et al., (2019)	Australia	Review	Healthcare providers, patients	—	—	Awareness of HeFH amongst healthcare providers and patients	The use of electronic databases, testing of children and patients with crdiovascular disease was recommended to

								improve identification.
13	Mues et al., (2018)	US	Quantitative modelling	Patients	Modelling using quantitative data	2,180	Identification of HeFH patients	The study highlighted difficulties experiences in modelling for HeFH idenitifcation.
14	Mühlbacher et al., (2018)	Germany	Discreet choice experiment (DCE), qualitative	Patients	Survey using DCE	348	Efficacy of medication, side-effects, injection site injury	Patients valued efficacy of medications more than other attributes. In some

			interviews					cases patients chose efficacy by any means.
15	Pang et al., (2019)	Australia, China, Hong Kong, Japan, Malaysia, New Zealand, Philippines, Taiwan,	Online questionnaires, email/ telephone interviews, email/ face-to-face conversations	Healthcare providers with expertise in cardiology, endocrinology, or internal medicine.	10 countries	–	Lack of Government funding, deficit in patient registries, training and research	–Government funding for PCSK9 inhibitors was only provided in the UK and Australia. Cost played an important role in this decision.

		Vietnam, South Africa and Brazil						
16	Rallidis et al., (2018)	Greece	Prospective hospital based study	Patients	Hospital	1,629	Categories of patients where lower LDLC levels are advised e.g. coronary artery disease (CAD)	Certain groups of patients require PCSK9i to achieve treatment targets.
17	Roth et al., (2015)	US, France, UK, Spain,	Self-administered interview	Patients, healthcare providers	6 countries	400	Perception of injections	The use of pre-filled pens or syringes did not influence the

		Germany, Italy	(questionnaire)					decision to use PCSK9i.
18	Zafrir and Jubran (2018)	Israel	Quantitative analysis	Patients	Regional lipid clinic	133	High cost, decision to return to statin use, fear of injections, competing health issues	Cost and medication nonadherence

2.3.5 Review

The current section used thematic summaries as outlined by Thomas et al. (2012) to synthesize the extracted data. Thematic summaries use conceptual similarities between studies to group by themes relevant to the review research questions. The main limitation of this method is the selection of themes is a subjective process (Snilstveit et al., 2012). In order to retain some objectivity, the inclusion and exclusion criteria of the review protocol were strictly adhered to ensuring that all studies left in the review addressed the research question as part of their outcomes.

2.3.5.1 Factors influencing PCSK9 inhibitor use

Direct barriers to the use of PCSK9 inhibitors were identified as cost and inaccessibility to medication in 8 (44%) of the total 18 papers selected. With the exception of Pang et al. (2019) that identified lack of government funding for PCSK9 inhibitor usage in some countries, the effect of cost manifests in prescription management processes developed to restrict the use of expensive medication. Further barriers revolved around inadequate identification of HeFH patients, and low levels of knowledge and awareness of HeFH and its associated management (n=6, 33%). Patient compliance, especially pertaining to perceptions on the use of injections and injection site reactions was addressed in four studies (n=4, 22%). Lack of government funding and insufficient support for HeFH management initiatives was cited in one study (Pang et al., 2019). Similarly, potential gaps in the management of certain categories of patients due to guidelines were discussed in another paper (Rallidis et al., 2018).

All but one of the studies concerning barriers to the access of PCSK9 inhibitors were conducted in the US, with the exception coming from Spain. The studies conducted in the US (Baum et al. 2017, Cheng, Gaudette & Goldman, Cohen et al. 2017, Doshi et al. 2018, Hess et al. 2017, Hopkins 2010, Knickelbine et al. 2019) appeared to be

driven by a high number of rejections of PCSK9 inhibitor prescriptions by payers. This was mainly because a large proportion of medicines in the US healthcare system are payed for by private health insurers, individuals or government programs that are independent of the healthcare system. Prescriptions, especially of new medication, are therefore often rejected or governed by policies that are designed to limit usage of expensive pharmacological therapies (Doshi et al., 2018). Baum et al., (2017) presented the findings of two meetings held by the American Society for Preventive Cardiology (ASPC) that discussed high PCSK9 inhibitors rejection rates of 80% - 90%.It was found that insurance providers applied formulary restrictions such as; requirement for prior authorisation (PA), the usage of other lipid lowering agents prior to PCSK9 inhibitor consideration and the inclusion of laborious appeals processes in the approval system. These processes demanded the provision of medical records that were not immediately necessary for the approval process for PCSK9 inhibitors. They also introduced bureaucracy that served to lengthen the approval process. Cohen et al. (2017) reported the results of an online survey of 434 healthcare providers on the challenges to the prescription of PCSK9 inhibitors. The findings echoed the results discussed by Baum et al. (2017); however Cohen et al. (2017) emphasized the availability of patient documentation as an important element in the approval process. The conclusions drawn from both papers suggested that the processes defined by clinical guidelines were clear, however, organisational implementation of the guidelines constituted high thresholds for medication use and an unnecessary administrative burden to prescribers (Hess et al. 2017).

Knowledge and awareness of HeFH among healthcare providers constituted the second most reported hindrance to PCSK9 inhibitors use; Arca 2017, Batais et al. 2017, Lan et al. 2019. These studies were conducted in Italy, Spain and Australia

respectively. Batais et al. (2017) studied the level of knowledge of healthcare providers on HeFH reporting substantial deficit in the identification and management of the disease. Knowledge was mainly associated with the detection of patients with certain studies focussing specifically on the matter. Evidence between the current results (Ceska et al. 2019, Mues et al. 2018) and other literature on HeFH (Rangarajan et al., 2016) indicated low levels of awareness of the disease that contributes to the deficiencies in diagnosis and treatment. Knowledge was evaluated by assessing physician actions in the recording of family histories of elevated LDLC of HeFH, awareness of diagnostic criteria et cetera as in Rangarajan et al. (2016). A direct result of low levels of knowledge was the potential of a lack of recording of patient data (Hopkins, 2010). These factors could potentially lead to a low identification of HeFH patients who require PCSK9 inhibitors, and difficulties to complete the requisite paperwork for prescription.

Other potential barriers to the use of PCSK9 inhibitors included expected lack of adherence due to the use of injections (Cohen et al. 2017, Alonso et al. 2020). However, studies directly assessing the perceptions of stakeholders on PCSK9 inhibitor formulation such as Roth et al., (2015) and Mühlbacher et al., (2018) have since found that patients did not view the use of injections negatively. Roth et al., (2015) involved 400 participants (200 patients and 200 clinicians) and assessed their views on the use of pre-filled pens and syringes. The medication formulation was viewed favourably by all groups involved in the study. In a discreet choice experiment conducted by Mühlbacher et al. (2018), it was found that patients valued efficacy in medication more than the formulation. With regards to PCSK9 inhibitors, patients were not deterred by the injection formulation, as their primary goal was to achieve low LDLC levels. Nonetheless, there may still be a minority of cases where the

formulation is either not tolerated (due to injection site reactions) or simply not preferred (Zafrir and Jubran (2018); this potentially suggests that patient perceptions remain crucial to effective adoption of PCSK9 inhibitors.

Finally, as mentioned at the beginning of this section, some studies identified barriers that were not immediately relevant to the NHS system. Pang et al., (2019) for instance, found that lack of government funding hindered medication provision for HeFH. The resultant effect was a deficit in the development of patient registries and opportunities for training and research were reduced. The NHS system has improved capacity to provide medication, and no studies suggested unavailability to funds to supply PCSK9 inhibitors. Nevertheless, studies on the current practices used to limit the use of costly medication (in this case, PCSK9 inhibitors) are also lacking. Rallidis et al., (2018) discussed the possibility of guideline related gaps due to the management of patients who required different therapeutic outcome. The study assessed patients with coronary artery disease (CAD) determining that they potentially required further lowering of LDL cholesterol than the current guideline recommendations for severe HeFH.

The overall search results suggested that the factors influencing PCSK9 inhibitor adoption were predominantly under researched; at least, from the perspective of stakeholders and the barriers and facilitators of usage. Furthermore, a limited number of these studies were conducted in the UK. This could possibly be explained by the relative novelty of PCSK9 inhibitors and the on-going trials on cardiovascular disease prevention. Nevertheless, studies on the potential determinants of PCSK9 inhibitor use in the UK would serve to increase knowledge in the use of the new class of medication.

2.3.6 Complete reference list

As described in section 2.3.2, the review of study titles resulted in the identification of 81 papers. Following further assessments (abstract review and full text review), 18 papers were found to be within the current study's topic area. Only the 18 relevant articles have been referenced in this thesis. The full list of 81 papers is however included in appendix 12. The complete list of articles obtained from the search (n=810) can be provided upon request.

2.4 Discussion of literature

The overall findings suggested that the factors influencing the use of PCSK9 inhibitors were largely under researched. Although 18 articles were included in the review, only 6 of the papers were focussed on evaluating barriers to the usage of PCSK9 inhibitors (Cohen et al. 2017, Doshi et al. 2018, Hess et al. 2017, Knickelbine et al. 2019, Roth et al. 2015, Zafrir and Jubran 2018). The other papers covered HeFH in general, but addressed topics that were linked to PCSK9 inhibitor use. For example, Batais et al., (2017) assessed the knowledge and awareness of physicians on HeFH management. Part of the study addressed medication use, including PCSK9 inhibitors, effectively identifying awareness deficits surrounding the medication.

Of the 6 papers that addressed barriers to PCSK9 inhibitor usage, 4 were conducted in the US and addressed prescription rejections and methods of improving approval rates (section 2.4.1). This did not appear to be a problem in other countries and suggests that it was caused by the difference in medication payment structure in the US. Nevertheless, the same factors identified in the US could still be of relevance to other countries to varying degrees. The 2 remaining papers studied stakeholder perceptions to the use of injections in PCSK9 inhibitors (Roth et al., 2015) and the

study of real-world PCSK9 inhibitor usage in a hospital setting (Zafrir and Jubran, 2018) that identified barriers experienced in the use of the medication.

In the following segment, the papers that covered topics that were deemed to be related to PCSK9 inhibitor use were synthesized; this involved the categorion of perceived barriers to PCSK9 inhibitor use into themes as described by Thomas et al. (2012). Four themes were identified; two papers were discussed for each theme followed by a summary of the results of the other literature. The summary of themes and selected papers are shown in table 2.6 below.

Category	**Author(s)**	**Title**
Access barriers to PCSK9 inhibitors	Baum, S. J. et al. (2017)	PCSK9 inhibitor access barriers-issues and recommendations: Improving the access process for patients, clinicians and payers.
	Cohen, J. D. et al. (2017)	Barriers to PCSK9 inhibitor prescriptions for patients with high cardiovascular risk: Results of a healthcare provider survey conducted by the National Lipid Association
Identification of patients eligible for PCSK9 inhibitors	Robinson, J. G. et al. (2019)	Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. A consensus statement from the National Lipid Association.
	Hess, G. P. et al. (2017)	Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Therapy: Payer Approvals and Rejections, and Patient Characteristics for

		Successful Prescribing.
Prescribing practices in early initiator's of PCSK9 inhibitors	Reynolds, T. et al. (2019)	A Retrospective Observational Study to Determine Baseline Characteristics and Early Prescribing Patterns for Patients Receiving Alirocumab in UK Clinical Practice.
	Knickelbine, T. et al. (2019)	A systematic approach for successful PCSK9 inhibitor prescribing in clinical practice.
The impact of guidelines on PCSK9 inhibitors use	Farnier, M., Civeira, F. and Descamps, O. (2017)	How to implement clinical guidelines to optimise familial hypercholesterolaemia diagnosis and treatment.
	Rallidis, L. S. et al. (2018)	Extreme-risk category: High prevalence among stable coronary patients and an emerging widening treatment gap in achieving LDL-cholesterol less than 55 mg/dL.

Table 2.6 Summary of themes and papers

2.4.1 Access barriers to PCSK9 inhibitors

The majority of studies that focussed on barriers to the use of PCSK9 inhibitors were conducted in the United States of America (US). Overall, 4 papers were found that directly addressed access to the use of PCSK9 inhibitors as the main topic; Baum et al., (2017), Hess et al. (2017), Cohen et al. (2017) and Doshi et al. (2018). All these papers were based on the US healthcare system. As a comparison, studies in the United Kingdom (UK) typically covered initial patterns in the adoption of PCSK9

inhibitors (Reynolds, T. et al., 2019), cost-utility studies (Crosland, P. et al., 2018), and initial experiences and patterns of using PCSK9 inhibitors (Kohli, M. et al., 2017). With the National Health Service (NHS) paying for medication, the UK structure consists of Area Prescribing Committees and Clinical Commissioning bodies that manage the payment and inclusion of medication into policy. It is likely that barriers in the provision of medication are therefore not anticipated as teams of healthcare specialists are involved in the medication provision pathway.

2.4.2 Identification of patients eligible for PCSK9 inhibitors

Several studies have focused on estimating the number of patients who were eligible for PCSK9 inhibitors based on clinical guidelines: Gencer et al. (2017), Glueck et al. (2016) and Jetty et al. (2017). Glueck et al. (2016) assessed the 734 hypercholesteraemic patients in order to determine the number that qualified for PCSK9 inhibitor treatment based on the Federal Drug Agency (FDA) guidelines and insurance eligibility criteria. 220 patients (30%) of the study cohort had HeFH with or without CVD and were eligible for PCSK9 inhibitors. The study also found that, assuming a 50% reduction in CVD, PCSK9 inhibitors would produce savings of up to $250 billion. This was of course, prior to the conclusion of studies that determined CVD reduction rates associated with PCSK9 inhibitors. However, the total expenditure on the new class of medication would range between $180-342 billion. A similar study by Jetty et al. (2017) investigated patient eligibility for both alirocumab (ALI) and evolocumab (EVO), and estimated savings achieved based on CVD reduction. The study had a population size of 1090 patients, the number of patients eligible for both ALI and EVO was found to be 13% (140). The study conducted a year later, and with a larger cohort of hypercholesteraemic patients found that a smaller number of patients were eligible for the new class for medication. The reduction in eligibility was mainly due to a difference in FDA and insurance eligibility

criteria; Glueck et al. (2016) considered patients who had HeFH and/ or CVD and an LDLC >100 mg/dl to be eligible for PCSK9 inhibitors, Jetty et al. (2017) included patients with definite CVD, HeFH and LDLC>100mg/dl as eligible candidates for the disease. Current practice suggests that the latter case is more accurate as a diagnosis of HeFH with LDLC>100mg/dl could still be required to demonstrate that conventional lipid lowering therapies were insufficient prior to PCSK9 inhibitor approval. Jetty et al. (2017) produced revised healthcare savings associated with PCSK9 inhibitor use could be estimated as ~$67 billion dollars. However, the researchers deemed this finding unclear as more specific CVD reduction results were being awaited; they therefore suggested that more study was necessary. The reasons for the differences with past literature were not discussed in the paper. However, the prevalence of HeFH patients, for instance, in the two cohorts were different; with Jetty et al. (2017) having a smaller number of HeFH patients. Statin intolerance was also observed less in the larger cohort; 51 in Jetty et al. (2017) versus 66 in Glueck et al. (2016). Jetty et al. (2017) also applied more modest estimates of 15-20% CVD reduction associated with PCSK9 inhibitors, compared to 50% used by Glueck et al. (2016). It is worth noting that both studies obtained the estimates of CVD reduction from clinical trials. However, initial CVD reduction rates for PCSK9 inhibitors were expected to be high, but as longer term studies were concluded, these rates were revised to ~20% (Sabatine et al., 2017).

Other studies on the patient eligibility included Robinson et al. (2019) which attempted to identify high risk groups of patients in which PSCK9 inhibitor use would be cost-effective. Of relevance to this body of work was the finding that HeFH was considered as one of the risk factors for CVD than necessitated PCSK9 inhibitor intervention. Although the paper supported the use of ezetimibe prior to the

consideration of PCSK9 inhibiting agents, it presented an argument for the direct use of PCSK9 inhibitors in high risk populations. Hess et al. (2017) investigated the characteristics of patients who were eligible for PCSK9 inhibitors. The results found that successful prescription of PCSK9 inhibitors occurred in older patients (>65), patients who had experienced a CVD event, and prescriptions by specialist consultants. Finally, Groves et al. (2017) conducted an eligibility study for maximally treated HeFH patients in the UK. Modest proportions of patients were found to require PCSK9 inhibitors at various LDLC thresholds based on NICE technical appraisal guidelines. The paper suggested that this could be due to the use of all available statin therapy prior to consideration for PCSK9 inhibitors. Furthermore, it was suggested that clinical guidelines at the time were based on limited data, and the release of secondary prevention data was expected to convey alterations to guidelines.

2.4.3 Prescribing practices in early initiator's of PCSK9 inhibitors

The primary research paper for this section is based on a retrospective observational study conducted in the UK (n=150) to determine HeFH patient characteristics and early prescribing patterns for PCSK9 inhibitors (alirocumab) Reynolds et al. (2019). The main results showed that HeFH patients who qualified for PCSK9 inhibitor use were older (mean=61.4, SD 10.5), 100 out of 150 (66.7%) patients had HeFH and 123 had suffered statin intolerance. This results echoes the findings from studies in the US (Hess et al. (2017) where patients on PCSK9 inhibitors were found to be older (>65) and had experienced an intolerance to statins. Reynolds et al. (2019) described patient's characteristics which included body mass index (BMI mean 29.1 SD 4.5) and 33 (37.5%) patients having a BMI ≥ 30; it was however found that these data were only available for 88 patients (58.7%). The lack of patient data has not been identified as a potential inhibitory factor to the prescription of PCSK9 inhibitors

in the UK. However, the finding is similar to those from American studies that perceived lack of patient data as a potential hindrance to PCSK9 inhibitor provision.

Knickelbine et al. (2019) investigated possible methods of improving PCSK9 inhibitor approval in the US based on the prescribing patterns following the approval of the medication. As such, the paper mainly dealt with matters identified in the US as discussed under section 2.4.1 (Access barriers to PCSK9 inhibitors). The study confirmed that modifiable barriers exist that influence the prescription of PCSK9 inhibitors. The study also revealed that collaboration between stakeholders in the provision of care for HeFH was crucial in improving the prescription of this new class of medication. The overall study result was an algorithm for improving PCSK9 inhibitor prescription. However, the model consisted of factors that were unique to the US, such as the existence of different payers for medication. It was therefore of little relevance to the UK. A further insight from the study was the confirmation of previous findings that documentation deficiencies, such as missing data or outdated laboratory test results, affected the approval process for medication. This finding may be relevant globally, because of the under-identification and under-diagnosis of HeFH. This could potentially produce cases where patients are deemed to require medication but do not have extensive medical histories due to the opportunistic identification of HeFH.

2.4.4 The impact of guidelines on PCSK9 inhibitors use

Several studies have focused on the effect of guidelines on the provision of PCSK9 inhibitors. A noteworthy summary could be produced from Orringer, C. E. (2019) who found that updated clinical guidelines and published studies provided a sufficient evidence base for the effective management of HeFH. The paper acknowledged the existence of therapeutic gaps in guidelines, and suggested the use of literature to support decision making. Farnier et al. (2017) presenting the results of an expert

working group discussion on the implementation of guidelines in order to optimise HeFH diagnosis and treatment in France. The paper reported that universal screening (including children), screening of high risk patients, better communication of elevated LDLC levels and improve of public awareness of HeFH were necessary in improving identification of patients. The paper also recommended the use of various guidance documentation and therapeutic targets in the management of HeFH. An emerging trend that is evident in the literature is that although studies on HeFH and PCSK9 inhibitors have been conducted in different countries, the issues identified are generally similar. The only differences observed were cases where the healthcare system varied greatly from the UK, and therefore significantly different prescription influencing factors were identified.

An interesting observation was the finding that the application of different clinical guidelines produced different proportions of HeFH patients that were eligible for PCSK9 inhibitors. Gencer et al. (2017) for instance, found that guidelines from the American College of Cardiology (ACC) (13.4%) produced 5-fold higher eligibility rates for PCSK9 inhibitors compared to the European Society of Cardiology/European Atherosclerosis Society consensus (2.7%) statement.

2.5 Gaps in literature and contribution to the thesis

The current literature on the barriers to PCSK9 inhibitor use was found to be limited, especially in the UK. Studies conducted in the UK on PCSK9 inhibitors mainly assessed patterns of use, and cost-effectiveness. The lack of studies on the barriers and facilitators to PCSK9 inhibitor use in the UK may be due to the structure of the National Health Service (NHS). In the UK, NICE acts as the price watchdog for medical interventions and determine usage based on evidence. Contrarily, in the US, payment for medication is mainly by insurance companies and third party

organisations such as those that care for war veterans among others; the debate about cost and accessibility to medication therefore begins as soon as a medication enters the market.

In a discussion about the future of PCSK9 inhibitors, Pandey et al. (2017) postulated that widespread adoption of the new class of medication will be determined by their effect on CVD reduction. However, the paper also asserted that the study of challenges and barriers would form an important part of optimising PCSK9 inhibitor usage. As this research is lagging behind in the UK, a gap exists that the current study intends to address.

The contribution of this chapter to the thesis lies in the identification of the gap in knowledge and the development of the research question(s). The themes discussed in section 2.4 inform chapters three, four and five as discussed below.

Four themes described the potential influencing factors of PCSK9 inhibitor use; access barriers to PCSK9 inhibitors (1), identification of patients eligible for PCSK9 inhibitors (2), prescribing practices in early initiators of PCSK9 inhibitors (3), the impact of guidelines on PCSK9 inhibitors use (4).

These themes suggested that potential research questions on the use of PCSK9 inhibitors in the UK would revolve around processes aimed at reducing PCSK9 inhibitor usage (because of cost) such as the Prior Authorisation system in the US. There is also no clear illustration of the typical HeFH patient journey towards the use of PCSK9 inhibitors, including the barriers experienced during this process. The extent to which guidelines can act as a barrier to medication use as described by Rallidis et al. (2018) has also not been assessed. Finally, there is little understanding of the potential effect that inadequate documentation/ patient records would have on

the use of PCSK9 inhibitors in the UK. In other countries, requirements for records of LDLC levels and the histories of statin and conventional lipid lowering therapy use served to hinder prescription in some cases.

In the context of the current study, all four themes suggested an exploratory qualitative study to assess the views and opinions of stakeholders on the barriers and facilitators to the use of PCSK9 inhibitors in the UK (chapter 5). Additionally, themes 1, 2 and 4 suggested an assessment of patient health records to determine; the number of patients who would not meet LDLC treatment guidelines and those who would be eligible for PCSK9 inhibitors, and to assess the overall utility of current health databases in identifying HeFH patients who may require PCSK9 inhibitors (chapter 4).

The current study therefore seeks to explore these potential barriers to the use of PCSK9 inhibitors in the UK. The aim of the project is twofold;

1) To study the barriers and facilitators to the usage of PCSK9 inhibitors by exploring the views and opinions of key stakeholders (patients, specialist consultants/GPs and nurses) in the care of HeFH in the UK.

2) To assess the feasibility of using the Clinical Practice Research Datalink (CPRD) database to develop a predictive model that can identify HeFH patients who meet the LDLC eligibility targets for PCSK9 inhibitors.

2.6 Conclusion

This chapter reported the conduct of a systematic review and narrative synthesis on the potential factors that could influence the use of PCSK9 inhibitors. The potential gaps in literature were presented and the aims for the current thesis were identified.

Chapter 3 Methodology

This chapter presents a discussion of the methodology adopted to address the two research questions outlined in chapter two:

1) To study the barriers and facilitators to the usage of PCSK9 inhibitors by exploring the views and opinions of key stakeholders (patients, specialist consultants/GPs and nurses) in the care of HeFH in the UK.

2) To assess the feasibility of using the Clinical Practice Research Datalink (CPRD) database to develop a predictive model that can identify HeFH patients who meet the LDLC eligibility targets for PCSK9 inhibitors.

The philosophical stance that underpins the multi-methods approach adopted in this study is discussed and the specific research designs employed are outlined. The chapter provides;

- In brief, a background to quantitative and qualitative approaches to research.
- An overview of the conceptual orientation of pragmatism as the worldview in which the current study is situated.
- The study design of the multi-methods approach employed in the study (Question 1 – qualitative approach, Question 2 – quantitative approach).
- The specific steps conducted in the quantitative and qualitative phases of the study.

3.1 Background to research methodologies

Research methodologies are composed of philosophical assumptions, theoretical or conceptual frameworks, and the specific procedures that constitute the conduct of the research process (Creswell and Creswell, 2018). The fundamental implication is that the selection of a research design is not an isolated undertaking. Rather, it is

based on a combination of considerations that lead to the development of the worldview adopted by the researcher. The worldview consequently guides the type of data to be collected; and the methods used (Cohen, 2007). As discussed by Creswell and Poth (2017), the worldview is based on the researcher's philosophical assumptions. These relate to how the researcher views their world (ontology), how the world is studied or known (epistemology), and the methodology employed to gather and analyse information.

Ontology is generally defined as the nature of existence or the constitution of reality (Crotty, 1998). The definition of ontology adopted by the SAGE Dictionary of Social Research Methods (Jupp, 2006) provides an illustration of some of the elements that establish reality; this is cited below.

"A concept concerned with the existence of, and relationship between different aspects of society, such as social actors, cultural norms and social structures."

Cited from Jupp (2006)

The existence of these 'elements of reality' independent of human beliefs and opinions results in an objectivist ontology. However, if the 'elements of reality' are dependent on human action, beliefs and decisions, a constructivist ontology is formed (Bryman, 2008).

Epistemology concerns the composition of 'human' knowledge, or the nature of knowledge as we understand it (Crotty, 1998). Epistemology essentially defines what is considered to be acceptable knowledge; consequently, this informs how the knowledge can be acquired and presented (Cohen, Manion and Morrison, 2007). The view that knowledge is objective conforms to a positivist epistemology. The collection of objective or hard knowledge can then be gathered using tests or measurements. On the contrary, the assumption that knowledge is subjective corresponds to an interpretivist epistemology. This suggests research methods that involve close

engagement with participants. The components of ontology and epistemology can be summarised as shown in table 3.1 below. The content of the table are adapted from Al-Saadi (2014).

	Ontology		**Epistemology**	
Definition	Nature of reality		Nature of knowledge	
Components of assumption	Objectivist	Constructivist	Positivist	Interpretivist
	Reality is independent of beliefs, opinions	Reality is a human construct	Knowledge is objective, hard or tangible	Knowledge is subjective
	Reality can be tested or measured	Reality is based in experience	Tests and measurements form the methods of data acquisition	Observation and a study of the subject motivations and experiences form the methods of data collection
Common research designs	Quantitative	Qualitative	Quantitative	Qualitative

Table 3.1 A summary of the characteristics of ontology and epistemology

Together, these assumptions determine the methodological approaches employed by the researcher. These philosophical perspectives are applied to research as research paradigms; a visual presentation of the relationships is shown in figure 3.1 below. Therefore, a research paradigm can be described as a collection of beliefs that govern the research process (Guba, 1990).

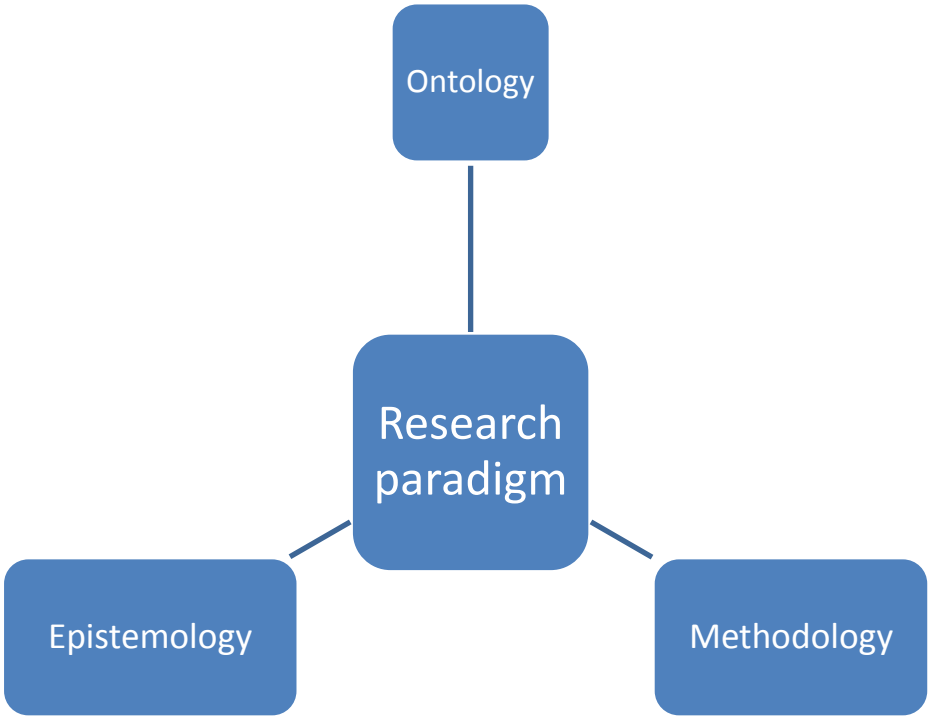

Figure 3.1 Relationship between philosophical assumptions and the research paradigm

3.2 Research design

Traditionally, research was categorized as either quantitative or qualitative. However, debate has persisted on the validity of either category as purist advocates argued for either side (Lincoln and Guba, 1989; Campbell, Stanley and Gage, 1963). Quantitative purists mainly maintain a positivist philosophy while their qualitative counterparts adhere to a constructivist or interpretivist philosophy. Advancements in the paradigmatic debate have led to the development of mixed methods approaches (Johnson and Onwuegbuzie, 2004). Other than the integration of qualitative and quantitative approaches, there is no well accepted definition of mixed methods

research (Johnson, Onwuegbuzie and Turner, 2007). Based on the definition of mixed methods research provided by Greene, Caracelli and Graham (1989), however, this combination of research methods is independent of traditional paradigmatic influences. Mixed methods research is therefore mostly situated within the pragmatic paradigm (Allmark and Machaczek, 2018).

3.2.1 Quantitative research

Quantitative research, broadly speaking, refers to the study of numerical data or statistics (Creswell and Creswell, 2018; Bryman 2008). It is however not sufficient to differentiate between the quantitative design and qualitative design (for instance) by the nature of the data gathered. The discussion of philosophical assumptions presented in the preceding sections is evidence of this. In quantitative research, a deductive approach underlies the data analysis process while the data collection phase is guided by a positivist epistemology. Ontologically, social reality is perceived to be objective with scientific tests and measurements being adopted as methods of inquiry. Quantitative research is therefore concerned with the testing of hypothesis and the study of relationships amongst statistical variables (Creswell and Creswell, 2018). Further considerations include the generalisability of data and an assessment of validity and reliability.

3.2.2 Qualitative research

Qualitative research is the study of human processes and 'lived experiences' through the collection of data from the participant's natural setting (Ritchie et al., 2013). In reality, the definition of qualitative research is continuously evolving; and as asserted by Creswell and Poth (2017), as it evolves it becomes increasingly difficult to describe. Nevertheless, this definition suggests that qualitative data is comprised of accounts of participant perceptions, experiences and beliefs; factors that determine

matters of importance to them, and influences their decision making process (Miles et al., 2014).

These definitions of qualitative research, however, do not fully highlight the philosophical component of the research design. When the ontological (constructivist) and epistemological (interpretivist) assumptions are included in the discussion of qualitative research, it is clear that a demarcation exists between qualitative and quantitative approaches.

Contrary to quantitative research, qualitative research mainly involves the study of 'emerging themes' from participants' accounts (Creswell and Creswell, 2018) and researcher observations. Data is primarily collected from the participants' setting and the interpretation process is largely inductive in nature.

3.3 Implications for the current study

In order to link the research philosophy to the methodology and methods, a framework is typically necessary. The implementation of a framework varies between disciplines and researchers. For instance, Creswell and Creswell (2018) refer to the interconnection of worldviews/ research paradigm, research strategy and research methods as the framework to design. An example of this framework could yield the following (Table 3.2).

Worldview	**Research strategy**	**Methods**
Positivism	Scientific experiments	Close ended-questionnaires

Table 3.2 An example of framework to design

In this example, the worldview (positivism) summarised the philosophical assumptions outlined in prior sections. These assumptions were derived from the

researcher's own beliefs and the research problem. Once an appropriate worldview is identified, there exists a choice(s) of research strategies and methods that are compatible with the worldview. Methods of data analysis are also linked to either worldviews or research strategies. The overall effect is that the worldview determines a framework that guides the choice of strategy and methods in a study.

The current study identified two key research problems from the literature review (chapter 2) that could be addressed using both qualitative and quantitative methods respectively.

1) To study the barriers and facilitators to the usage of PCSK9 inhibitors by exploring the views and opinions of key stakeholders (patients, specialist consultants/GPs and nurses) in the care of HeFH in the UK.

2) To explore the relationship between HeFH patient clinical attributes and LDLC reduction following statin use and by extension PCSK9 inhibitor eligibility.

In order to facilitate the selection process for a suitable research design to address these two research problems, the design framework developed by Crotty (1998) was employed. This framework is shown in figure 3.2 below. As identified by Crotty (1998), the purposes of this framework were twofold. Firstly, it provided a system that aided the selection of appropriate methodology and methods for the study. Secondly, it enabled the justification of the use of these methods by allowing for the application of research philosophy to the research question(s).

Crotty's framework puts into consideration four elements of the research process. This can be applied to the two research questions as shown in table 3.3 below. It is worth mentioning that the framework seemingly omits ontology from the discussion. However, the claim is made that both ontology and epistemology describe the nature

of the research topic with the final outcome as the latter. The framework therefore only includes epistemology even though ontological decisions have been considered.

Research question	Epistemology	Theoretical perspective	Methodology	Methods
What are the perceived facilitators of, and challenges to the use of PCSK9 inhibitors amongst stakeholders in the care for HeFH?	Constructivism	Interpretivism	Thematic analysis	Interviews
To what extent do patient clinical attributes influence the prescription of PCSK9 inhibitors?	Objectivism	Positivism	Data analysis	Statistical analysis

Table 3.3 Application of Crotty (1998) research design framework to the current research questions

Evidently, a parallel existed between the methods required to address each of these research questions. This suggested the adoption of a multi-methods research (MMR) approach which is a form of mixed methods research. Morse (2003) describes multi-methods research as:

"qualitative and quantitative projects that are relatively complete but that are used together to form essential components of one research program" (Morse, 2003).

This indicated that the overall research question determined the components that each phase of the study evaluates. The multiple phases serve the overall function of

addressing sub-questions or objectives relevant to the overall research question but that are different.

As a form of mixed method research, multi-methods research shares the similar principles and rationale with mixed methods research. In the current study, the strengths of mixed methods research inherent in the integration of data will be adopted by conducting partial integration of descriptive quantitative results and qualitative results in chapter 6 of the current thesis. For this reason, the rationale and the conceptual orientations adopted in this study are briefly discussed from the perspective of mixed methods research.

The reasons for adopting MMR in this case would be for the purposes of comprehensiveness, complementarity and corroboration. The qualitative phase of the project deals with the core research focus; which is, essentially, an assessment of the factors that could potentially influence the use of PCSK9 inhibitors. The quantitative phase of the study is concerned with the potential role that the recording of HeFH patients' clinical attributes hold in the attainment of LDLC. The quantitative phase of the study is therefore smaller in scale compared to the qualitative component. It therefore serves to complement, and to corroborate the qualitative results.

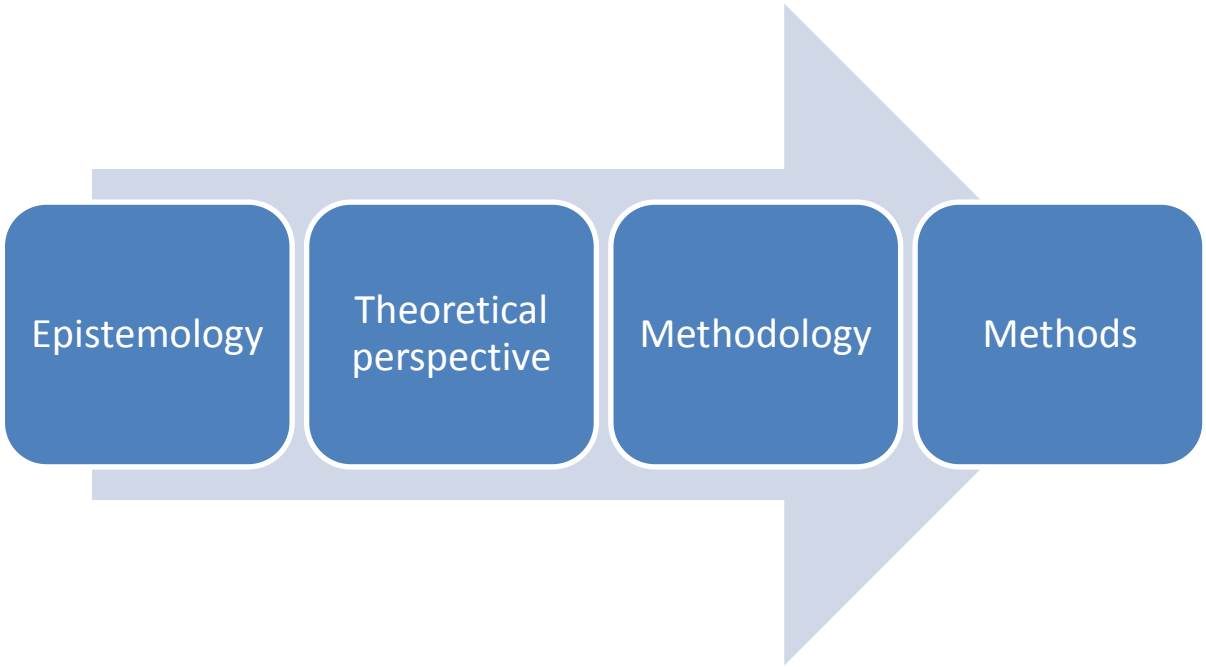

Figure 3.2 Crotty (1998) framework to research design

3.4 Conceptual orientations in multi-methods research

The adoption of MMR introduces the debate on appropriateness of methodology. As previously mentioned, this matter is generally addressed through the research paradigm. It is therefore important to discuss pragmatism, as the worldview in which the current body of work is situated. Herein, a brief history of the arguments for and against MMR is presented, followed by the links to worldviews and methods.

For a long period of time quantitative and qualitative purists considered the two traditional research methods to be incompatible; and of course, advocated for their individual philosophical stances. This period is often referred to as the 'paradigm wars' (Oakley 1999), or the 'paradigm debate' (Creswell and Plano Clark 2007). Most arguments against MMR cite epistemological discordance; however, Bazeley (2009) suggested that this claim was contradictory to current practice. Bazeley's (2009) was that corroboration between qualitative and quantitative results are often accepted as a means of improving research validity, however, the mixing of these two research methods continue to face debate. Furthermore, differences in epistemology have been creatively addressed in past MMR studies. Kane and Trochim (2007), for

instance, adopted a concept analysis approach that suggested that qualitative results could be effectively presented quantitatively, and quantitative results could be justified qualitatively. Given the continued but gradual acceptance of MMR, these debates could be said to have delayed the acceptance of the system. However, the debates undoubtedly also caused a development of MMR techniques.

Although the worldview debate is always evolving, many proponents of MMR adhere to a pragmatist worldview. A smaller group adopt a realist standpoint. The difference between these two viewpoints is that pragmatism focuses on the research topic. Consequently, the methods employed are based on the achievement of the research goal (Maxwell, 2008). On the other hand, realism is considered to ontologically affirm scientific objectivism, while it epistemologically proposes that scientific theory provides knowledge on reality independent of human action (Allmark and Machaczek, 2018). Such a line of thought is not necessary for this body of work, it was therefore suggested that pragmatism was the appropriate research paradigm in this context.

The direct effect of pragmatism's emphasis on the research question is flexibility in methods. This, of course, supports multiple methods approaches (Creswell and Poth, 2017). However, the research paradigm offers more, and perhaps, deeper philosophical advantages to the researcher. From the outset, pragmatism addresses the researchers' beliefs and assumptions as proposed by Morgan (2007). Although it is acknowledged that the researcher's worldview has potential influence on practice, this effect is generally not addressed by many research paradigms. Pragmatism also offers an opportunity for epistemological interchangeability; an opportunity to combine the subjective and objective, the inductive and the deductive (Teddlie & Tashakkori, 2003). Finally, pragmatism allows for the study of cases that prove too complex for conventional research methods. These could range from relatively

simpler research for the assessment of action and effect, policy research where the subjective intertwines with the objective, to cases with conflicting findings between stakeholders (Evans, Coon and Ume, 2011). As cited from Schon (1983), pragmatism fills the gap for cases where research;

"…is more a craft than a slavish adherence to methodological rules"

Cited from Schon, 1983, (p.43)

The current study does not fall into the category of 'complex cases'. However, the literature in the area, as discussed in chapter 2, showed that the study of stakeholder perceptions was a key method of identifying the factors that affected the process of medication provision and use. The literature also showed, specifically, that availability or non-availability of patient records affected the use of PCSK9 inhibitors. In order to account for both of these ontologically different elements of the use of PCSK9 inhibitors, pragmatism and multi-methods research were deemed to provide a creative and effective framework.

3.5 Study design and methods

Several MMR typologies have been advanced in the past (Creswell, 1994: Morgan, 1998, Tashakkori and Teddlie, 1998); consequently, there are a number of considerations for the selection of an MMR design. For example, MMR designs can be based on the stage of the research process where mixing occurs (Tashakkori and Teddlie, 1998). The status of either component (quantitative or quantitative) could also influence design choice (Morgan, 1998); for instance, the study components may possess equal status, or one could be more dominant than the other. Finally, the sequence in which the individual studies are adopted typically leads to sequential or concurrent designs (Johnson and Onwuegbuzie, 2004).

For the purposes of this study, the time ordering and the status of each phase were considered. The qualitative phase constituted the dominant component of the current

study, while the quantitative phase provided comprehensiveness and corroboration. The two phases of the study were independent of each other and were therefore conducted concurrently; this is then followed by convergence in the integration stage. The resulting design was a concurrent triangulation MMR study that can be summarised as shown below:

QUALITATIVE + quantitative

A schema of the study processes are shown in figure 3.3 below.

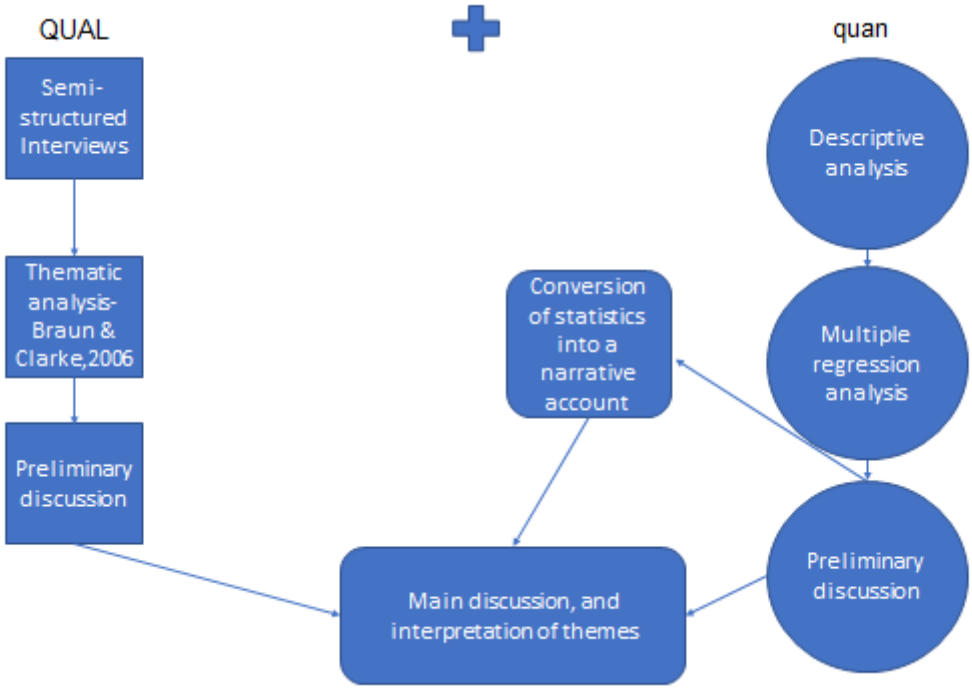

Figure 3.3 The current study's methods

As previously mentioned, the integration of the qualitative and quantitative elements of the study is an important process in MMR (Johnson and Onwuegbuzie, 2004). In the current study, integration mainly occurred at the interpretation level (chapter 6 of this thesis). Broadly speaking, integration involves the identification of similarities/ differences between qualitative and quantitative data; these similarities/ differences are then evaluated and meaning is drawn from them. Integration can also be

achieved by transformation of data to allow for comparison, for example, quantitative data can be transformed into a narrative account to allow for qualitative interpretation (Creswell and Plano Clark, 2007).

At this juncture, it is important to briefly revert back to the reasons an MMR approach was selected, and to focus on justifying the choices made. Based on the five broad rationales for MMR proposed by Greene, Caracelli and Graham (1989), this study serves to provide corroboration, complementarity and expansion. Over the past three decades, several efforts have been made to elaborate on the roles of MMR (Creswell and Plano Clark, 2007; Morgan, 1998: Tashakkori and Teddlie, 1998). Whereas these expansions add value to the discussion, the Greene et al. (1989) model effectively summarises these additions. Using Greene et al.'s model therefore (table 3.4 below) incorporates the reasons MMR was selected for the current study, and the stages in which the researcher anticipated the fulfilment of these reasons.

Reasons for using MMR	**Description**	**Achievement of purpose**
Corroboration	Seek convergence or disagreement in study results	Qualitative views of stakeholders on the use of patient records would be compared to the quantitative assessment of patient records.
Complementarity	Elaborate, illustrate or clarify matters identified in one phase of the study	Quantitative analysis would illustrate prescriptions patterns identified from qualitative

		accounts.
Expansion	Increasing the extent of inquiry, particularly to include an element of the study that was absent if only one method was used.	Without the quantitative phase of the study, the qualitative phase would not be able to elaborate on the state of patient clinical attribute records, or the effect it potentially has on prescription.

Table 3.4 Structure for the achievement of MMR purposes

3.6 Qualitative phase of the study

As mentioned earlier, the qualitative phase of the current study was based on a constructivist/ interpretivist philosophy. This asserts that reality is a construct of people's beliefs, opinions and actions. These views are negotiated during interactions with other people; the philosophy is therefore referred to as social constructivism. This phase of the study aimed to explore the views and perceptions of healthcare stakeholders (i.e. Consultants, nurses, GPs and patients) on a new type of medicine: Proprotein Convertase Subtilisin/Kexin Type-9 (PCSK9) inhibitors.

3.6.1 Sampling of interview participants

3.6.1.1 Sample size

In qualitative research, sample sizes are usually comparatively smaller than quantitative research (Ritchie, Lewis and Elam, 2003). Several reasons exist for this; firstly, when developing themes in qualitative analysis there can be an element of diminishing returns if no new themes are being identified (Mason, 2010). The amount of thematic output reduces as the sample increases. Secondly, time and funding constraints can often reduce the time availed to a study. Compared to quantitative

research, qualitative research involves the logistics of meeting with participants, or arranging for telephone interviews, to conduct the study.

Although there are suggestions that qualitative works, irrespective of method, should enrol at least 15 participants Bertaux (1981), some studies have over 50 participants (Mason, 2010). In a study on the mean number of participants in qualitative PhD projects, Mason (2010) reported an average of 28 participants (standard deviation 18.7), with a mode of 20 and 30.

3.6.1.2 Eligibility Criteria

It was important to select a sample of participants who were knowledgeable about PCSK9 inhibitors, and those involved in the care of HeFH patients who may require the medication. This required a purposeful approach to sampling. A list of inclusion and exclusion criteria was therefore developed to ensure that each participant was knowledgeable of, or had experience with PCSK9 inhibitors and/ or HeFH as shown in table 3.5 below. Some healthcare practitioners (e.g. nurses and GPs in primary care) may not be aware of PCSK9 inhibitors but are involved in the identification or signposting of HeFH patients to secondary care where they may be prescribed the medication. In some cases, this lack of knowledge could act as a barrier to PCSK9 inhibitor use. For this reason, it was deemed acceptable to include healthcare providers who dealt with HeFH patients but were not aware of PCSK9 inhibitors in the study. The participants included in the study were; HeFH patients, lipid clinic consultants, GPs and nurses.

The inclusion of different stakeholders in the care for HeFH was intended to provide a comprehensive account of viewpoints relevant to the therapeutic management of HeFH with PCSK9 inhibitors. Senior consultants and prescribing nurses are involved in the prescription of medicines, nurses monitor medication usage and interactions,

GPs monitor patients once they are discharged from secondary care; while patients can report on the experience with the medication.

Participant group	**Inclusion criteria**	**Exclusion Criteria**
Consultants/ GPs	• Involvement in the prescription of lipid management therapies. Involvement in the prescription of this new type of medicine	• Consultants who are not involved in lipid management
Patient groups	• Past or current NHS patients of high cholesterol or complicated cases of high cholesterol • Who have received or are receiving any lipid lowering treatment • Patients who have received this new type of medicine • Patients who cannot tolerate statins • Patients who are not	• Patients with learning disabilities, incapable of understanding the research, under the age of 18, patients who have not given consent

	responsive to statins	
Nurses	• Registered nurses who routinely care for people with high cholesterol and HeFH • Nurses who have cared for patients taking this new type of medicine • Nurses who work in lipid clinics	• Nurses who have not prescribed cholesterol-reducing medicine before

Table 3.5 Inclusion and exclusion criteria

3.6.2 Study setting

Discussions were held with two cardiology specialists in order to explore potential methods of carrying out this study. It was determined that this new type of medicines will be used in NHS hospital departments that provide treatment for complicated cases of high cholesterol. This is usually NHS lipid clinics; however, some hospitals' biochemistry departments care for these patients. The type of medicine under study is relatively new, therefore, only a small number of patients are on the medication per research setting. It is therefore necessary to conduct a multicentre study in order to obtain a sample size that is adequate for the study.

A list of NHS hospitals that have a lipid clinic was obtained from the heartuk.org.uk website. Contact was made with the NHS trust's research and development departments (R&D - http://www.rdforum.nhs.uk/content/contact-details/) and access and ethics approval were arranged for organisations that agreed to participate in the

study. Recruitment took place at Fenton GP practice and in lipid clinics at; the Manchester University NHS Foundation Trust, the University Hospitals of North Midlands.

3.6.3 Data collection techniques

Semi structured interviews were used for data collection. The development of topic guides was based on literature and the information gathered through the conduct of preliminary discussions with two cardiology specialists who were academics at Keele University. These discussions described the treatment of HeFH and the stakeholders involved in the management of the condition. It was determined that HeFH patients were mostly identified in primary care by general practitioners (GPs) and nurses; patients were referred to secondary care (lipid clinics) if their LDLC levels were not reduced by 50% using conventional lipid lowering therapies. PCSK9 inhibitors could then be prescribed to these patients in lipid clinics by consultants. Topic guides were developed for each group of stakeholders (Appendix 6-7). They were kept brief, to allow for an open exploration of viewer experiences. Open ended questions were used to encourage comprehensive accounts of the participants' views. Probing questions were asked for clarification or to elicit further comment on emerging themes (Whiting, 2008). The interviews were audio-recorded, audio consent was confirmed at the beginning of each interview in addition to the written consent.

3.6.4 Methodological rigour

Methodological rigour was assessed using the strategies developed by Lincoln and Guba (1986). These criteria include credibility, dependability, confirmability and transferability.

Credibility – This was concerned with methods taken to ensure that the data collected by the interviewer, and the responses given by participants were valid. Three steps were adhered to for the achievement of this purpose:

- There was prolonged engagement with each study setting. The study was conducted across 4 clinical establishments; the study was kept open in all the settings for the entire duration of data collection (4 months). This encouraged reflections among the participants and they were able to contact the research team in case of any additional comments.
- The interviewer received extensive training on the conduct of qualitative interviews and subsequent analysis techniques using NVivo through course modules. The interviewer was also in contact with a qualitative specialist within the university who advised on the project. Prior to the current research project the interviewer had been trained to the Master of Pharmacy (MPharm) level on research methods included qualitative work.
- The interview process and material was testing on two university academics involved in the care for patients with cardiovascular diseases – interventional cardiologist and general practitioner. This process helped to streamline the interview protocol, adjust interview times and better anticipate the conditions required for the different stakeholders that participated in the study.

Dependability – The strategies in this section ensured that the data collected could be reproduced if conducted on the same cohort of participants or were analysed by different coders. The strategies included:

- The study protocol was detailed to ensure that different researchers would follow the same procedure in the conduct of the study. Its development included input from academic researchers, clinicians and research approval bodies. The protocol was assessed by the research team for appropriateness and correctness, the University research ethics team and it was approved by participant's organisations and external research approval bodies.

- The data collection processes was detailed in each setting's site file. There was a clear process developed for any changes made to the protocol that involved reassessment by the academic research team and research approval bodies.
- The coding process was shared with the supervisory team on a weekly basis. The discussions of the findings and the analysis process helped to ensure reflexivity on the part of the research and aided in the planning for further appropriate action.

Confirmability – The methods in this strategy provided confidence that the results produced could be confirmed by other researchers.

- The application of multi-methods (quantitative and qualitative approaches) provided a method to confirm the data being collected in the study (data source triangulation). Quantitative data gave a general indication of the management of HeFH while qualitative interviews with stakeholders served to elaborate on the issues identified in quantitative analysis, and vice versa.
- The involvement of different stakeholders also provided a form of triangulation on the interview data. Stakeholders commented on the involvement of other healthcare professionals confirming or disproving their accounts of the issues surrounding PCSK9 inhibitor usage.

Transferability – This concerned the ability of the results to be transferred or applied to other clinical settings. Two techniques were adopted with the aim of achieving this transferability:

- Purposive sampling was used to ensure that participants involved in the study were involved in the management of HeFH and the use of PCSK9 inhibitors.

All stakeholders involved in the use of the medicine were also included ensuring that the same sample would be drawn from any hospital setting.

- Saturation was achieved ensuring that no new views could be found in the accounts of the participants. This increased the likelihood that all the opinions and perspectives of stakeholders in the research sites had been assessed.

3.6.5 Data analysis

Included in Creswell's (2013) definition of qualitative research is a description of the qualitative data analysis process. This is partially quoted below:

"…data analysis that is both inductive and deductive and establishes patterns or themes. The final written report or presentation includes the voices of participants, the reflexivity of the researcher, a complex description and interpretation of the problem, and its contribution to the literature or call for change. "

(Creswell, 2013, p.44)

Braun and Clarke (2006) hold the view that thematic analysis should be recognised as a qualitative data analysis method. This is in contradiction to Boyatzis (1998) and other researchers who believe that thematic analysis is a process situated within established qualitative analysis methods. Although thematic analysis has previously been considered to be located within the realist paradigm (Roulston, 2001); Braun and Clarke (2006) argued that the method is free of attachments to theoretical frameworks. This argument contends that thematic analysis offers flexibility that makes it accordant with different thematic frameworks. Thematic analysis therefore provides an analysis method that fits the pragmatic philosophy that governs the overall multi-methods approach adopted by this research (Aronson, 1994).

Some considerations were made in the decision to adopt thematic analysis in this study. Based on the overarching conceptual framework for this project, it was

determined that the results of the qualitative phase of the study would be composed of themes pertinent to the research question, and identified from the data. Other analysis methods exist for the assessment of patterns in qualitative data (Holloway and Todres, 2003); these include, grounded theory, interpretative phenomenological analysis (IPA) et cetera. However, these methods are either tied to philosophical stances that do not support this research, or they focus on explaining elements of the data that do not inform this study. The method of identifying themes was mostly theoretical; it was intentionally driven by the primary research question, and factors identified from the literature review (Prosser, 2003). Themes were identified at a semantic or surface level (Boyatzis, 1998), and were intended to explain the entire data set i.e. the responses from all stakeholders in the study. Having made these considerations, it was determined that the choice thematic analysis was justified for this study.

The analysis was conducted using analysis software NVivo. Bazeley and Jackson (2019) was used as the main reference material for the use of NVivo. Further clarification of the analysis procedure was obtained from Bazeley (2013). The thematic analysis process was based on the framework developed by Braun and Clarke (2006). Braun and Clarke (2006) proposed a stepwise approach for the conduct of thematic analysis. This is outlined in figure 3.4 below.

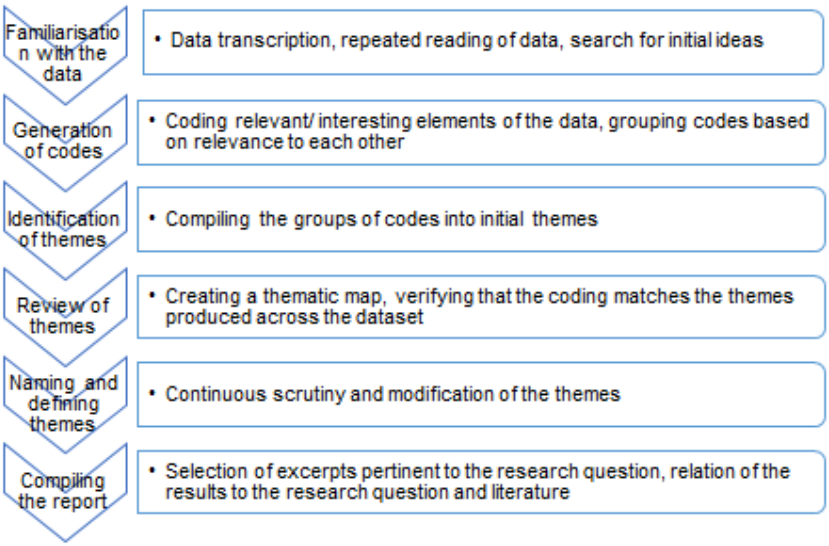

Figure 3.4 Braun and Clarke (2006) thematic analysis procedure

A theoretical thematic approach was adopted in the analysis. Open coding was used, meaning that the researcher did not include pre-determined codes in the analysis process.

3.6.6 Ethical considerations

Prior to the commencement of the study, a favourable opinion will be sought from an NHS Research Ethics Committee (REC). The Health Research Authority (HRA) assesses all research projects carried out within NHS England where the NHS has a duty of care to the participants. HRA approval will be required for this study and it will not commence until NHS REC/HRA approval is obtained. However, only one application has to be submitted to obtain approval from both bodies. All the research material (i.e. the research protocol, informed consent forms, study summary, invitation letters) will be submitted for review to NHS REC/HRA via the Integrated Research Application System (IRAS) website. All correspondence with NHS REC will be retained. The researcher will also submit an annual progress report (APR) every year until the research is completed. This will be done within 30 days of each annual

anniversary. Any changes to the study will not be implemented until an amendment of the protocol has been submitted for review and approved. Amendments will be categorised as either substantial or non-substantial and be submitted to the HRA, with substantial amendment sent to the NHS REC for review. Amendments will be recorded in appendix 8 of the research protocol. Finally, the CI will inform the NHS REC if the research is terminated prematurely, or when the research is completed. Following completion of the study, a report with the findings, publications or abstracts will be sent to the REC within a year of the results being obtained.

3.6.7 Negotiation of access and participant documentation

Following the receipt of the ethical approval documentation, this information was relayed to the research and development (R&D) departments of each participating organisation. The NHS trusts issued an NHS passport that allowed the research access to the primary coordinator and the research premises.

The primary researcher then liaised with the primary coordinator (the head of the lipid clinic) to present the research documentation to potential participants. The documentation included, invitation letters, research information sheet and consent to contact and study consent forms. These are attached in Appendix 1-5.

3.7 Quantitative phase of the study

The quantitative phase of the current study was designed to study the potential predictive effect of HeFH clinical attributes on LDLC attainment following statin use. By extending the LDLC attainment to the thresholds required for PCSK9 inhibitor use, a successful model would be able to predict PCSK9 inhibitor eligibility. Data was obtained from the Clinical Practice Research Datalink (CPRD) for secondary analysis. CPRD is a database that gathers anonymised patient records from general practitioner (GP) practices across the UK. The primary care data can be linked to secondary care datasets, hospital episode statistics (HES), admitted patient care

(HES APC) data, and other health related datasets in order to produce a representative sample for the general UK population. CPRD was established more than 30 years ago, it spans across 42 million patient lives and currently contains 13 million registered patients (CPRD, 2019).

3.7.1 Sampling strategy

All patient data with a diagnosis of FH were extracted from the CPRD database. The dataset was filtered to include data that was considered acceptable for research based on CPRD quality standards (CPRD, 2017). FH was represented by the NHS Read Code "C32" and daughter codes (Attached in appendix 13). The diagnosis and treatment of FH is based on low density lipoprotein cholesterol (LDLC) measurements. The sample was therefore refined to include patients with at least two LDLC test records that were more than a year apart of medication usage.

3.7.2 Quality considerations

This section discusses the quality considerations extended to the quantitative phase of the project. Steyerberg (2009) presents steps that are required for the development of a clinical risk prediction model. We discuss the steps relevant to this section as follows:

(I) Determination of the prediction problem

It is important to select a relevant research problem that is directed by clinical guidelines and/or evidence. The aim of the current study was to assess the feasibility of predicting HeFH patients that would require PCSK9 inhibitors using the CPRD database. The rationale for this aim was based on the systematic review (chapter 2) results that identified patient clinical data as a potential barrier to PCSK9 inhibitor use.

(II) Definition of the outcome of interest

The outcome of interest should ideally be guided by clinical guidelines or clinical professional opinion/ consensus. This makes the overall model applicable to patients or the clinical setting. HeFH management is based on the control LDLC; subsequently, the prescription of PCSK9 inhibitors is dependent on the LDLC levels remaining above 5mmo/l in primary prevention despite the use of conventional lipid lowering therapy. The outcome of interest was therefore an LDLC above 5mmol/l despite the use of lipid lowering therapy to determine PCSK9 inhibitor eligibility; as stipulated by NICE guidelines (NICE technology appraisals TA 393 and 394).

(III) Determination of predictors

The variables tested in the current analysis were obtained from literature; mainly Weng et al. (2015) and Mata et al. (2011). As mentioned above, the management of HeFH revolves around the control of LDLC. Some clinical attributes associated with effective LDLC control have been assessed in longitudinal studies such as the SAFEHEART study (Mata et al., 2011), and the successful predictive modelling for potential HeFH diagnosis in Weng et al. (2015). No further methods were used for feature/ variable selection as these were readily available in literature.

(IV) Selection of study database

The current study aimed to develop a predictive model that could be used in the primary and secondary care hospital settings. For this reason it was necessary to use a clinical database that contained patient data routinely collected in primary care. This could potentially serve to inform clinical practice in primary care with regard to referral to secondary care for PCSK9 inhibitor consideration; and in secondary care it could help to determine the patients who are at a higher risk of not achieving target LDLC and would therefore require PCSK9 inhibitors.

(V) Assessment of CPRD data suitability

Of the 11 clinical variables considered, only three of them (maximum LDLC record, maximum triglyceride record, age at diagnosis) were continuous with the rest being categorical data. Normality tests were conducted on the three variables, presenting the skew, kurtosis and histograms. Nevertheless, for ease of computation and uniformity the three continuous variables were converted into binary variables based on clinical guideline specified thresholds. For example, final LDLC achieved following treatment was categorised as above or below 5mmol/l, which represents the NICE defined threshold for the initiation of PCKS9 inhibitors. Correlation analysis between the variables was also conducted to assess covariance and significant associations with the dependent variable.

(VI) Assessment of final and split dataset for derivation and validation

The derivation and validation cohort data were assessed via a two tailed independent sample T-test to assess homogeneity. The result was presented as; the t statistic, p value, mean and standard deviation.

(VII) Model evaluation and validation

The model presented included the following results; beta coefficients, standard error, Wald statistic, degrees of freedom, significance value, odds ratio (exponential of the B coefficient), upper and lower limits at 95% confidence interval.

Model discrimination was assessed using sensitivity, specificity and ROC c-statistic. Calibration was to be assessed by the Hosmer-Lemeshow goodness-of-fit test statistic following effective discrimination.

3.7.3 Study Variables

The covariates used were based on the variables used by Weng et al. (2015) to predict the diagnosis of FH. The nine indicators used in Weng's model are age, triglyceride concentration, lipid lowering drug usage, family history of familial hypercholesterolemia, raised cholesterol or myocardial infarction, and the diagnosis of either diabetes or kidney disease. Hypothyroidism and drug groups (shown in table 3.6 below) can affect LDLC levels in the body; these variables were therefore added as covariates in this study. The study variables were split into categories prior to analysis. The full list of covariates for the study is shown below:

Study variables	**Variable categories**
Age at diagnosis	1: 0-40 2: more than 40
Gender	1: male 2: female
Maximum low density lipoprotein cholesterol (ldlc) measurement	1: 0-5 mmol/L 2: more than 5 mmol/L
Maximum triglyceride measurement	1: 0-1.7mmol/L 2: more than 1.7 mmol/L
Family history of familial hypercholesterolemia	1: yes 2: no
Family history of myocardial infarction	1: yes 2: no
Family history of high cholesterol	1: yes 2: no
Diagnosis of hypothyroidism	1: yes 2: no
Diagnosis of kidney disease	1: yes 2: no

Diagnosis of diabetes	1: yes 2: no
Prescribed drug groups following diagnosis	1: statins 2: statins + ezetimibe 3: statins + ezetimibe+ fibrates 4: medication not recorded 5: combinations of lipid therapies

Table 3.6 Study variables and categories

3.7.4 Outcome variables

NICE technology appraisals (393, 394) recommend that PCSK9 inhibitors are initiated when LDLC levels are above 3.5mmol/l and 5mmol/l in secondary and primary prevention treatment respectively despite lipid lowering treatment. Therefore, in order to predict potential PCSK9 inhibitor requirement, the outcome variable for this study was based on the LDLC level achieved at the end of the follow up period (variable in dataset: final LDLC reading on record). Additionally, NICE guidelines for PCSK9 inhibitor use are divided by primary and secondary prevention treatment resulting in two outcome criteria (LDLC 3.5 and 5mmol/l). The dataset was therefore split into secondary prevention treatment and primary prevention treatment cohorts and assessed separately.

3.7.5 Data analysis

NICE guidelines for the initiation of PCSK9 inhibitors are divided into primary and secondary prevention treatment. The guidelines recommend LDLC levels consistently above 5mmo/l and 3.5mmol/l for primary and secondary treatment respectively, despite maximal treatment with other lipid lowering therapies. Due to this difference in LDLC outcome, the dataset was spilt into two cohorts based on primary and secondary treatment requirement and parallel analysis conducted. Patients who had a recorded event of ischaemic heart disease (IHD) and myocardial infarction (MI) were deemed to require secondary prevention treatment; while

patients without these conditions represented the primary prevention cohort. The outcome for the primary prevention cohort was calculated as the cases that retained an LDLC level of 5mmol/l at the end of the follow up period; whereas, the outcome for the secondary prevention cohort was based on a final LDLC reading of 3.5mmol/l. Chi square tests and correlation analysis were carried out to assess the correlation between the independent variables and the outcome variables for each cohort. Binary logistic regression analysis using the forward stepwise method was then conducted to produce the predictive model.

The model was validated by calculating predicted probabilities and group membership for the validation cohort. An area under the AUC curve was constructed to quantify accuracy of the model (AUC value or Harrell's c-statistics) and to estimate sensitivity and specificity. Calibration was conducted by comparing the predicted and observed events stratified by deciles. The functionality of the predictive model relative to the predictor parameters was assessed and reported based on the decile category. All data analysis was conducted using the IBM Statistical Package for the Social Sciences (SPSS) program version 24.

3.7.6 Power calculation

Estimates for multiple regression power and sample size calculations were calculated using G-Power. G-Power is a calculation tool based on Faul et al (2009); this was accessed from the Intellectus Statistics website (https://www.intellectusstatistics.com/sample-size-write-up/sample-size-multiple-regression/). Power analysis was conducted for multiple regression with ten predictors using an alpha of 0.05, a power of 0.80 and a small effect size (f2=0.02)(Faul et al., 2013). Based on these parameters, the desired sample size was determined to be 822. This indicates that this study should have more than 822 participants in the derivation and validation cohorts. This should provide enough

statistical power to detect correct relationships between the variables and to develop a stable predictive model.

3.8 Conclusion

This chapter outlined the methodology of the present study. The study employed a multi-methods approach consisting of one qualitative and one quantitative component. The justification for the choice in research design was accomplished by describing general philosophical underpinnings of multi-method research followed by an assessment of the study's research questions in the ensuing context. Chapter four presents the results of the quantitative phase of the study, while chapter five addresses the qualitative component. Finally, the integration and discussion of the results are covered in chapter six.

Chapter 4 Quantitative analysis and results

This chapter presents the results and analyses of the quantitative phase of the current project using both descriptive and inferential statistics. The chapter addresses the following research questions as identified in chapter 2:

- To assess the feasibility of using the Clinical Practice Research Datalink (CPRD) database to develop a predictive model that can identify HeFH patients who meet the LDLC eligibility targets for PCSK9 inhibitors.

4.1 Background

The rationale for this section of the thesis was based on literature that identified the inadequate recording of heterozygous familial hypercholesterolemia (HeFH) patients' clinical attributes as a potential barrier to the prescription of proprotein convertase subtilisin kexin-type 9 (PCSK9) inhibitors (Cohen et al. 2017, Baum et al. 2017). Cohen et al. (2017) described patient clinical attributes that were relevant to PCSK9 inhibitor prescription as; records of the use of statins/ other lipid modification agents, records of low density lipoprotein cholesterol (LDLC) measurements, and history of cardiovascular disease (CVD).

Current United Kingdom (UK) clinical guidelines recommend initiation of PCSK9 inhibitors following the failure of statin therapy and associated adjuvant medication to regulate LDLC levels. Records of patient clinical attributes are used to ascertain these requirements as follows. A record of statin therapy confirms that the step therapy system stipulated by the National Institute for Health and Clinical Excellence (NICE) guidelines is followed prior to consideration of PCSK9 inhibitors. Similarly, records of low density lipoprotein cholesterol (LDLC) measurements are used to determine whether the guideline recommended LDLC thresholds for PCSK9 inhibitor use have been met. Finally, the presence of CVD is associated with a higher severity

of HeFH; guidelines recommend lower LDLC thresholds for PCSK9 inhibitor initiation in these cases. The unavailability of these records was associated with high rates of rejection of PCSK9 inhibitor prescriptions.

Given the parallel between inadequate recording of HeFH data and the reliance on said data to determine PCSK9 inhibitor prescription; the present chapter investigated the relationship between recorded patient clinical attributes and LDLC reduction required for PCSK9 inhibitor initiation. Under the current NICE guidelines PCSK9 inhibitor prescription is dependent on the failure of statins to reduce LDLC levels below 5mmol/l, PCSK9 inhibitor prescription was therefore based on this therapeutic target.

4.2 Database access

The Clinical Practice Research Datalink (CPRD) is a database that gathers anonymised patient records from general practitioner (GP) practices across the UK (CPRD, 2019). CPRD data consists of primary care consultation records that document basic patient demographic details, medical history events (including symptoms, signs and diagnoses), clinical tests conducted and their results, records of prescriptions and reasons for referral to secondary care among other patient related clinical attributes. CPRD data is composed of 1,800 primary care practices and includes 50 million patients, of which 14 million are actively registered. The data is also aligned with UK demographics with respect to age and sex (CPRD, 2019). CPRD therefore provides longitudinal data that allows for both retrospective and prospective analyses. CPRD data allowed for longitudinal follow up of HeFH patients while accounting for the use of lipid lowering agents and the monitoring of LDLC target achievement.

4.3 Summary of data definitions

The rationale for the quantitative phase of the thesis was based on the results from the systematic review (chapter 2) as described in section 4.1 above. However, other variables associated with LDLC management have been identified and exist in other literature. It is therefore important to note that variable selection for the study was based on published literature as discussed below; and not on the systematic review that solely focused on the influencing factors of PCSK9 inhibitor use.

Two publications were used to inform the selection of variables; Weng et al. (2015) and Mata et al. (2011). Weng et al. developed a successful diagnostic predictive model using HeFH clinical attributes while Mata et al. presented the association of some clinical characteristics with LDLC. Predictive modelling with regards to PCSK9 inhibitors is understudied, hence the current project sought to assess the feasibility of such a model by assessing several potential clinical attributes. HeFH treatment is associated with the management of LDLC and clinical attributes that can influence LDLC levels; these attributes were selected from the studies as potential predictors in the current study.

The outcome of the study was based on NICE guidelines for the prescription of PCSK9 inhibitors i.e. an LDLC value consistently above 5mmo/l despite statin treatment.

4.4 Data extraction procedures

HeFH was represented by the NHS Read Code “C32” and daughter codes (Attached in appendix 13). The start and end of follow up was based on the first and last LDLC measurements during the one year period of medication usage. The data covered the period of 1 January 1999 until December 2017 or the latest time which CPRD had data that was eligible for the study. Patients should have received lipid lowering

medication for a period or one year or more to ensure enough time for step therapy with statins and other conventional medicines.

The complete CPRD dataset consisted of 5656 patients with familial hypercholesterolemia and other related diseases. CPRD medical codes were used to obtain patients with a diagnosis of pure HeFH; this resulted in a total of 5134 individuals. 3761 patients were found to have at least one LDLC measurement in their record. However, in order to ensure that the reduction in LDLC levels could be determined, at least two readings were required per case (n=3297). The dataset was further filtered to exclude cases that had not received lipid lowering medication for a period of one year or more (n=2949). The final study cohort therefore consisted of 2949 cases that could be analysed for the purposes of this research study. A summary of the selection process is provided in figure 4.1 below.

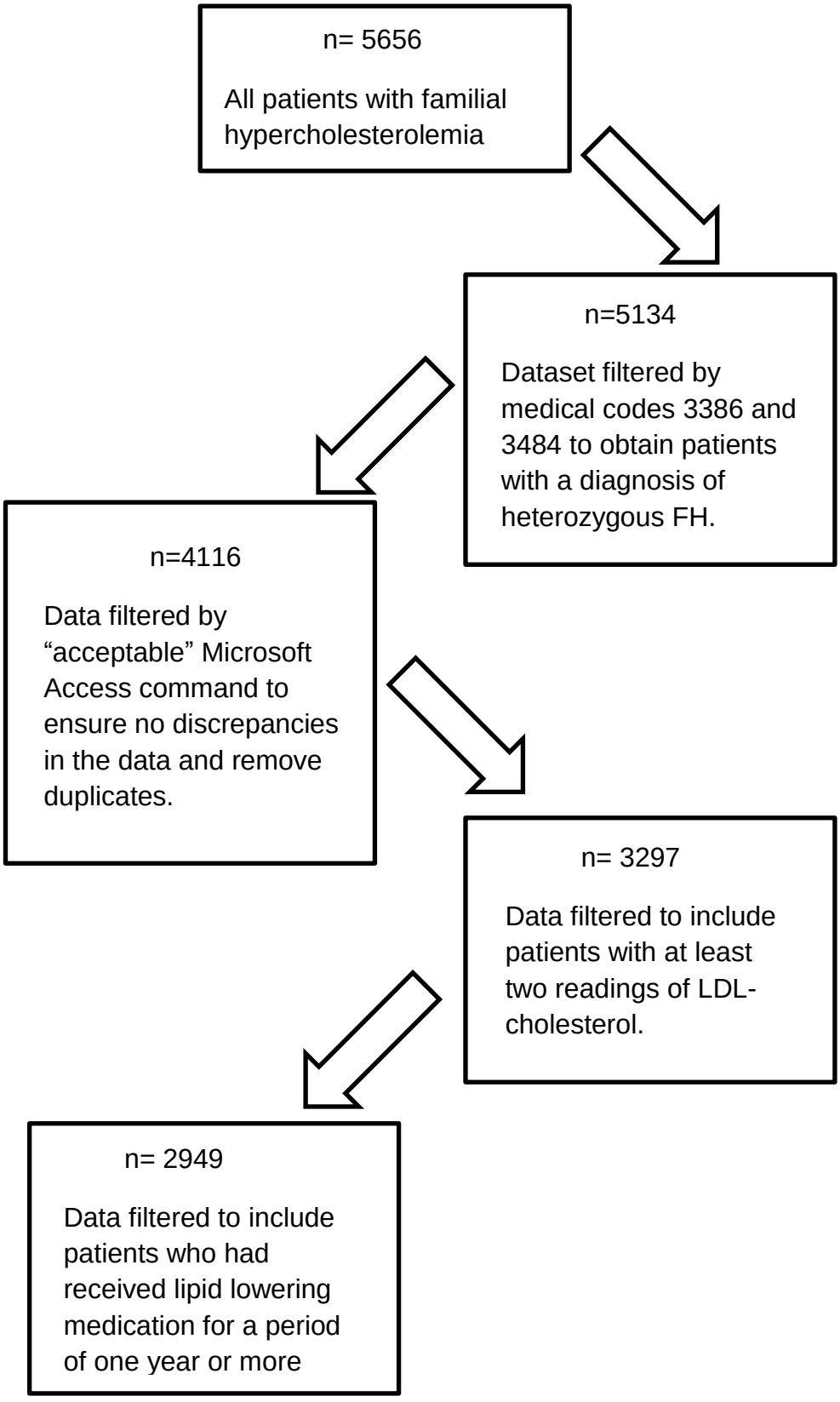

Figure 4.1 Summary of the sample selection process

4.5 Methods

NICE technology appraisals (TA) 393 and 394 (for alirocumab and evolocumab respectively) recommend that PCSK9 inhibitors are initiated when LDLC levels are persistently above 5mmo/l and above 3.5mmo/l for primary prevention and secondary prevention treatment respectively. This is following the use of the maximum tolerated doses of other lipid lowering agents possible. These two targets determine when PCSK9 inhibitors can be used and would therefore form the primary outcome of these analyses.

The dataset was therefore split into primary and secondary treatment cohorts; the secondary prevention treatment cohort was composed of patients who had suffered a CVD event (such as acute coronary syndrome, coronary heart disease; ischaemic stroke; peripheral arterial disease.), while the patients in the primary prevention treatment group had not recorded a CVD event.

All the patients in the secondary treatment cohort met the outcome target of 3.5mmol/l, and were therefore eligible for PCSK9 inhibitors based on NICE guidelines. This could be possibly be explained by the fact that patients who have experienced a CVD event are deemed to be at a high risk of suffering a recurrent event. For this reason, a lower LDLC threshold for PCSK9 inhibitor requirement is set for this group of patients, i.e. 3.5mmo/l. No further analysis was therefore conducted to this cohort; figure 4.2 below presents a summary of the steps conducted in this section.

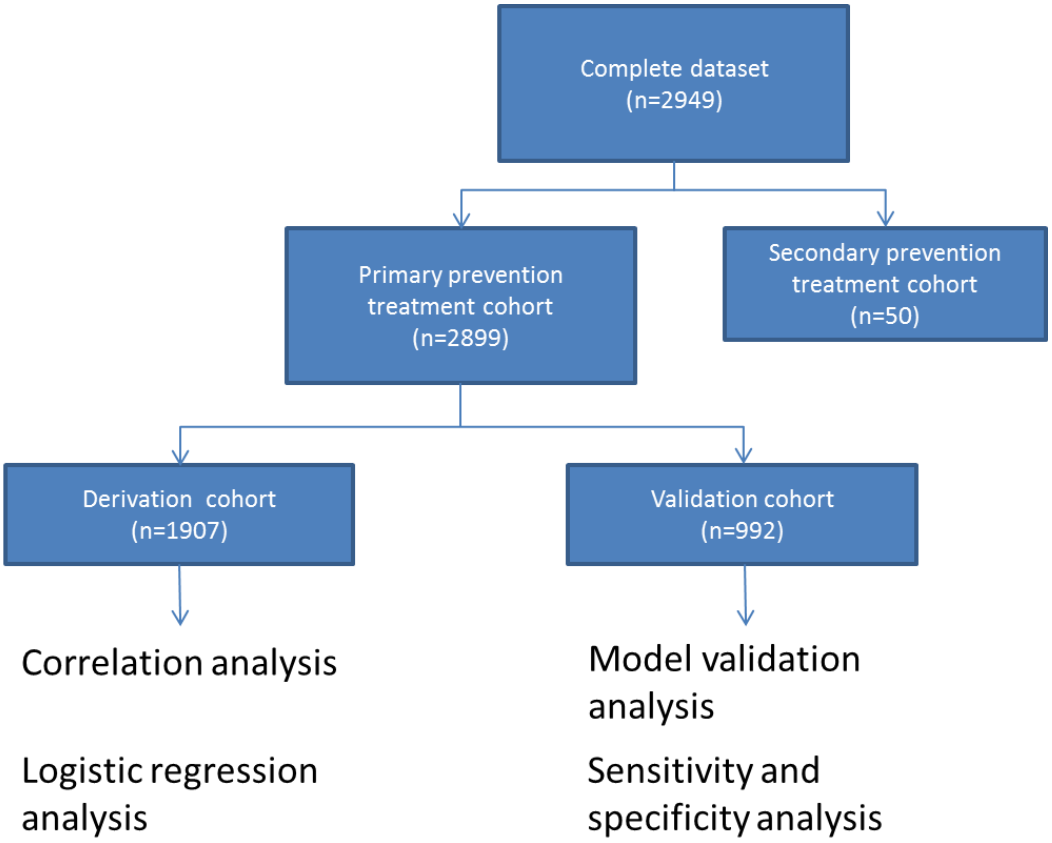

Figure 4.2 Overview of the research methods

The primary cohort (n=2899) was split into a derivation cohort for the development of the predictive model, and a validation cohort to test model performance. There is no concise recommendation on which method to use when dividing a study cohort for validation purposes. However, the derivation cohort needs to be as large as possible in order to more closely reflect the characteristics of the general population. For example, a study on predictive modelling for HeFH (Weng et al., 2015) split their modelling cohorts by 75/25. Therefore, to ensure that we achieved appropriate power (discussed in section 4.7) whilst maintaining a large derivation cohort, the study cohort was split by 65/35. The derivation cohort therefore consisted of 1907 cases while the validation cohort contained 992 cases.

4.6 Quantitative analyses

Correlation analysis was conducted using Chi square tests. The analysis assessed the relationship between the outcome variable (final LDLC record attained) and each predictor variable. The significance level (p value) for each variable was calculated to determine whether the relationships were statistically significant.

Regression analysis describes how a predictor variable is numerically related to the outcome variable. Univariate regression analysis therefore assessed the relationships between each individual predictor variable and the outcome variable without controlling for the other variables.

Stepwise logistic regression was used to develop the predictive model. The process evaluates the cumulative predictive effect of the predictor variables on the outcome variable. Using the stepwise approach, the effect of each variable on the model was assessed and the variable was subsequently added or removed from the model (Field, 2005).

The area under receiver operating curve (AUC) was used to determine the best cut off value for predicting an observation categorised as (0) or (1). In the case of the current study, the outcome variable shows whether the LDLC value of a HeFH patient is above or below 5mmol/l following statin treatment; thereby predicting PCSK9 inhibitor eligibility.

The AUC is calculated using the sensitivity and specificity values of the model. Specificity refers to the ability of the model to correctly identify patients who have a positive outcome, while sensitivity is the ability of the model to identify a negative case.

The model was validated by calculating predicted probabilities and group membership for the validation cohort. An area under the AUC curve was constructed to quantify accuracy of the model (AUC value or Harrell's c-statistics) and to estimate sensitivity and specificity. Calibration was to be assessed by the Hosmer-Lemeshow goodness-of-fit test statistic following effective discrimination. The functionality of the predictive model relative to the predictor parameters was assessed and reported based on the decile category. All data analysis was conducted using the IBM Statistical Package for the Social Sciences (SPSS) program version 24.

4.7 Power calculation

Estimates for regression analysis power and sample size were calculated using G-Power. G-Power is a calculation tool based on Faul et al (2009); this was accessed from the Intellectus Statistics website (https://www.intellectusstatistics.com/sample-size-write-up/sample-size-multiple-regression/). Power analysis was conducted for multiple regression with eleven predictors using an alpha of 0.05, a power of 0.80 and a small effect size (f2=0.02) (Faul et al., 2013). Based on these parameters, the desired sample size was determined to be 900.

4.8 Results

4.8.1 Descriptive analysis

The study contained a total of 11 independent variables (covariates) obtained from past research studies (Mata et al., 2011; Weng et al., 2015). Nine of these covariates were based on Weng's model; these were age, triglyceride concentration, lipid lowering drug usage, family history of familial hypercholesterolemia, raised cholesterol or myocardial infarction, and the diagnosis of either diabetes or kidney disease. Mata et al. (2011) also found significant statistical associations between hypothyroidism and drug groups and LDLC levels in the body; these were therefore added as covariates in this study. For ease of analysis and presentation of results all

variables were transformed into dichotomous values for each case represented in the study. The full list of covariates is shown in table 4.1 below:

Study variables	**Variable categories**
Age at diagnosis	1: 0-40 2: more than 40
Gender	1: male 2: female
Maximum low density lipoprotein cholesterol (ldlc) measurement	1: 0-5 mmol/L 2: more than 5 mmol/L
Maximum triglyceride measurement	1: 0-1.7mmol/L 2: more than 1.7 mmol/L
Family history of familial hypercholesterolemia	1: yes 2: no
Family history of myocardial infarction	1: yes 2: no
Family history of high cholesterol	1: yes 2: no
Diagnosis of hypothyroidism	1: yes 2: no
Diagnosis of kidney disease	1: yes 2: no
Diagnosis of diabetes	1: yes 2: no
Prescribed drug groups following diagnosis	1: statins 2: statins + ezetimibe 3: statins + ezetimibe+ fibrates 4: medication not recorded 5: combinations of lipid therapies

Table 4.1 Study variables and categories

Other than the ‘yes’ ‘no’ categories, gender and the medicines covariates, the creation of the remaining covariate dichotomous groups were based on literature. The mean age of onset of cardiovascular disease (CVD) is 40 (Robinson and Goldberg, 2011), age was therefore split as 0-40 and >40. Triglycerides levels above

1.7mmo/l and LDLC levels above 5mmo/l are considered to be high (Watts et al., 2012). The clinical attributes of the final study cohort (n=2949) are presented in the table 4.2 below.

Clinical attributes	**Count(n)**	**Percentage (%)**
Age at diagnosis		
1:0-40	542	18.4
2:more than 40	2405	81.6
Gender		
1:male	1193	40.5
2:female	1756	59.5
Maximum LDLC measurement		
1:0-5mmol/L	1068	36.2
2:more than 5mmol/L	1881	63.8
Maximum triglyceride measurement		
1: 0-1.7mmol/L	884	30.0
2: more than 1.7 mmol/L	2064	70.0
Family history of familial hypercholesterolemia		
1:yes	305	10.3
2:no	2644	89.7
Family history of myocardial infarction		
1:yes	152	5.2
2:no	2797	94.8

Family history of high cholesterol		
1:yes	154	5.2
2:no	2795	94.8
Diagnosis of hypothyroidism		
1:yes	179	6.1
2:no	2770	93.9
Diagnosis of kidney disease		
1:yes	1	0.03
2:no	2948	99.97
Diagnosis of diabetes		
1:yes	48	1.6
2:no	2901	98.4
Prescribed drug groups		
1: statins	1762	59.7
2: statins + ezetimibe	423	14.3
3: statins + ezetimibe+ fibrates	122	4.1
4: medication not recorded	381	12.9
5: combinations of lipid therapies	261	8.9

Table 4.2 Frequency values for main study cohort

Outcome variable

NICE technology appraisals (TA 393, 394) recommend that PCSK9 inhibitors are initiated when LDLC levels are above 5mmol/l in primary prevention in patients with primary HeFH. Therefore, in order to predict potential PCSK9 inhibitor requirement, the outcome variable for this study was based on the LDLC level achieved at the end of the follow up period (variable in dataset: final LDLC reading on record). For example, category 1= LDLC < 5mmol/l while category 2=LDLC >5mmol/l. Group 2

would therefore form the category of interest, and represents the HeFH patients that were eligible for PCSK9 inhibitors.

4.8.2 Quality considerations

- There were three continuous variables in the final dataset; LDLC, triglyceride measurements and age at diagnosis. Tests for normality were conducted for these variables at a 95% confidence interval for mean and the results are presented in full in appendix 15; these included tests for skewness, kurtosis and associated histograms. It is important to note that all other variables under study were categorical, and these three variables were converted into categorical variables using clinically defined thresholds for ease of analyses. Secondly, due to the fact that this was a feasibility study, the effect of all related clinical attributes within CPRD were included. These have been shown to produce a successful diagnostic model for HeFH in Weng et al. (2015).

  In total, four variables were tested - the LDLC variable was divided into maximum LDLC on record and final LDLC measured as these are relevant to PCSK9 inhibitor indication. Age at diagnosis (skewness 0.364080863, kurtosis 0.054316286) and maximum LDLC on record (skewness 0.1190817

  , kurtosis 0.2061561) were normally distributed.

  Final LDLC on record had a kurtosis value of 28.0509855 and a skewness value of 2.7314077 indicated that the distribution was not normal. From a clinical perspective however, the data reflected the current management of LDLC levels in HeFH treatment. Final LDLC measurements were concentrated on between the 3.5 and 6mmol/l, at this point the LDLC level would still be considered unhealthy but would fall at a region of uncertainty

with regard to PCSK9 inhibitor prescription which requires a final LDLC value of 5mmol/l. Similarly, irregular triglycerides levels are typically associated with irregular LDLC levels and the distribution was understandable from a clinical point of view (skewness 3.90079023, kurtosis 1.79035318).

- The derivation and validation cohorts were also assessed to ensure homogeneity. The full details of the analyses are included in appendix 18 and include; the number of cases in each cohort, frequencies and percentages between the cohorts and T-tests for the cohorts. Provided in table 4.3 below is a summary of the F-test for variance. At an Alpha value of 0.05, F value was smaller than critical so the samples are the same.

F-Test Two-Sample for Variances

	Variable 1	*Variable 2*
Mean	448	862.5555556
Variance	139830.231	523750.4872
Observations	27	27
df	26	26
F	0.26697871	
P(F<=f) one-tail	0.00062949	
F Critical one-tail	0.51834617	

Table 4.3 F test for the derivation and validation cohorts

4.8.3 Correlation analysis

The correlation analysis and cross tabulation tools were used to assess the relationships between the 11 independent variables and the outcome variable (outcome=5mmol/l). The aim of the process was to identify the independent variables that were statistically significant (p value) to the outcome variable. The Chi square tests showed three predictor variables had a significant correlation to the final LDLC

level attained. These were family history of HeFH (p=0.008), age at diagnosis (p=0.000) and maximum LDLC on record (p=0.000).

These results can be interpreted as; patients who were diagnosed past 40 years of age were less likely to attain the LDLC treatment target of less than 5mmol/l. Similarly, patients with a family history of HeFH and a high maximum LDLC on record were also not likely to achieve the treatment target. Statistical significance between the variables ensured that there was a possibility for regression analysis and informed the logistic regression analysis phase.

Table 4.4 below shows the correlation analyses between all the variables.

Correlations

		gender Gender	famfh1 Family history of FH	famhc1 Family history of high cholesterol	effect2 Therapetuctic effect categorised as whether the medication worked or not	hpy1 Patients with hypothyroidism	kd1 Patients with kidney disease	diab1 Patients with diabetes	fammi1 Family history of MI	druggroups1 Medications taken	ldl2 Maximum value of LDLC on record for patient	tri2 Maximum value of triglyceride on record for patient	agediag1 Age at diagnosis
gender Gender	Pearson Correlation	1	.027	-.039	.011	-.107**	-.019	.075**	.025	.013	.082**	-.048*	-.010
	Sig. (2-tailed)		.231	.090	.631	.000	.408	.001	.265	.557	.000	.033	.676
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
famfh1 Family history of FH	Pearson Correlation	.027	1	.050*	-.054*	-.003	.065**	-.003	-.026	.021	-.074**	.004	.060**
	Sig. (2-tailed)	.231		.027	.017	.880	.004	.891	.259	.364	.001	.862	.009
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
famhc1 Family history of high cholesterol	Pearson Correlation	-.039	.050*	1	-.003	.008	-.005	-.011	.003	.043	-.066**	-.006	.001
	Sig. (2-tailed)	.090	.027		.879	.739	.812	.620	.906	.056	.003	.793	.949
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
effect2 Therapetuctic effect categorised	Pearson Correlation	.011	-.054*	-.003	1	.014	.010	.009	.006	-.064**	.170**	.005	.016
	Sig. (2-tailed)	.631	.017	.879		.538	.665	.707	.801	.005	.000	.843	.475

as whether the medication worked or not	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
hpy1 Patients with hypothyroidism	Pearson Correlation	-.107**	-.003	.008	.014	1	-.006	.057*	.015	-.018	-.002	.081**	.053*
	Sig. (2-tailed)	.000	.880	.739	.538		.801	.013	.501	.435	.941	.000	.019
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
kd1 Patients with kidney disease	Pearson Correlation	-.019	.065**	-.005	.010	-.006	1	-.003	-.005	.016	-.017	-.003	-.002
	Sig. (2-tailed)	.408	.004	.812	.665	.801		.900	.809	.488	.448	.882	.932
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
diab1 Patients with diabetes	Pearson Correlation	.075**	-.003	-.011	.009	.057*	-.003	1	-.030	-.052*	.104**	-.015	-.008
	Sig. (2-tailed)	.001	.891	.620	.707	.013	.900		.183	.021	.000	.507	.720
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
fammi1 Family history of MI	Pearson Correlation	.025	-.026	.003	.006	.015	-.005	-.030	1	-.025	.009	-.003	-.010
	Sig. (2-tailed)	.265	.259	.906	.801	.501	.809	.183		.280	.693	.895	.652
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
druggroups1 Medications taken	Pearson Correlation	.013	.021	.043	-.064**	-.018	.016	-.052*	-.025	1	-.139**	.005	.005
	Sig. (2-tailed)	.557	.364	.056	.005	.435	.488	.021	.280		.000	.817	.838
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941

ldl2 Maximum value of LDLC on record for patient	Pearson Correlation	.082**	-.074**	-.066**	.170**	-.002	-.017	.104**	.009	-.139**	1	.046*	-.034
	Sig. (2-tailed)	.000	.001	.003	.000	.941	.448	.000	.693	.000		.043	.135
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
tri2 Maximum value of triglyceride on record for patient	Pearson Correlation	-.048*	.004	-.006	.005	.081**	-.003	-.015	-.003	.005	.046*	1	-.004
	Sig. (2-tailed)	.033	.862	.793	.843	.000	.882	.507	.895	.817	.043		.857
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941
agediag1 Age at diagnosis	Pearson Correlation	-.010	.060**	.001	.016	.053*	-.002	-.008	-.010	.005	-.034	-.004	1
	Sig. (2-tailed)	.676	.009	.949	.475	.019	.932	.720	.652	.838	.135	.857	
	N	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941	1941

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4.4 Correlation statistics for all variables

4.8.4 Logistic regression analysis

The three variables that had a significant relationship to the outcome variable were; medication use (p= 0.001), the maximum value of LDLC measurement (p= 0.000) and age at diagnosis was found to have a significant association to treatment outcome (p=0.002). All these clinical attributes are categorical as described in sections 4.8.1 and 4.82.

Stepwise logistic regression was conducted to derive the predictive model based on all study variables. The optimal multivariate model was composed of 3 predictor variables; maximum low density lipoprotein cholesterol (LDLC) measurement, medication use and the age at diagnosis (table 4.5). The Nagelkerke r2 value (NV) shows the variance explained by a model with 1 representing a perfect score. The NV value for this model was (0.285); this indicates that the best model explained 28.5% of the outcome variance.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	1=0-5(1)	-3.966	.415	91.372	1	.000	.019	.008	.043
	Constant	-.853	.064	176.557	1	.000	.426		
Step 2[b]	1=0-5(1)	-4.222	.424	99.040	1	.000	.015	.006	.034
	Whether the patient took medication or not(1)	-.967	.234	17.117	1	.000	.380	.241	.601
	Constant	.044	.225	.039	1	.844	1.045		
Step 3[c]	AgeAtDiagnosis(1)	.467	.152	9.431	1	.002	1.595	1.184	2.148
	1=0-5(1)	-4.208	.425	98.276	1	.000	.015	.006	.034
	Whether the patient took medication or not(1)	-.995	.235	17.977	1	.000	.370	.233	.586
	Constant	-.032	.227	.020	1	.889	.969		

a. Variable(s) entered on step 1: 1=0-5.

b. Variable(s) entered on step 2: Whether the patient took medication or not.

c. Variable(s) entered on step 3: AgeAtDiagnosis.

Table 4.5 Optimal multivariate model results

The odds ratios of the three variables that were significantly correlated to LDLC reduction can be interpreted as follows. Patients who were diagnosed with HeFH at an age <40 were less likely to attain an LDLC level lower than 5mmol/l and would therefore require PCSK9 inhibitors. Patients who were taking lipid lowering medications and those that had a maximum value of LDLC less than 5mmol/l were more likely to attain an LDLC reduction that was less than 5mmol/l and would therefore not require PCSK9 inhibitors.

The complete sets of analyses conducted as part of the logistic regression are attached in appendix 16.

4.8.5 Model validation

The model developed through logistic regression analysis produces a log scale that group membership predictions (predicted logit) are based upon (A visual representation of this distribution is shown in figure 4.4 below). The validation process involves the calculation of predicted logit values for the study's validation cohort. This computation utilises the beta coefficients (B) and constant value from the regression model. As previously discussed, the conversion to log enables the simulation of a linear relationship; the linear equation model of y=mx+c (m=gradient, c=constant) can be applied in this case. The resulting equation as seen in SPSS syntax is:

```
COMPUTE predicted_logit = (-0.032) + (0.467*AgeAtDiagnosis) + (-
4.208*LDLCmaximumvalue) + (-0.995*MedicineUse).
EXECUTE.
```

Further computation was conducted to convert the predicted logit into predicted probabilities for group membership. The equation is shown below:

```
COMPUTE PredictedProbabilities = (2.718281828**predicted_logit)/
(1+2.718281828**predicted_logit).
EXECUTE.
```

Following these calculations, the predicted logit and probabilities for group membership were compared with the observed cases in the validation cohort. For this purpose, the area under receiver operating curve (ROC – we refer to this as area under the curve (AUC) herein) command was used. The resulting curve presents a platform to decide the optimal model cut-off point and presents the sensitivity and specificity values for model predictions. This forms the model calibration process and determines model accuracy and discrimination.

4.8.5.1 Sensitivity and specificity analysis

Shown below (Figure 4.3) is the result of the AUC calculation. The diagonal reference line represents a 50/50 prediction, therefore the area between the line and the curve formed by the model prediction represents the extent to which model performance is better than chance. A perfect prediction would meet the top left corner, a sensitivity of 1and a specificity of 1.

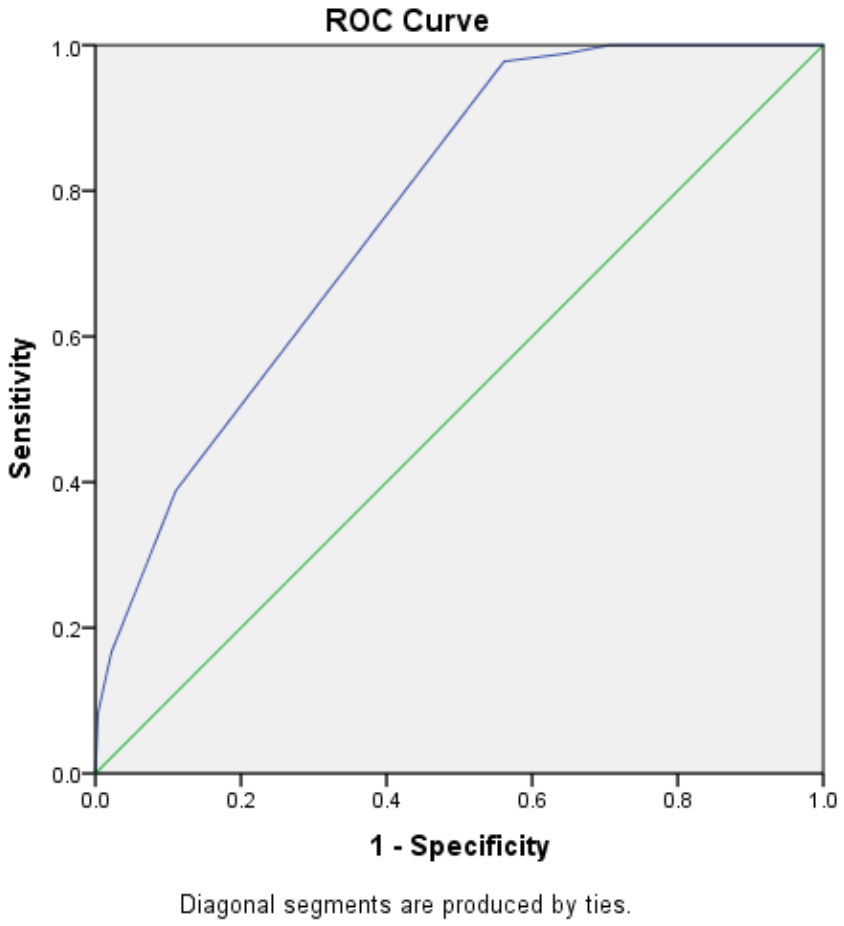

Figure 4.3 Area under receiver operating curve for the model

A sensitivity of 0.967 and a specificity of 0.447 were attained for the ideal cut off point. The highest point of the curve corresponding to these cut-off points was 0.001667. The sensitivity value obtained suggests that there is a 96.7% chance that a prediction of a patient requiring PCSK9 inhibitors is indeed correct. The specificity value indicates that a prediction that a patient does not require PCSK9 inhibitors will be true 44.7% of the time. An AUC value of 0.774 was achieved indicating substantial discrimination between the outcome cases; this suggests that any model prediction will be 27% better than a prediction by chance (50%).

The complete set of analyses conducted using AUC-ROC is attached in appendix 17.

A visual representation of this result is shown is in figure 4.4 below.

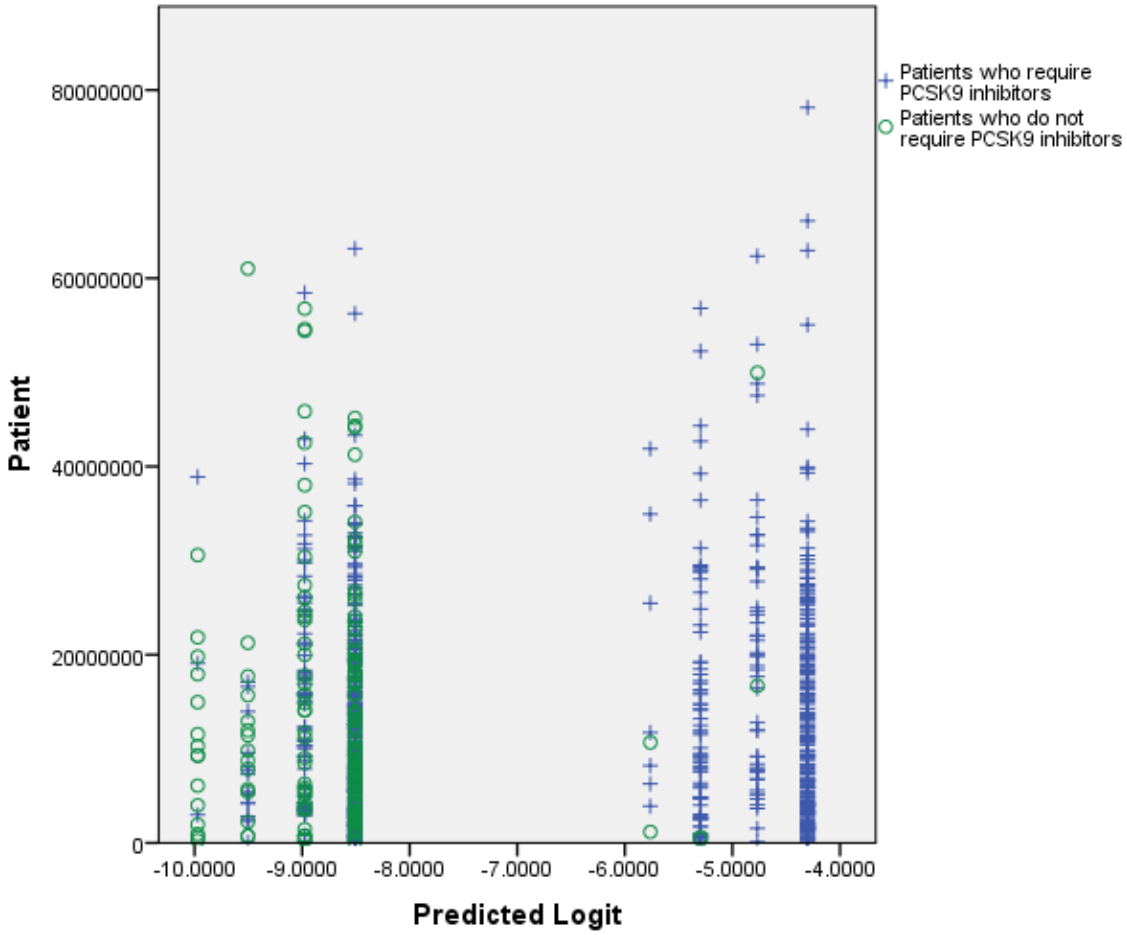

Figure 4.4 The predicted distribution for the requirement of PCSK9 inhibitors

Figure 4.4 shows the distribution of each patient in the validation cohort on a scale of predicted probabilities. (+ represents patients who require PCSK9 inhibitors, O represents patients who would not require PCSK9 inhibitors). Assuming a cut-off point of -7.0 on the diagram, the right side of the cut-off point would represent cases that require PCSK9 inhibitors and the left side would represent cases that do not require the medication. A prediction for PCSK9 inhibitor requirement would be correct 96% because of the partitioning achieved by the model. However, a prediction on the left side of the plot (patients who do not require PCSK9 inhibitors) would be prone to error as almost 50% of that population is made up of patients who would require the

medication. Whereas, the model can partition between the cohorts to some degree, the discrimination between the cases is sub-optimal.

4.8.6 Interpretation of modelling results

The sensitivity and specificity values for the model can be interpreted as follows. When it predicts that a patient would require PCSK9 inhibitors (positive prediction), the prediction would be correct 96.7%. However, when the model makes a negative prediction, it is only right 44.7% of the time. This reduced the discriminatory accuracy of the model as shown in fig. 5 above. Although positive predictions will be correct most of the time, many true positive cases will not be recognised by the model and will be classified as a negative prediction. Negative predictions would therefore contain many false negatives. These results can be further summarised by the AUC value of 0.774; this translates to a 27% chance that the model prediction is better than chance. Overall, this predictive model showed that three clinical attributes of HeFH patients can be explain some part of final LDLC as a study outcome. This is quantified by the Nagelkerke r2 value (NV) score of 28.5%. However, this was not sufficient to produce significant discriminatory accuracy.

4.9 Discussion of quantitative analysis results

The analyses in this chapter studied the HeFH patient clinical attributes that were related to LDLC attainment following statin use, and could potentially predict PCSK9 inhibitor eligibility. This section presents a discussion of the findings from these analyses and their potential implications.

4.9.1 Patient clinical attributes that could potentially influence LDLC attainment

A survey by Cohen et al. (2017) found that a lack of or insufficient recording of patient clinical attributes for HeFH patients was a major barrier to PCSK9 inhibitor prescription in the US. The main records required for HeFH patients included medical

information, genetic records (for confirmation of HeFH diagnosis), complete set of laboratory values (including LDLC), history of statin use and requirement for maximum doses to be used (or reasons for their omission).This information was not always available at the point of prescribing. These clinical attributes are similar to CPRD records on HeFH patients; with the exception that genetic information is not included.

The first observation was made during the implementation of the inclusion criteria. The main inclusion requirements were that patients had at least two LDLC values and medical records for a period of 1 year. This filter reduced the complete dataset of HeFH patients (n=5656) by 48% to obtain the final study cohort (n=2949). 3761patients were found to have at least 1 record of LDLC whilst 3297 had at least two values on record. These findings are in agreement with past studies that have reported low levels of recording of HeFH patient data (Cohen et al., 2017). From a statistical perspective, this study lost 2707 potential cases due to non-availability of records. It is not possible to ascertain the effect this could have had on the regression analysis, however, larger sample sizes often serve to improve the performance of statistical analyses (Field, 2005).

A comparison between the clinical characteristics of HeFH patients in the CPRD dataset and longitudinal study (Mata et al., 2011) revealed higher prevalence rates in the research setting. Possible reasons for this could potentially revolve around known differences between study and real-world data (Razek et al., 2018). It is expected that more comprehensive patient data are collected within a research setting, such as a longitudinal study.

In HeFH in particular, barriers to treatment related to low patient identification and poor awareness of disease risk among patients may cause irregular and low

recording of patient information (Hardcastle et al., 2015; Alonso et al., 2020) For example, due to the asymptomatic nature of HeFH, patients with no secondary illnesses may not fully commit to treatment until a cardiac event occurs and they understand the severity of the disease. This could potentially translate into irregular hospital attendance and non-compliance with medication prior to a cardiac event. The clinical records of these patients could therefore contain gaps. Furthermore, until 2016 HeFH (and familial hypercholesterolemia in general) did not have a unique International Classification of Diseases (ICD-10) code. This meant that HeFH was classified and treated as a typical form of hypercholesterolemia. As such, clinical attributes which are important in the management of the condition may not have been documented appropriately.

4.9.2 Is the available data sufficient to develop and validate a predictive model for PCSK9 inhibitor requirement?

The present study used 11 clinical attributes of HeFH patients that were recognised to be associated with LDLC modification in past literature (Mata et al., 2011; Weng et al., 2015; Masson et al., 2014; Perez De Isla et al., 2016). These clinical attributes were used to develop and test a mathematical model for the prediction of patients who were likely to require PCSK9 inhibitors.

Firstly, an assessment of normality for the three continuous variables showed that LDLC and age at diagnosis were normally distributed while triglyceride and final LDLC on record were not normally distributed. However, from a clinical perspective, the distribution of these data was understandable. In the case of final LDLC reading following the use of conventional lipid lowering therapy; LDLC levels were generally be reduced achieving lower mean. Relatively smaller numbers of patients who did not register much LDLC reduction were then distributed towards the higher end of the spectrum. The potential implication here was that these data were suitable for

assessment by parametric means. Covariance was also weak (less than 5 in all cases) between the four continuous clinical variables. In general, the data quality was sufficient for analyses.

Secondly, three clinical attributes of HeFH patients had a significant correlation to the final LDLC achieved following treatment with currently available medication. These were; age at diagnosis, maximum LDLC on record and the use of lipid lowering medication. The relationship between these variables and final LDLC achieved gave a prediction 27% better than a prediction due to chance. Nevertheless, the model could not discriminate between patients who required PCSK9 inhibitors and those who did not with sufficient accuracy.

These results suggested that there was potential for predictive modelling for PCSK9 inhibitor requirement based on the ROC value of 77.4%. A potential resolution could be found in the inclusion of more clinical variables related to LDLC attainment. For example, past studies have identified associations between Lipoprotein a (Lp (a)) and LDL-cholesterol (Donnelly et al., 2013). These have led to the inclusion of Lp (a) in modelling analysis for HeFH identification (Sun et al., 2019) improving past results. Similarly, studies on LDLC attainment in HEFH such as Perez De Isla et al. (2016), found that defective allele mutations was an additional determiner for LDLC target attainment. The introduction of novel and more accessible genetic testing methods (Jiang et al., 2018) increases the chances of using genetic data for modelling studies in the future. However, as mentioned above, the recording of HeFH patient clinical attributes in practice remains poor in most cases (Cohen et al., 2017). This increases the number of challenges to the modelling for HeFH and PCSK9 inhibitor use in general. With more complete data and an increase in the number of predictor variables, there could be potential improvement in the modelling capability of

databases based on clinical practice such as CPRD. Currently, CPRD data does not appear to be sufficient for the development of predictive models for PCSK9 inhibitor eligibility in HeFH patients.

4.9.3 Implications for predictive modelling for HeFH lipid lowering therapy

The current study supported results by Mata et al., (2011) and Perez de Isla et al., (2016) that reported significant relationships between LDLC reduction and the clinical variables; age, history of CVD, type 2 diabetes mellitus and the use of lipid lowering medication. This suggested that further study on predictive modelling for PCSK9 inhibitor eligibility may be possible; but this may require an improved database of HeFH records and additional predictor values for LDLC attainment.

The prevalence rate of some of the clinical attributes in HeFH was less than 10% in the current study sample. A literature search revealed similarly low prevalence rates in the HeFH population (Mata et al., 2011; Besseling et al., 2015; Perez De Isla et al., 2016); however, values in the CPRD dataset were lower. These observations suggested that data from CPRD may currently not be suitable in statistical modelling for LDLC goal attainment. Data from longitudinal studies on HeFH, such as the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART – clinicaltrials.gov ID: NCT02693548) with higher levels of recording of HeFH patient clinical attributes than CPRD may provide more utility in the development of predictive modelling. Furthermore, the assessment of the genetic component of HeFH in these studies could potentially add useful variables to improve statistical modelling.

However, tests for normality of data in the current study suggested that ongoing feasibility studies were possible. Following the adoption of an independent ICD code for HeFH (2016) and the launch of PCSK9 inhibitors, it is could be expected that data

on HeFH patient management would develop at a faster rate than previously recorded. It may be possible to continue testing the feasibility of developing a predictive model for PCSK9 inhibitor use as databases such as CPRD continue to collect data on HeFH.

4.10 Conclusion

The current study found that there is potential to predict HeFH patients who could potentially benefit from PCSK9 inhibitors using CPRD patient data; however, the current data was not sufficient to sustain the development of a clinically significant predictive model. The use of other health databases or improved CPRD records for HeFH patients could potentially serve to improve the functionality of the current model.

In summary, the predictive model developed retained three patient clinical attributes (age at diagnosis, maximum LDLC on record and the use of lipid lowering medication) and produced a predictive ability that was greater than chance. However, the model could not distinguish between positive and negative cases sufficiently and therefore the predictive result was not clinically significant.

With regard to the overall aim of the study of assessing potential barriers and facilitators to the prescription of PCSK9 inhibitors; descriptive analysis of the data found that a large proportion of HeFH patients did not have clinical attributes relevant to PCSK9 inhibitor prescription on record. This supported results from other studies that suggested low levels of recording of HeFH patient clinical attributes (Cohen et al., 2017). Compared to HeFH patient data from longitudinal studies (Mata et al., 2011; Perez De Isla et al., 2016), CPRD data was found to have a lower recording of these patient attributes. It was also found that about 80% of patients did not meet

guideline recommended LDLC treatment targets; and 63.9% of these patients did not meet the LDLC threshold for PCSK9 inhibitor prescription.

Chapter 5 Qualitative data analysis and results

5.1 Introduction

This chapter presents the results and analyses of the qualitative phase of this project. The chapter addresses the following research questions as identified in chapter 2:

- To study the barriers and facilitators to the usage of PCSK9 inhibitors by exploring the views and opinions of key stakeholders (patients, specialist consultants/GPs and nurses) in the care of heterozygous familial hypercholesterolemia (HeFH) in the UK.

The rationale for this section of the thesis was based on the finding that the knowledge, attitudes and experiences of stakeholders (patients, consultants, nurses, GPs etc.) influenced the care for HeFH and provision of HeFH. The literature review conducted in chapter 2 found that the prescription of PCSK9 inhibitors was influenced by bureaucratic processes and clinical guidelines in the US and other countries. This research was lacking in the UK. The current chapter focussed on exploring the opinions of stakeholders in the care of HeFH to determine the potential barriers and facilitators to PCSK9 inhibitor use in the UK.

The section begins with a brief description of the data collection and analysis methods. This is followed by an account of the participant demographic information and a summary of the characteristics of participants. The results are then presented in five themes identified via thematic analysis as described by Braun and Clarke (2006). The chapter concludes with a discussion of the themes and sub-themes emerging from the analysis.

5.2 Sampling of interview participants

A total of 17 people participated in the study. Saturation was monitored through the data collection and analysis processes. No new themes emerged after 13 interviews;

however, 4 more interviews were completed. Saturation was determined by an 'inductive thematic' approach as discussed by Saunders et al., (2018). This meant that further data collection only contributed to the themes that had already been identified as opposed to producing new themes. Additionally, there appeared to be consensus across participants on specific themes and the overall patient journey to the use of PCSK9 inhibitors. For example, lipidology consultants (prescribers of PCSK9 inhibitors) expressed the existence of restrictive LDLC thresholds for PCSK9 inhibitor usage that were not achieved in some HeFH patients.

"…less than 50% reduction but the LDL, they've not got cardiovascular disease and the LDL is less than five, then we've got no other option…" (A5, consultant)

"There is no way round this but the big issue is that certain patients try very hard and their LDL may come down to 3.8 and they're not eligible for PCSK9s." (A3, consultant)

Differences did exist in participant experiences, but these experiences expressed similar themes. In the case of patient participants, for example, some patients described having high LDLC levels but HeFH was not suspected for prolonged periods of time in primary care. Whereas some diagnosed HeFH patients felt that they were treated insufficiently for long periods of time before they were referred to secondary care to be considered for PCSK9 inhibitor use. These experiences both suggested concerns with the level of awareness of HeFH and PCSK9 inhibitors in primary care.

For these reasons, the study was able to capture the complexity of the HeFH patient journey towards the use of PCSK9 inhibitors and associated barriers. The results allowed for the illustration of a patient journey between primary care and secondary

care that retained relevance across the stakeholder groups. The sample size was also in line with past studies on the factors that affected prescription.

5.3 Data analysis

The process was driven by the primary research question and involved the identification of relevant excerpts of text called codes that depicted a barrier to PCSK9 inhibitor use. Codes were therefore identified as participant statements that constituted potential factors that could affect the use and provision of PCSK9 inhibitors. For example, figure 5.1 below shows a portion of an interview conducted with a consultant. When asked about the accessibility of PCSK9 inhibitors, the participant describes the Blueteq process that outlines the requirement of LDLC records prior to approval. As this was perceived as a barrier, the highlighted portion of the excerpt was coded. 147 codes were deemed to be relevant to the research question (Appendix 11).

The identification and categorisation of codes involved an iterative process composed of line by line code selection and the development of themes. Associated codes were grouped together in an initial categorisation process. Themes were considered to be patterned responses in the identified codes. The surface level descriptions of the initial categories were therefore used to name the themes (Thomas and Harden, 2008).

I: I see. You mentioned the purchasing prices and purchasing it privately. Would you comment on the accessibility of it? When you need to prescribe it, is it available or does the CCG (or purchasing body) control it?

IV: It is available and there is a bit of a postcode lottery at the moment. It is available but the process is deferring from CCG to CCG. In North Staffs, for the CCG, there's a blue tick that has to be filled. They require two LDLs above the threshold which is not in the NICE Guidelines. There are certain other CCGs which want three and again, isn't in the NICE Guidelines. In Birmingham North and East, at the moment, they're not doing them. They're following the NICE Guidelines. The biggest issue with this is that these patients are going to have a high level and so they will be started on it but it will probably delay everything by six months for them to have two or three blood tests to prove it. It also makes the patients quite irritable because these are very high risk patients and they would rather get on to it than having to

Figure 5.1 Example of coding excerpt

There was no explicitly stated number of references required to make a theme, each resulting theme had at least 35 references within each stakeholder group as shown in figure 5.2 below.

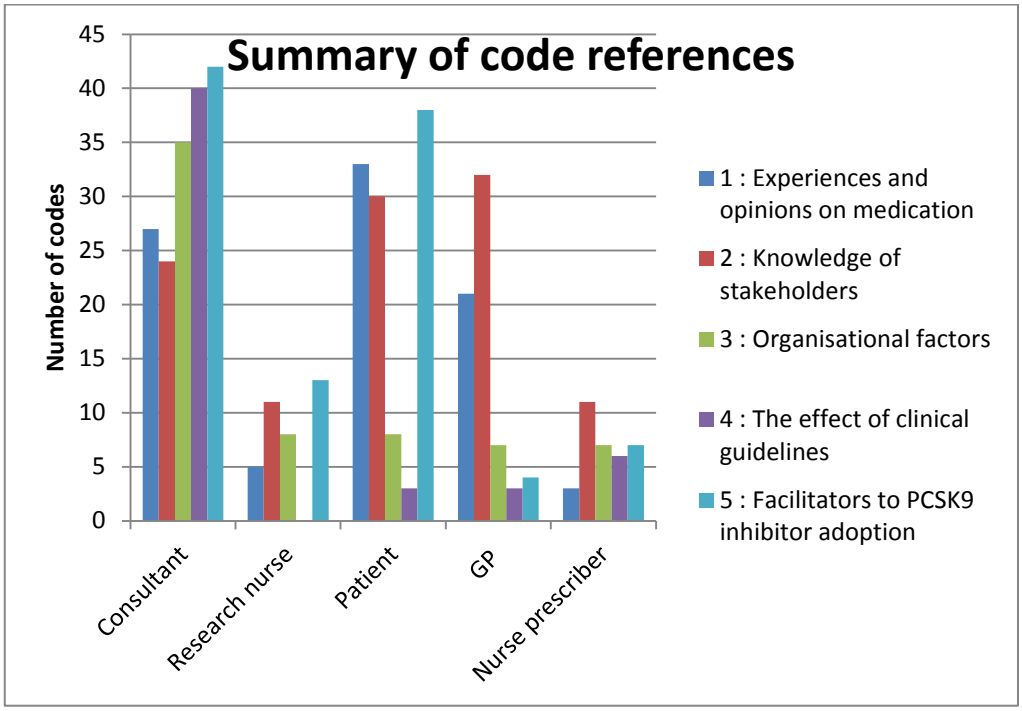

Figure 5.2 Summary of code references

5.4 Participant demographics

In total, 17 participants were recruited from 3 NHS lipid clinics and a local GP practice. 64.7% of the total participants were male, 35.3% were female. Of the total number of participants, 7 were consultants, 2 were nurses, 3 were GPs, and 5 were patients. All patients had a diagnosis of HeFH and had been referred to one of the lipid clinics. All health care providers (HCPs) were involved in the management of HeFH patients at different capacities. All HCPs had been working in lipid management for more than 5 years (participant A17 had started a new role in preventive cardiology, but had more than 5 years' experience in lipid management). A summary of participant characteristics are shown in table 5.1 below.

ID	Stakeholder	Sex	Number of years with working in HeFH

A1	Consultant	M	13
A2	Consultant	M	12
A3	Consultant	M	15
A4	Research nurse	F	5
A5	Consultant	F	16
A6	Patient	M	-
A7	Patient	F	-
A8	Consultant	M	14
A9	Patient	F	-
A10	Patient	M	-
A11	GP	F	10
A12	Patient	M	-
A13	Nurse prescriber	F	16
A14	GP	M	10
A15	GP	M	18
A16	Consultant	M	13
A17	Consultant	M	1.75

Table 5.1 Summary of patient characteristics

All participants in lipid clinics were recruited through the lead consultants in the lipid clinics. Letters of invitation were sent to the clinics and the investigator only pursued potential participants that responded to the invitation. There was no variation in the recruitment process. Similarly, invitation letters were sent to the local GP practice through a lead collaborator, the investigator only pursued the respondents. For details on the letters of invitation; see appendix 4-5.

5.5 Results

A total of 17 interviews were conducted (telephone n=12, 70.6%, face to face n=5, 29.4%). The average length of the interviews was 19.7 minutes (SD=7.11).

5.5.1 Coding and initial categorisation

In total, five initial themes were identified; these were

- Experiences and opinions on HeFH treatment
- The effect of clinical guidelines
- The knowledge of stakeholders
- Organisational factors
- Facilitators of PCSK9 inhibitor adoption

'Experiences and opinions on HeFH treatment' explored the views and perceptions held by stakeholders, and how these could potentially impact the use of lipid lowering agents. 'The effect of clinical guidelines' explored the potential impact of clinical guidelines in relation to the decision making processes of HCPs. 'The knowledge of stakeholders' focussed on the awareness levels of clinicians and patients on HeFH and the treatment pathway for the disease. 'Organisational factors' focused on factors revolving around NHS trust prescription policies and the collaboration between HCPs in delivering care to HeFH patients. The theme of facilitators of PCSK9 inhibitor use consisted of three sub-themes. 'Influence from pharmaceutical companies' identified the methods used by pharmaceutical companies in order to facilitate medication adoption. 'Patient awareness of HeFH severity' was found to be a motivational factor for patients to learn and engage with the treatment process. 'Views on medication use' focussed on the opinions on medication that increased the participant's likelihood to seek or prescribe PCSK9 inhibitors.

5.5.2 Reassessment of themes

The initial set of themes was refined following further analytical assessment of the categories as discussed by Thomas and Harden (2008). The categories were

renamed in order to align with the overarching research question and to reflect the barriers to PCSK9 inhibitor use demonstrated by the excerpts. The table (table 5.2) below shows the final list of themes and subthemes identified from the data.

Broad Categorisation	**Themes**	**Sub-themes**
Barriers to PCSK9 inhibitor adoption	Low referral rates to secondary care	
	Therapeutic gaps in clinical guidelines	The use of clinical guidelines for lipid management in HeFH
		Strict clinical guidelines on PCSK9 inhibitor provision
	Low levels of knowledge and awareness of HeFH	Low awareness of HeFH amongst clinicians
		Inadequate understanding of HeFH in patients
	Inhibitory organisational prescribing policies	Inhibitory prescription policies for PCSK9 inhibitors
		Lack of consensus on stakeholder roles in the care for HeFH
Facilitators of PCSK9 inhibitor adoption	PCSK9 inhibitor use support from pharmaceutical companies	
	Patient awareness of disease severity	

	Negative views on the use of statins	

Table 5.2 Final list of themes and sub-themes

5.5.3 Barriers to PCSK9 inhibitor adoption

An illustration of the HeFH patient journey towards the use of PCSK9 inhibitors with the potential barriers highlighted at the typical points of occurrence in the treatment process is shown in figure 5.3 below. Barriers in primary care resulted in delays and low referral rates of HeFH patients for consideration of PCSK9 inhibitor use in secondary care. In secondary care barriers were mainly associated with strict clinical guidelines for the initiation of PCSK9 inhibitors and inhibitory policies targeted at reducing the use of costly medication such as PCSK9 inhibitors. The following sections present the views and opinions of stakeholders as pertains to the identified themes.

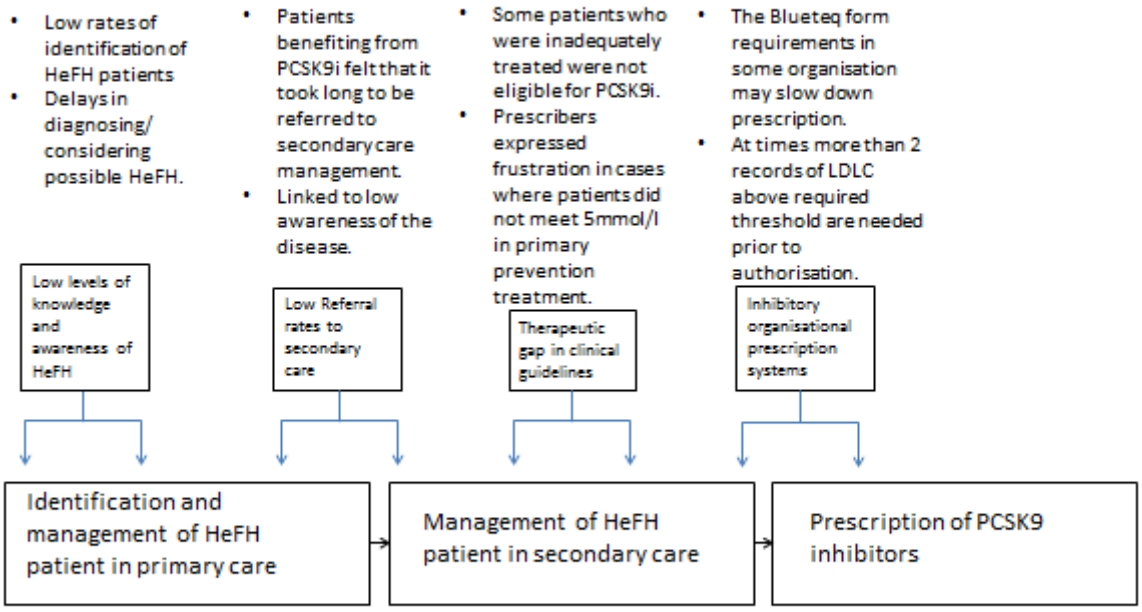

Figure 5.3 The HeFH patient journey to PCSK9i use and associated barriers

5.5.3.1 Low referral rates to secondary care

5.5.3.1.1 The HeFH patient journey

The primary care clinician mainly identified markedly elevated LDLC levels, referrals were then made to secondary care based either on LDLC values or a combination of LDLC values and family history of cardiovascular disease (CVD).

"…we see patients for NHS health checks who are not on a register, so they have erm, they come and a have a cholesterol and a glucose check… so they'll have bloods done. Often those bloods come back to me so I sort of action the blood results based on the sort QRISK score… and if that becomes over 10% for patients, irrespective of where the cholesterol sits then I ask to see them erm, with obviously sort of the guidelines or if we're over 10% with some of these patients dependent on obviously history and lifestyle, you know, recommend that they have statins." (A13, prescribing nurse)

"Right, so a good scenario would be we'd do a routine screening for a patient that comes in and says yeah they want an NHS health check or maybe you're just suspecting that I should check the lipid profile in this particular patient. And within a week the results come back and yes, if the total cholesterol is raised the patient will then come to us, we'll make them aware of the condition and then we'll do an immediate referral to the lipid clinic at the UHNM. That tends to be an urgent referral, but they probably would be seen within maybe four weeks to eight weeks or even prolonged much more than the eight weeks…. they get seen at the lipid clinic, the specialist would probably start statins like atorvastatin or maybe ezetimibe and write a letter back to us telling us to continue with that medication and put the medication on repeat prescription." (A11, GP)

Secondary care clinicians provided similar accounts to the treatment journey described by clinicians in primary care. In the secondary care setting, however, referrals were received from two sources; primary care or other secondary care consultants.

"So, the referrals are in two different routes. The majority are through GPs but we also get referrals sent from secondary care so from the cardiologist. And particularly since PCSK9 inhibitors have been introduced cause they are not prescribers of them, so patients who come in with myocardial infarction and they thought they may have FH and maybe a candidate for PCSK9 inhibitors."(A5, consultant)

"The typical patient can either come from primary or secondary care. They start at primary care and the patient would see the GP and there would be an indication as to why their lipids are carried out. This could be from the NICE Guidelines or from QOF… With secondary care, the referrals will usually be from either Cardiology or Stroke Medicine."(A3, consultant)

The treatment journey described by patient participants differed from the typical treatment journey explained by clinicians. Patient accounts involved the occurrence of a cardiac event, or cardiac event(s) in close family members, necessitating checks for familial hypercholesterolemia.

"Okay, so back in December 2014, is when I had a heart attack and then had a stent fitted as a result. Now, at that point, although up until that point, although I had sort of, you know, I wasn't aware my cholesterol levels were, they weren't particularly high but they weren't in the preferred range, they were in the region of five to six effectively, in that sort of area."(A10, patient)

"I've had the high cholesterol for a good few years now. It's hereditary obviously via me father. He had angina and died of a heart attack at 62, and I think then after that we were told to go for a test. So me dad's been dead probably 20 years so, 24 years, so probably about 20 years ago they started keeping a good eye on me."(A12, patient)

"It was probably through my brothers cause they've had it as well, my dad had angina and heart problems and died of a heart attack. So, the doctors really saying, we'll get your tested out for your cholesterol and yeah, things like that."(A6, patient)

Patient perceptions of the process of diagnosis and the provision of medication were mostly negative.

"I think sometimes they try you on different, it's a bit hard to tell 'cause I was a bit different so, you know, try you on this tablet and try you on that. There were times I felt a little not guinea piggy but, you know…'" (A12, patient)

"…it all feels a little bit reactive, you know, it all feels as though, you know, people didn't really pick up on really on the high, you know, the five is high in terms of cholesterol levels or I'd had a heart attack, I think from there on in, its felt pretty, you know, obviously you've got a history there then all of a sudden, my local health authority, they suddenly became very active…"(A10, patient)

Patient A9's account also stated that they were attended to by various specialist consultants during the course of their treatment journey. They had an LDLC reading of 9 and a family history of cardiac events; however, HeFH was not considered until later in the treatment process. Other participants described similar experiences suggesting that the typical treatment journey was disorderly in some cases and was different from the system identified by clinicians.

"…at the time I saw them(the GP), they might actually have some tests, you know, and it was never really identified as being a problem at all, you know, no one ever said, you should probably do something about it because it was just deemed to be, you know, because everything else was normal"(A10, patient)

In one case (A6), the patient provided an account where he was happy with the treatment process. The patient's case did not appear to be as severe as the other cases as he had not suffered a cardiac event. The patient was identified through cascade screening following cardiac events in family members.

"I just think that everything that's been done has been great. The treatment has been alright, you know, fine, tablets are working so yeah, I'm happy."(A6, patient)

Participant views on the treatment process differed, especially between patients and clinicians. It appeared there was a consistent treatment journey for the patient with severe HeFH. This consisted of identification and management by GPs and nurses in primary care followed by referral to lipid consultants in secondary care.

5.5.3.1.2 The efficacy of the HeFH patient identification pathway

When questioned about the efficiency of the identification pathway, there was general congruence amongst clinicians that the system needed improvement. The reasons for, and the degree of acceptance to these inefficiencies varied amongst the stakeholders. These views are explored below.

Secondary care clinicians identified low levels of knowledge in primary care, and the lack of genetic testing services as the main reasons for the limitations in the patient identification pathway. For example, participant A8 (consultant) described the identification of HeFH patients in primary care as *"incidental"* and in secondary care as *"sporadic"*.

"I mean we know that a large number of patients with FH are not identified and unfortunately, we don't have access routinely at the moment to genetic testing and so we're not, we're not being effective in introducing cascade testing as well in those patients that we've identified."(A5, consultant)

Consultants did not identify knowledge as a barrier to care provision amongst secondary care clinicians (research nurses, specialist consultants). However, participant A4 (a research nurse) indicated cases where the specialist pharmacist and cardiology specialist (secondary care clinicians) displayed a lack of knowledge or admitted insufficiencies in HeFH management. An excerpt from participant A4 is provided here, but the theme of knowledge is elaborated further under the section 'low awareness of HeFH amongst clinicians'.

"So, I think in primary care in GP practices it's probably not as good as secondary care. I think we're getting better in secondary care in that cardiology seems to know about PCSK9 inhibitors but I think there probably is a lot more you know, education that needs to be done around FH in general, which will then obviously a lot of the time lead on to PCSK9 as well." (A4, research nurse)

This view supported patient accounts which suggested that the care pathway was inefficient in some cases, both in primary and secondary care. GPs were not confident that there was enough knowledge on HeFH in primary care. Additionally, GPs were not aware of what occurred in secondary care following a referral. GPs reported the use of QRISK scores and NICE guidelines to detect HeFH (further discussion provided under 'the effect of clinical guidelines').

"…so then we refer to lipid clinic to go and find out really if it is familial and I guess they look into the genetic side of it. I don't know if they do any special blood test or family tree tracing, I don't know what they do, but it really is the specialist that takes over at that time."(A11, GP)

"We don't have a specific template for that but we do use the QRISK scores in general for any kind of primary or secondary prevention but apart from that, we don't have any specific tools."(A14, GP)

In summary, it appeared that the HeFH patient identification and referral pathway may not be as organised as described in clinical pathways. All clinicians provided descriptions of methodical approaches to the management of HeFH as stipulated in clinical guidelines; this was contrary to patient accounts that cited delays in disease identification and referral to secondary care for effective medication provision. Both primary and secondary care clinicians identified inefficiencies in patient identification in primary care that appeared to support the patient participant accounts. The reasons provided for these inefficiencies revolved around awareness of the disease.

5.5.3.2 Low levels of knowledge and awareness of HeFH

This section presents the results of the stakeholder opinions on the level of knowledge on HeFH, and the disease treatment pathway. Participant accounts within this theme were obtained using direct enquiries about opinions on levels of knowledge. The excerpts also included cases where participants were not clear on certain issues during interviews; and accounts of other HCPs displaying low levels of knowledge.

5.5.3.2.1 Low awareness of HeFH amongst clinicians

The overall finding was that specialist lipid consultants had a better understanding of HeFH and its associated care than GPs and nurses in primary care. Two excerpts regarding the question of general HCP knowledge from secondary care clinicians are provided below.

"I think especially in primary care in GP surgeries; they don't have as much knowledge of FH and PCSK9. A lot of patients come to me and say, you know, I spoke to my GP about going on this medication and they… about the PCSK9 inhibitors and they don't know what it was. So, I think in primary care in GP practices it's probably not as good as secondary" (A4, research nurse)

"No, I don't think there is enough knowledge there, I mean I can't comment very much about pharmacists, but I think amongst GPs and nurses the knowledge is, you know, it's not really high enough..." (A8, consultant)

GPs and nurses did not object to the assertion that there were low levels of knowledge in primary care. Participant accounts were replete with cases of HCPs' lack of awareness as regards HeFH and PCSK9 inhibitors, especially in primary care. An example of such a case involved an account of a nurse prescriber who provided statins without further referral for a patient with an LDLC of 'about eight' (Participant A11, GP).

"in terms of the knowledge I would probably think some people(GPs) might sort of confuse it with ordinary polygenic hyperlipidaemia and just 'Oh it's raised cholesterol, all I need to do is just do a QRISK and start statin and invite the patient to see the nurse and discuss about healthy lifestyle advice'. And I believe that's a clinical error if that happens. If they mistake it for just normal hypercholesterolemia without ruling it out that it could be familial, I believe that will be a clinical error." (A11, GP)

Further cases involved GPs stopping medication inappropriately due to LDLC levels being lowered.

"… some doctors sometimes see that the cholesterol's gone quite low with the PCSK9 inhibitors and on a couple of occasions, we've had them reduce the statin or take the statin off them or the fibrate or what have you and then we've seen them next, we've seen the cholesterol go up and then there's questions as to why and they've said oh, well, my cardiologist for example, stopped my statin." (A4, research nurse)

Specialist consultants mostly considered knowledge of PCSK9 inhibitors and HeFH in secondary care to be sufficient. However, based on the accounts of nurses the perceived lack of knowledge was not limited to primary care. Participant A4 (a research nurse) noted a conversation she had with a cardiovascular surgeon that felt that some, potential, HeFH patients had missed clinical diagnosis because they were already being treated for other conditions in separate specialist clinics. Participant A4 also recounted her experience dealing with a new specialist pharmacist that had to be educated on HeFH and PCSK9 inhibitors.

"I know that initially when we got the pharmacist involved, he didn't have, he may have had a little knowledge of familial hypercholesterolemia but generally that's been the knowledge that he's had to learn through you know starting these PCSK9 inhibitors… putting for example, possible or definite familial hypercholesterolemia, he was getting a bit confused what a possible and definite meant. Because he was saying, surely if they're possible, they can't go on the injections…" (A4, research nurse)

“I think we’re getting better in secondary care in that cardiology seems to know about PCSK9 inhibitors but I think there probably is a lot more you know, education that needs to be done around FH in general, which will then obviously a lot of the time lead on to PCSK9 as well.”(A4, research nurse)

Participant A5 corroborated this account and reported increased referral from other secondary care consultants. However, the participant attributed this increase to the fact that these consultants could not prescribe PCSK9 inhibitors.

“I think the cardiologists are increasingly gaining knowledge, so we’re getting more referrals from our cardiology team as this patient may have FH and I think they might be eligible for PCSK9 inhibitors. So, we’re getting, you know, perhaps a referral every couple of months from our cardiology team which didn’t use to happen and that’s because this new treatment’s opened up which at the moment, they're not able to prescribe.” (A5, consultant)

Participant views from both primary and secondary care suggested that knowledge on HeFH and PCSK9 inhibitors was low in primary care, and was improving in secondary care. The researcher also identified cases where primary care participants were not familiar with certain processes or terms commonly used in the management of HeFH. For instance, a GP (A11) was not aware of the term ‘cascade screening’, but went on to describe that the families of HeFH patients needed to be informed of the condition later in the interview. The participant also stated that they were not aware of what happened in secondary care.

“So that’s really from my point of view the patient’s journey towards the lipid clinic. What happens in the lipid clinic I really don’t know.” (A11, GP)

The following participant (a GP), was not aware of the severity of HeFH and the need to identify the condition in primary care.

"…when they talked about the lipid lecture, that I mentioned, they were not quite emphasising on the severity or the importance of this topic. Now having spoken to you it looks like it needs to be made aware more prominently to primary care, when to refer and what to do so this is quite a serious topic, I think more awareness needs to be created…" (A14, GP)

A nurse prescriber (A13) in primary care had never heard of PCSK9 inhibitors; in response to the question the participant was quoted as saying, "Nobody's mentioned any injection to me". Whilst referring to PCSK9 inhibitors two GPs stated the following:

"…(talking to patients) so it's telling them about all the other options, your project about… the project you know about biological treatment, I'm not so sure if we have any of the patients taking these medications, I need to do a search to look into that." (A15, GP)

"I've been to one of the lipid lectures recently, so they did mention about this new medication which is still completely in research." (A14, GP)

Participant A14 (above) stated that PCSK9 inhibitors were completely in research when they had been approved for use in HeFH for the past 4 years.

In summary, there was general agreement from both primary and secondary care clinicians that the knowledge of HeFH and PCSK9 inhibitors in both sectors. Secondary care clinicians believed that the level of knowledge on HeFH and PCSK9 inhibitors was low in primary care. Primary care clinicians did not dispute this claim, and evidence of low levels of knowledge also emerged from interview responses. There was also an acknowledgement that the level of knowledge in secondary care was lacking in some aspects, but was improving.

Primary care participants also felt that some more education on HeFH and PCSK9 inhibitors would benefit HCPs. Example of suggestions provided to rectify this was provided by GPs as shown below.

"I think it would be a good idea that maybe a workshop is done for GPs and nurses on probably, I don't know if the incidence is rising of FH, but I think a workshop will do the clinicians a world of good." (A11, GP)

"…with regards to improvements erm…I think more awareness needs to be created in terms of education meetings or even sending newsletters to all the GPs and nurses." (A14, GP)

5.5.3.2.2 Inadequate understanding of HeFH in patients

Patient knowledge was perceived to affect the use of PCSK9 inhibitors as both a barrier and a facilitator. Lack of patient knowledge, of either HeFH or its associated medications, was thought to reduce patient compliance and engagement with treatment processes. This therefore functioned as a barrier to the general use of medication. Conversely, an increase in patient knowledge, especially regarding disease severity, was generally found to improve acceptability of medication. These cases are discussed under section 5.5.4.2 below.

HeFH patients in secondary care were generally aware of the disease; however, most patients did not fully understand the condition. The patients understood that the disease was hereditary, and they were aware of the need to inform family members about the condition. They also understood the heightened risk of CVD and the requirement to take a lifelong regimen of lipid lowering medication. Sample quotes from the data illustrated various levels of awareness.

"Yeah, my condition is familial hypercholesterolemia; I think there's one that's called hytro… with the one gene, so that's the one that I have." (A9, patient)

"Interviewee: High cholesterol, I've had it for a few years now, yeah…

Interviewer: Do you know which particular type of high cholesterol you have?

Interviewee: I haven't got a clue, no, off the top of my head, I don't know what it is." (A6, patient)

"I've had the high cholesterol for a good few years now. It's hereditary obviously via me father… Now I'm a little bit statin intolerant. I was statin intolerant until me heart attack and then they, I didn't have a choice. I was getting the statins put in me mouth [laughs] in a nice way." (A12, patient)

From the perspective of HCPs, there were differing views on patient knowledge between primary care and secondary care clinicians. This was largely because HeFH patients referred to secondary care had experienced some form of disease related complications; for example, cardiac events or statin intolerance. These patients engaged with the treatment process more, and understood the risks that they faced. The resultant effect was an increased willingness to use statins (despite experiencing side-effects), and general acceptance of PCSK9 inhibitors.

"On the whole, a lot of the patients are fine; they understand why they need to take it and the risks of not taking cholesterol medication in terms of heart disease etc. And in terms of the injections, they are quite happy in taking an actual injection as well, not many of them are worried about injecting themselves." (A4, research nurse)

"Acceptability (of PCSK9 inhibitors) is excellent because most of the patients we have tried are patients who are statin intolerant." (A3, consultant)

"I think when you're explaining, educating the patient, say them to look, you know, this is really important for your cardiovascular health, we're trying to stop you from getting heart attacks. I think if you explain the reasoning behind it, you know, most patients agree to use it." (A8, consultant)

In contrast, primary care clinicians felt that HeFH patients in primary care were not sufficiently knowledgeable about the condition. This resulted in reduced engagement and non-compliance with treatments.

"A lot of them don't know and the funny thing is that when you're explaining the condition to them, some of them might say 'Yeah, but I'm not fat, I'm not obese.'" (A11, GP)

"…I was talking in the pub and me mate's said, he doesn't take them anymore cause he gets this, this and this, so I thought I'm going to do that, so they listen a lot to the media and also what their friends think." (A13, prescribing nurse)

Patients felt that GPs and nurses in primary care did not inform them appropriately about the severity of the disease. Additionally, patients expressed concern about delays in diagnosis despite the existence of family history of cardiac disease.

"I feel they did give me the medication but I think they didn't make me aware of how important it was for me to take this? It was just, you know, they've done some bloods, come and pick your medication up or if I have made an appointment with the doctors, oh you know, you have cholesterol, you've got to take this, you know, the importance of it is not made, it's not taken seriously at all with the cholesterol.." (A9, patient)

"They could let people know, I don't know how you do that, how you go about doing that. Maybe your GP, you know, but the chance that you'd got it and because you have to go for regular blood tests at the GP surgery, so if they suspect that you've got it, they could give you more information about it." (A7, patient)

"I'm thinking, now at this stage and I'm just turning forty-one but obviously three years ago, I was in my thirties, late thirties and I knew about this that you know, I just feel that if I knew about this a little bit earlier I could have, there's a lot of things that I could have helped myself..." (A9, patient)

Finally, it was observed, in both primary and secondary care, that some patients took medication (statins) intermittently regardless of knowledge of the disease. In primary

care this was attributed to influence from peers and information in the media regarding statins by the nurses (as described in excerpt A13, above). In secondary care, side-effects were recognised as the cause of this non-adherence.

"I think as well, if patients aren't taking the statin as often as they should, and you explain to them, that you know, when you were taking your statin, your cholesterol came down to X and now you've, you know, only taken it every few days, or when you remember it, it's now gone up to Y, and they tend to understand that you know…" (A4, Research nurse)

These results suggested that more knowledge about HeFH was required in patients. In most cases, the disease was taken seriously only after a cardiac event was experienced. Patients felt that prescribers in primary care could improve the information they provided about the disease.

5.5.3.3 Therapeutic gaps in clinical guidelines

5.5.3.3.1 The use of clinical guidelines for lipid management in HeFH

NICE guidelines were found to be the main reference resource for healthcare providers (HCPs), and were used by all clinicians in both primary and secondary care.

5.5.3.3.1.1 Stakeholder level of knowledge on clinical guidelines

In primary care, there was general awareness that markedly elevated LDLC levels, with or without a history/ family history of cardiac events, warranted secondary care referral. However, HCPs in primary care rarely mentioned specific details from NICE guidelines. In some cases, it was evident that the thresholds described differed from NICE recommendations (excerpt A14, below).

"Depends on the levels of the cholesterol, so I've had lectures where they say it's above 10, you need to start treatment straight away." (A14, GP)

"Well basically our target is, for diabetes, heart disease and cholesterol, below four, or certainly four or below and an LDL of two. For sort of people with just say for example,

hypertension without diabetes, without cardiovascular disease then erm, we target that to be less than five."(A13, prescribing nurse)

In contrast, HCPs in the secondary care management of familial hypercholesterolemia were more knowledgeable about guidelines, and also discussed specific thresholds regarding PCSK9 inhibitors.

"At the moment, for FH without established cardiovascular disease, the LDL threshold (after maximum tolerated medication) is 5 mmol/L; whilst for the very high intensity that is more than one event or two bed event, it's 3.5; whilst if it's just one event or one single bed, it's 4 mmol/L." (A3, consultant)

"Okay, so generally speaking we aim for, a cholesterol of less than four LDL cholesterol, less than two. But if we can't achieve that because there're too ambitious lipids then we aim for an LDL reduction of 50% or more from the baseline figure." (A8, consultant)

Additionally, secondary care clinicians were found to use European guideline therapeutic LDLC targets for HeFH. This was mainly because NICE guidelines recommended a percentage LDLC reduction compared to concrete values presented in the European guidelines.

"Obviously, for secondary prevention there are targets. We use the European target of 1.8 mmol/L. That's the threshold."(A3, consultant)

"If patients have got FH and vascular disease, then we would aim for even lower LDL cholesterol so less than 1.5, even we would go down to less than 1.5, if we can." (A8, consultant)

5.5.3.3.1.2 The potential overuse of QRISK

An emerging concern, raised by a consultant, was the use of QRISK in HeFH patients in primary care.

"What really should happen is there should be a discussion with the patient as to what the risk is and what the pitfalls of the risk algorithm are which is very difficult in primary care but

also what the potential benefit would be. That never happens. What really happens is that they go into the QRISK algorithm which is primary prevention and if they are above the 10% threshold, bang! They're given statins." (A3, consultant)

QRISK scores are a guideline based tool used in the prevention of CVD. QRISK estimates the 10 year risk of CVD based on patient risk factor profile. NICE guidelines stipulate that a QRISK score of 10% or more indicates the need for a full assessment and potential treatment with statins. NICE also recommends that the QRISK assessment tool is NOT used in patients with HeFH (NICE CKS, 2019).

Nevertheless, most clinicians from primary care mentioned the use of QRISK as the general practice for managing patients with elevated cholesterol. Nurses generally conducted NHS health checks, they were key to referring potential HeFH patients for further assessment y GPs. An account by participant A13 (prescribing nurse), confirmed participant A3's (consultant) description of the process of treatment in primary care.

"…we see patients for NHS health checks who are not on a register… the QRISK score and if that becomes over 10% for patients, irrespective of where the cholesterol sits then I ask to see them erm, with obviously sort of the guidelines… or if we're over 10% with some of these patients dependent on obviously history and lifestyle, you know, recommend that they have statins." (A13, prescribing nurse)

A similarly important observation was that secondary care clinicians who were not specialised in lipid management also prioritised the use of QRISK. There was no acknowledgement that QRISK scores could potentially mask HeFH, as the score was based on several risk factors that were not all relevant to the HeFH.

"I think we shouldn't be too fixated about lipids because don't forget that patient risk factor profile is not just about lipids it's interaction between multiple risk factors so blood pressure smoking history lipids family history hmm you know weigh height so forth. All this factors are

put in a risk calculator so QRISK in the UK or JBS3 which is currently recommended which is based on QRISK." (A17, cardiology consultant)

A prescribing nurse noted cases where patients with elevated cholesterol (potential HeFH according to NICE guidelines) did not score above 10% in QRISK. The participant was however not clear on the reasons behind this. As previously mentioned, NICE guidelines do not recommend the use of QRISK scores on HeFH patients because the risk score may be underestimated due to the asymptomatic nature of HeFH (NICE CKS, 2019). The prescribing nurse did not appear to be aware of this guideline.

"Well you know, we have this QRISK, you know, about the QRISK now sometimes I can have somebody who can have a cholesterol of eight or nine, erm over the age of 40, weight might be okay, no family history, don't smoke, blood pressure is okay and the risk comes less than 10… so I think sometimes you have to be careful, the computer can give you false reassurance." (A13, prescribing nurse)

Some clinicians in primary care, acknowledged the use of QRISK scores, but were aware of the inappropriateness of QRISK scores in HeFH patients. They also reported that clinicians possibly mistook HeFH for normal hypercholesterolemia and therefore treated it using QRISK scores.

"And the reason why is because normally any blood result that comes back even with a raised total cholesterol, you look at the age, you look at other factors involved, do the patients … do they smoke an all that and then we do what we call a QRISK. But even in such patients you shouldn't even be doing a QRISK too because the total cholesterol is really high…

I would probably think some people (primary care clinicians) might sort of confuse it with ordinary polygenic hyperlipidaemia and just 'Oh it's raised cholesterol, all I need to do is just

do a QRISK and start statin and invite the patient to see the nurse and discuss about healthy lifestyle advice'." (A11, GP)

The resultant effect of these cases was that HeFH patients in general, were not signposted to appropriate medical services effectively. This, consequently, may have resulted in patients who required PCSK9 inhibitors not being identified in a timely manner.

"…no one has really spotted anything really as being an issue to a certain degree. It wasn't really regarded; no one mentioned that actually you should do something about that really (referring to high LDLC levels). I think it was, I mean one of the things that hadn't been actively monitored, so I knew it was around five, you know, it was never much more than that but you know, therefore I was aware, even at the point when I had my MI, I think they mentioned it then, it was about 5.5 at the point." (A10, patient)

In summary, clinicians in the secondary care of HeFH (consultants in lipid clinics, research nurses) were more knowledgeable about HeFH specific guidelines than clinicians in primary care. Clinicians in primary care (GPs, nurses) and secondary care specialist in fields other than lipidology were knowledgeable about general CVD prevention guidelines but not HeFH specific guidelines. In such cases, it was reported that some clinicians would incorrectly use QRISK scores to assess and manage patients, even those that could potentially have HeFH. This theme focussed in the use of HeFH guidelines. The further theme of 'knowledge' emerged from this discussion. This theme is discussed under the section 'low awareness of HeFH amongst clinicians'.

5.5.3.3.2 Strict clinical guidelines on PCSK9 inhibitor provision

Of the participating stakeholders, clinicians in primary care did not comment on matters concerning guidelines in PCSK9 inhibitors. Only lipid specialist consultants discussed this issue, this was likely because only these consultants were allowed to

prescribe this new class of medication as indicated by participant A2 (cardiology consultant).

Amongst the lipid specialist consultants, there was general consensus that PCSK9 inhibitor prescription was strictly based on NICE guidelines. In fact, the main issue identified was a perceived defect of clinical guidelines; strict LDLC targets. Participants thought that this had the potential to deny PCSK9 inhibitors from patients who were deemed to require them.

"In terms of introducing PCSK9 inhibitors, we have to abide by the NICE guidance so we follow the NICE guidance." (A8, consultant)

"…so we can only use PCSK9 inhibitors in line with the guidance, you know, the TA guidance from Nice." (A5, consultant)

"And I think you know there are sort of very strict criteria in terms of which patients benefit from PCSK9 inhibitors and which don't benefit, because even then it's a very small pool of patients with PCSK9 inhibitors that are allowed to use it."(A2, consultant)

The strict criteria referred to are NICE (National Institute of Health and Care Excellence) technology appraisals (TA -393 and 394) and NICE clinical guidelines (CG71) on HeFH. These guidelines stipulate when PCSK9 inhibitors should be initiated in an effort to ensure appropriate and cost-effective use of the medication. The guidelines recommend the use of PCSK9 inhibitors when LDLC levels are consistently above 3.5mmol/l and 5mmol/l in secondary and primary prevention treatment respectively despite maximum and ineffective use of conventional lipid lowering therapies such as statins. This theme was extensively elaborated in the excerpt below.

"There is no way round this but the big issue is that certain patients try very hard and their LDL may come down to 3.8 and they're not eligible for PCSK9s. You may find another

patient with the same clinical pattern who doesn't try very hard. They take the tablet and maybe their compliance isn't brilliant and the patient denies it but with the diet, you know there is a little bit of cholesterol but perhaps not that much. They don't try very hard and their LDL is 4.2. The person, who doesn't try very hard, with poorer compliance which we know nothing about, is eligible for PCSK9; whilst the patient who plays by the book and tries very hard is not eligible. There is unfairness but I don't know how the system can get round that. That is a major unfairness."(A3, consultant)

"…it may be that they've got less than 50% reduction but the LDL, they've not got cardiovascular disease and the LDL is less than five, then we've got no other option…" (A5, consultant)

To clarify this comment, HeFH patients are required to meet the recommended LDLC thresholds in order to qualify for PCSK9 inhibitors. In some cases, the LDLC levels of patients deemed to require PCSK9 inhibitors by lipid consultants are below these targets, and therefore these patients are not eligible for the medication.

In summary, lipid specialist consultants were in agreement that strict NICE guidelines were directing the use of PCSK9 inhibitors. These guidelines could potentially restrict the provision of PCSK9 inhibitors to patients who were deemed to require them. This section is concluded with an excerpt describing a consultant's view of clinical guideline. This participant (A3) was a member of the area prescribing committee and was therefore involved in the inclusion of medication to organisational formulary. This allowed insight that the other consultants did not have as they were not part of this process.

"My main point is that I have a major problem with a lot of the guidelines that come out. My biggest issue is that they are practical and pragmatic but they do not look at the disease… There isn't enough information about the differences between the drugs. It's all about the pathway. With pathways, you do not talk about what the underlying risk factors are. What is

the best drug? What is the most appropriate drug for this patient? For instance, fibrates are not covered." (A3)

The excerpt discussed matters that revolved around 'mechanical prescribing' of statins as discussed in section 5.5.3.3.1 (The use of clinical guidelines for lipid management in HeFH). However, it also discussed a potential lack of specification in guidelines as regards medications. This introduced an element of flexibility with respect to the interpretation of guidelines into organisational policy. The effect of this flexibility was observed in the development of organisational policies as discussed in the section 5.5.3.4 (Inhibitory organisational practices).

5.5.3.4 Inhibitory organisational practices

This theme explored the organisational factors that had the potential to influence PCSK9 inhibitor use. Organisational policies for the management of HeFH, and multi-disciplinary cooperation in the care for the disease were identified as key sub-themes. The theme was mainly discussed by HCPs in various capacities.

5.5.3.4.1 Inhibitory prescription policies for PCSK9 inhibitors

Organisational practices varied between the primary and secondary care treatment setting for HeFH. These differences were based on NICE guidelines and revolved around the roles served in each setting.

At the primary care level, patient care was focused on disease detection as discussed under section 5.5.3.3.1 (The use of clinical guidelines for lipid management in HeFH). There were no specific organisational procedures set up for the identification of potential HeFH patients in primary care. Instead, general practices in CVD detection and prevention were presumed to cover HeFH patients. This included the use of QRISK and the reliance on NHS health checks to screen for HeFH.

"I don't think they have a structure in place but… they do have a national health screen for… diabetes and familial hypercholesterolemia. So I think the 40's the Government does have a screening and anyway all people that have health conditions like diabetes, they do have their annual or six-monthly check anyway. So I do think there are systems in place for people to be picked up with familial hypercholesterolemia but if it's very strong history of, you know, in their early 20's then we don't have a check or a screen for them…" (A14, GP)

Similarly, the nurses who were in charge of conducting heath checks felt that the system for identifying HeFH was adequate. In response to the question on the role of primary care in HeFH management, a nurse prescriber provided the following response.

"…when we identify the patients, that cascading about getting the siblings you know, or children checked etc. particularly if you've got, you know, sudden death and a lot of cardiovascular problems within in a family, you know, at a young age to about 86, often we look at them. I think otherwise, other than what we're doing erm, you know, sort of screening patients over 40 and obviously that's just picking out the ones that erm, they've got significant family history that makes you think like that." (A13, prescribing nurse)

The responses suggested NHS checks for patients over 40, and annual reviews for patients with chronic illnesses were used to opportunistically identify HeFH patients. However, this system had the potential of disregarding patients with HeFH under the age of 40.

The secondary care setting involved the treatment of complicated cases of HeFH, and therefore, the use of PCSK9 inhibitors. The main influential factor was found to be organisational policies; these policies dictated the prescribing practices. Lipid specialist consultants are the only HCPs permitted to prescribe PCSK9 inhibitors; this section therefore included limited contribution from the other stakeholders in the

study. The following excerpts are provided to describe the process through which PCSK9 inhibitors are made available in the formulary of NHS trusts.

"…each hospital has a committee that looks at a particular drug, the benefits the costs associated with it and then they would make the clinical decision as to whether it would go onto hospital formulary or not. And they'll be different service users that'll be on that committee there would be hospital pharmacists they'll be doctors with an interest in that area. So you know, it may be lipidologists it may be cardiologists I'm not involved in that process." (A17, consultant)

"Each of the CCGs still has an Area Prescribing Committee. I actually sit on the APC in xxx. If the NICE Guidelines come up (and a lot of doctors are not aware of this), it is up to the APC to make absolutely certain that it's in the formulary within a three month period. Lots of doctors aren't aware of this. It is up to the APC to go and find the appropriate clinician to fill in an abbreviation form and then it has to be stamped by the CCGs, come what may." (A3, consultant)

Once PCSK9 inhibitors were approved by NICE, the Area Prescribing Committees (APC) included the medication in organisational formulary of their member hospital trusts. This recommendation is presented to the Clinical Commissioning Group (CCG) which then sets prescribing policies for the medication. There was general agreement amongst the consultants that prescription of PCSK9 inhibitors strictly adhered to these organisational policies.

"…so although we prescribe it (PCSK9 inhibitors), it then has to go on a database and goes to the CCG for approval… we put it onto a blueteq form… they go to the commissioning groups and it's the commissioning groups who then agree whether they can, the prescription can be renewed when they come up to a year. And sometimes they're actually turning them down although we think that they meet the criteria." (A5, consultant)

"So, we have to complete the blueteq forms and then once the blueteq form is completed, we can write a prescription, and that is, it is dispensed by the hospital pharmacy and then, they either continue to get the drug from the hospital pharmacy or we use the home delivery services and that works reasonably well." (A8, consultant)

The blueteq forms had variations amongst CCGs but they were based on NICE guidelines. As described by participant A5, the forms in their CCG required that other lipid lowering agents be used before trying PCSK9 inhibitors.

"Yeah, I think the criteria, they're not, they use a NICE criteria but it's a criteria really about, whether the patients have got LDL cholesterol, say take someone without CVD, has got an LDL above five, but it's a criteria about whether every possible lipid lowering therapy other than PCSK9s has been tried. So, I might say, well they've tried all the statins they've tried pravastatin, they've tried atorvastatin then they might say well have you tried fluvastatin."(A5, consultant)

Similar points were raised by other consultants. However, further comments revealed that some blueteq forms required multiple LDLC readings above the NICE threshold in order to ascertain the fulfilment of this requirement.

"It is available (PCSK9 inhibitors) and there is a bit of a postcode lottery at the moment. It is available but the process is deferring from CCG to CCG. In xxx, for the CCG, there's a blueteq that has to be filled. They require two LDLs above the threshold which is not in the NICE Guidelines. There are certain other CCGs which want three and again, isn't in the NICE Guidelines. In xxx, at the moment, they're not doing them. They're following the NICE Guidelines." (A3, consultant)

Although consultants were in agreement that PCSK9 inhibitors should be provided after the use of other lipid lowering agents; there was concern that the unstandardized blueteq system had the potential to cause delays in medication provision. This, in turn, would cause frustration in HeFH patients.

"…it will probably delay everything by six months for them to have two or three blood tests to prove it. It also makes the patients quite irritable because these are very high risk patients and they would rather get on to it than having to come back in two or four months for the next step. Of course, what actually happens if, for instance, an LDL in a secondary prevention patient – high risk but not extreme risk which is one event – is, say, 4.1 and the next time they come at 3.9 and the following time, it's 4. These patients do get quite frustrated." (A3, consultant)

This section is concluded with excerpts from patient participants who experienced these delays.

"They need to know which one is which and it just takes such a long journey, the appointments come every three months or every four months, by the time they've taken the bloods after four months when they're going to call you back again, so then they will do your bloods again, then it's another four months, by the time, they've written to your doctors…" (A9, patient)

"…actually the recommendation was get off statins cause its causing all these other issues, but there was nothing quickly, you know, it was nine months before I actually I got onto the new drug, you know, cause there's lots of tests and procedures to go through to get to that point…" (A10, patient)

5.5.3.4.2 Lack of consensus on stakeholder roles in the care for HeFH

This sub-theme set out to assess the role of multi-disciplinary cooperation in the management of HeFH. Divergent views regarding collaboration were elicited from stakeholders. The data so far suggests that nurses (in primary care) were involved in the identification of potential HeFH patients. In secondary care, nurses were involved in patient education and training as regards the use of PCSK9 inhibitor injections. GPs were involved in the management and monitoring of HeFH patients, however, they were also tasked with referral of patients to secondary care. Specialists in

secondary care manged complicated cases of HeFH (statin intolerance, markedly elevated LDLC etc.)

Some consultants felt that the use of PCSK9 inhibitors was a clinical decision that had to be left to the specialists. Participant A3 (excerpt below) also felt that the involvement of other HCPs in the prescription of other medication was not always advantageous.

"No, I don't think they actually have a role here because this is actually a clinical decision. It's based on NICE. It's an expensive drug. It's a new drug and even the primary care are not allowed to use it. The PCSK9 is specifically secondary care and that's the way it should be. When it comes to other treatments, yes and no. I've seen places where statins are used by pharmacists. By and large, it's okay but a lot of what I hear is a load of rubbish." (A3, consultant)

Similar accounts regarded pharmacists, nurses and GPs as providing support rather than being involved in the direct management of patients.

"We haven't used them in that way, we've mainly used them to discuss particularly when we started to prescribe PCSK9s and helped us with making sure that we have identified the correct patients and the system for prescribing which is obviously because we can't, normally if we prescribe, if I prescribe a statin, it's the GP that does the prescribing." (A5, consultant)

Conversely, some consultants suggested that trained specialist nurses and pharmacists could be involved in either prescription or support services in order to help with workload. Examples were provided of research nurses and pharmacists running clinics under the consultant during clinic trials for PCSK9 inhibitors.

"…it doesn't need to be the cardiologist or the lipidologist, lots of this can be managed by specialist pharmacists and specialist nurses." (A16, consultant)

"And then I think more resources in terms of specialist nurses and lipid specialist nurses, I think to help us in clinics, I think that would be very welcome." (A8, consultant)

Nurses felt that they could be more involved in the treatment journey of HeFH patients. Suggestions provided included increased involvement in education of both patients and HCPs. In some cases, nurses (participant A4) were also aware of services for HeFH blood testing within organisations that clinicians were largely not familiar.

"…a lot of it would need to come from us to initiate it or with the help from some of the drug companies as well to set up meetings for various people. But I think its about us, you know doing the education and educating other people in the hospital. And to know where they can refer to, it's not always easy knowing who to refer to or where to refer." (A4, research nurse)

On the other hand, GPs felt that the current roles were sufficient; with pharmacists verifying prescriptions and nurses running screening services. However, they noted that improvement could be made to the roles of the pharmacists and nurses.

"…with the nurses, they could be given more erm, kind of update and learning knowledge about picking up familial hypercholesterolemia and how they can do it, certainly, you know, the nurses can be educated more…" (A14, GP)

In summary, the opinions on multi-disciplinary collaboration were mixed. Recommendations largely involved the increase of knowledge in certain roles, and suggestions of services that were not being used effectively. Overall, it seemed that there was a need to re-organise the treatment process for HeFH management as regards multi-disciplinary collaboration. This suggestion was mentioned by a consult (participant A8) who felt that other HCPs could be more involved in the treatment process.

"I think, reorganise the workforce in such a way that it would be more effective, I think definitely, yes, you can utilise them in a slightly different way to provide a more efficient service." (A8, consultant)

5.5.4 Facilitators of PCSK9 inhibitor adoption

Fewer facilitators were identified compared to barriers to the use of PCSK9 inhibitors. The sub-themes of 'patient awareness of disease severity' and 'views on medication use' were generally considered to facilitate PCSK9 inhibitor use amongst different stakeholders. However, the sub-theme on 'influence from pharmaceutical companies' was discussed by three consultants that had previously worked in clinical trials of medication. The sub-themes are only discussed briefly.

5.5.4.1 PCSK9 inhibitor use support from pharmaceutical companies

Pharmaceutical companies were found to deal mainly with consultants in the care for HeFH. Other stakeholders did not directly work with pharmaceutical companies. However, a research nurse believed that working with companies increased scope to educate HeFH patients about PCSK9 inhibitors.

"I mean obviously I think a lot of it would need to come from us to initiate it or with the help from some of the drug companies as well to set up meetings for various people." (A4, research nurse)

This was echoed by a consultant that had worked with a pharmaceutical company.

"The pharmaceutical companies have put money forward for education. They haven't had any say about policy and that; I can categorically say…The reason is because Sanofi offered us free patient access to the Nursing Service. We didn't have the capacity in the clinic to teach patients how to use it. Amgen was slow off the mark. They've got a policy in now and now, the prescribing will be around even, so 50% for each." (A3, consultant)

The provision of a nursing service helped to improve HCPs knowledge on PCSK9 inhibitors; and therefore increase the turnover of patients who required PCSK9

inhibitors. Sponsorship was also associated with the use of the company's medication as is evident from the quote below:

"They probably do get a little bit upset because if you look at my practice, about 80% plus are on the Sanofi drug and so Amgen would be quite upset."(A3, consultant)

5.5.4.2 Patient awareness of disease severity

Patient awareness of disease severity was identified as a facilitator to the use of PCSK9 inhibitors, and statins among other lipid lowering agents. Patients agreed to take statins despite experiencing side-effects once knowledge of the disease was improved. PCSK9 injections were also found to be well accepted.

"..I think so and I think after having a heart and a bypass you seem to make it a bit more tolerant, don't you, you know, like [laughs]. Prevention is better than cure they say but after that really I just go along with it and, to be fair, sometimes if I think they're a bit much I'll miss the odd day out of the statin and then take them where last time I just thought I can't, that I can't handle this, and then I was back to the doctors trying to sort things out." (A12, patient)

"On the whole, a lot of the patients are fine; they understand why they need to take it and the risks of not taking cholesterol medication in terms of heart disease etc. And in terms of the injections, they are quite happy in taking an actual injection as well, not many of them are worried about injecting themselves." (A4, research nurse)

Intolerance remained problematic even though patients agreed to stay on statins. Despite knowledge of disease severity, intolerance reduced patient adherence as seen in excerpt <A12> above. This served to further increase acceptance of PCSK9 inhibitors in such cases.

5.5.4.3 Negative views on the use of statins

In patients, negative perceptions of statins due the reports in the media were perceived as a barrier to the use of statins, but a facilitator to the use of PCSK9 inhibitors. It is also worth noting that patients who were referred for PCSK9 inhibitor

use (therefore, all patients in this study), had either experienced side-effects or insufficiency with statins. It is therefore unsurprising that their views on statins may largely not be positive.

A nurse in primary care, for example, noted that the link made between statins and diabetes in media reports was a common concern for patients.

"I think some of the reasons are obviously there's been quite a lot of erm, press erm, awareness about statins being linked with diabetes… there's been quite a lot of awareness about statins that it raises the blood sugar, that's one." (A13, prescribing nurse)

"…you know for some people there is quite a big resistance and they, you know, they sort of and you know in the media they are starting sort of looking at treatment options so it's demonised so we tend to have some issues with that, you know, patients stop taking and obviously the risk is high…

…" (A15, GP)

"I was talking in the pub and me mate's said, he doesn't take them anymore cause he gets this, this and this, so I thought I'm going to do that. So they listen a lot to the media and also what their friends think and say so there's definitely an element sometimes can be around compliance."(A13, prescribing nurse)

Similar views were observed in the secondary care management of the disease.

"There are a handful of patients, because they are on statins and they've got a lot of bad press, you know, in the newspapers and things like that, they're a bit cautious, you know, to take them. But generally, on the whole, people are okay" (A4, research nurse)

In some cases, patients requested to be taken off statins once they were using PCSK9 inhibitors.

"A lot of people, when they go on the PCSK9 inhibitors, ask if they can then reduce or come off the statin. So, we just have to explain to them, that you know, the studies show that taking

them both together is of greater benefit than just taking one or the other. And so, they tend to understand that and continue on the statin as well." (A4, research nurse)

Some patients also showed the willingness to use PCSK9 inhibitors because of negative perceptions towards statins.

"And there are a few patients who surprisingly seem to be happier to take you know, an injection of a new largely, you know, we've not got years of evidence base about effectiveness and safety, but they're happy to do that than take statins because there's a lot of adverse publicity in the national press about statins." (A5, consultant)

On the contrary, views on PCSK9 inhibitors were generally positive amongst both HCPs and patients.

"On the whole, a lot of the patients are fine; they understand why they need to take it and the risks of not taking cholesterol medication in terms of heart disease etc. And in terms of the injections, they quite happy in taking an actual injection as well, not many of them are worried about injecting themselves." (A4, research nurse)

"No, no, I've been taking the tablets and the injections as well. So, the injection seems to have fetched it right down, my cholesterol." (A6, patent)

"Acceptability is excellent because most of the patients we have tried are patients who are statin intolerant. Altogether, I probably have close to 70 patients across both sites…" (A3, consultant)

"I'm fine with it. I just think this, the injection thing that is working. It works. I think statins just seem to have a bit of a bad press, don't they, so, and people talk about them, there's so many on them and that, but maybe I wouldn't have had them either." (A12, patient)

Some patients were hesitant to use injections but acclimatised to the use of PCSK9 inhibitors due to increased LDLC reduction and insufficiency of statin treatment.

These patients retained negative thoughts on PCSK9 inhibitors despite their acceptance to use the medication.

"Well at first I wasn't too keen on the injection, I really wanted the tablets to work and it just wasn't happening. They were pushing me to take these tablets and really told me to take the injection and I was just a bit optimistic about taking the injection, I just really hoping that it come down with the tablets but it just didn't, for me. It would not come down with the tablets alone, and when they put me on the eighty, that was affecting the liver so I didn't want that either. So, my only other option was to try this injection so, when I did go and get the injection, and it has brought it down dramatically, which, you know, I'm really pleased. But, you know, my only other thing I'm thinking, will I have to be on this for life?" (A9, patient)

Finally, polypharmacy was identified as a concern by some patients. This was often associated with reduced levels of LDLC following the initiation of PCSK9 inhibitors. Patients suggested a reduction to the amount of medication taken, or objected to the addition of medication to their treatment regimen. In these cases, an acknowledgement of the effect of PCSK9 inhibitors was reported. This suggested that the patients would not want to PCSK9 inhibitors to be removed from their treatment regimen, but questioned the need for other medication.

"I found the tablets alone didn't bring my cholesterol down, they wanted it to come down. And with the injection and taking the tablet, it's come down to four. Yes, this is just recent and the LDL is 2.1 and now they want to put me on ezetimibe just to bring the LDL one down but I'm not sure if I want to go on because I already take enough medications…" (A9, patient)

"I think it's difficult, cause for me one, what's interesting for me now is, with statins I understand and obviously with the evolocumab because obviously it's doing a positive thing it's keeping your cholesterol below a certain level… I queried why, you know, even though I'm on a low dose of things like ramipril, as to why I need to continue to be on them…" (A10, patient)

5.6 Discussion of qualitative analysis results

This chapter identified potential barriers and facilitators to the adoption of PCSK9 inhibitors using thematic analysis of interviews with stakeholders. Five key themes emerged from the analysis.

The theme on 'Low referral rates to secondary care' described the patient identification pathway and the process of receiving lipid lowering medication. The overall implication was that a small number of HeFH patients were being identified and referred to secondary care. Specialist consultants felt that the identification and referral of patients to secondary care was 'incidental'. By contrast, clinicians in primary care felt that the use of NHS health checks and patient medical reviews were sufficient to identify HeFH. However, there were no specific systems set up to detect HeFH. Patient accounts supported the consultants' viewpoint; these suggested that HeFH was mainly considered when a cardiac event occurred in a patient. Following a cardiac event, cascade screening provided an avenue for the patient's family to be identified.

'Therapeutic gaps in clinical guidelines' assessed specific processes in the management of HeFH and the provision of PCSK9 inhibitors. Two key results were extracted from this theme. Firstly, GPs and consultants felt that there was a possibility that clinicians in primary care treated HeFH as the non-familial versions of the disease. Some participants (GPs) reported that some clinicians possibly calculated a QRISK score and prescribed statins without realising other signs for HeFH, such as family history of elevated cholesterol or heart disease. The accounts of other primary care clinicians appeared to support this claim. GPs and nurses reported the use of QRISK and general CVD prevention guidelines for patients. HeFH was identified by markedly elevated LDLC levels combined with a history or family history of CVD. However, some GPs noted that the recording of cardiac event

history was ‘random’, and suggested that all healthcare providers pro-actively seek to establish accurate medical histories. Secondly, the use of NICE guidelines for the prescription of PCSK9 inhibitors was described as ‘strict’ by specialist consultants. Consultants found that some patients, who were deemed to require PCSK9 inhibitors, were denied the medication because they did not meet the set LDLC thresholds.

Healthcare practitioners in secondary care acknowledged that the level of knowledge of HeFH was increasing in secondary care. However, there was general congruence that the level of knowledge in primary care was significantly lower. The interviewer encountered participants in primary care (GPs and a prescribing nurse) who were not aware of PCSK9 inhibitors. These corroborated accounts from secondary care that reported failed attempts by patients to discuss PCSK9 inhibitors with some primary are clinicians. Furthermore, a GP admitted to not knowing how serious HeFH was, and the fact that more was expected from primary care with regard to the identification of patients. Patients asserted that the severity of the disease was not expressed to them in a timely manner. GPs and nurses felt that patients did not take the disease seriously and were influenced by negative media reports on statin use. Patients felt that they were not informed about the disease severity; they also felt that HeFH was considered by primary care clinicians when it was too late. This had the dual effect of delaying HeFH diagnosis, reducing patient engagement with treatment.

Organisational factors affected the prescription of PCSK9 inhibitors by increasing the time required to receive the medication. In primary care, the lack of a structured system of HeFH identification delayed referral times for patients that would end up using PCSK9 inhibitors. Once in secondary care, the prescription of PCSK9 inhibitors was defined by organisational policy. Consultants were required to fill in the Blueteq form for each patient that required PCSK9 inhibitors. The Blueteq form was mainly

used to ensure that the patient had used other available lipid lowering agents before PCSK9 inhibitors were indicated. The form also ensured that that the patient met the LDLC thresholds stipulated by NICE guidelines for PCSK9 inhibitor use. However, additional requirements were included in the Blueteq forms of some organisations. For example, consultants reported that some organisations required two or three LDLC readings above the recommended threshold in order for the patient to qualify for the treatment. Patients found the system frustrating as it further delayed treatment, and in some cases, they had to attend LDLC profile tests over several months.

The final theme constituted the factors that were perceived as facilitators to the use of PCSK9 inhibitors. One factor that was independent of the stakeholders was the influence of pharmaceutical companies. Secondary care clinicians reported that assistance from pharmaceutical companies helped to improve patient education on the use of safety syringes. Participant A3 (section 5.5.4.1) indicated that the pharmaceutical company's support allowed for the setup of a nursing service that allowed for the training of patients on PCSK9 inhibitor injection/ pen use. A research nurse (A4) also indicated that provision of training helped to facilitate the process of prescribing PCSK9 inhibitors. Negative views on statins were also found to be potential facilitator for the use of PCSK9 inhibitors. Clinicians reported patients asking to be taken off statins once their LDLC levels were reduced by PCSK9 inhibitors. One patient noted that they would have preferred to have statins removed from their treatment regimen but were informed that they had to take both medications. Finally, opposite to the theme on lack of awareness, it was found that an understanding of disease severity improved both clinician and patient engagement with the HeFH treatment pathway.

5.7 Conclusion

The current chapter presented the views and opinions of stakeholders in the care for HeFH patients who use PCSK9 inhibitors. 5 themes emerged from interview data following thematic analysis. In primary care, barriers associated with HeFH management were found to indirectly affect eventual PCSK9 inhibitor use. For example, low awareness of both HeFH and PCSK9 inhibitors led to low rates of referral to secondary care where PCSK9 inhibitors were considered. In secondary care, prescription of PCSK9 inhibitors was found to be reliant on LDLC measurements. Barriers to medication use were related to inhibitory prescription policies for PCSK9 inhibitors using the Blueteq system, and clinical guidelines that were perceived to be restrictive. Comments on facilitators to PCSK9 inhibitor use were minimal, however, patient understanding of the disease, negative views on statin use and the influence of pharmaceutical companies in improving PCSK9 inhibitor use were found to increase the use of the new class of medication.

Chapter 6 Discussion

The aim of this thesis was to identify the potential facilitators of, and barriers to the adoption of proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors. This resulted in two research questions as outlined below:

1) To study the barriers and facilitators to the usage of PCSK9 inhibitors by exploring the views and opinions of key stakeholders (patients, specialist consultants/GPs and nurses) in the care of heterozygous familial hypercholesterolemia (HeFH) in the UK.

2) To assess the feasibility of using the Clinical Practice Research Datalink (CPRD) database to develop a predictive model that can identify HeFH patients who meet the LDLC eligibility targets for PCSK9 inhibitors.

A multimethod approach was adopted; with quantitative methods being used to address question 2 (chapter 4), while qualitative methods were used to address question 1 (chapter 5).

This chapter consolidates the thesis chapters by discussing and integrating the results of chapter 4 and 5 in relation to the overall research aim. The chapter also conceptualises the results and outlines their importance to current medical practice.

6.1 Summary of thesis chapters

Chapter One: A background to the thesis. The chapter introduces HeFH, PCSK9 inhibitors and provides a rationale for studying the barriers and facilitators to the adoption of PCSK9 inhibitors.

Chapter Two: A systematic search and narrative synthesis of studies specifically focusing on PCSK9 inhibitor use in clinical practice and the associated barriers and facilitators to their use. The chapter identifies the gaps in literature and outlines the two research questions addressed in the thesis.

Chapter Three: A discussion of the multimethod approach adopted to address the two research questions.

Chapter Four: Presents and discusses the results and analyses of the quantitative phase of the project using both descriptive and inferential statistics.

Chapter Five: Presents and discusses the results and analyses of the qualitative phase of the project illustrating the themes identified as potential barriers or facilitators to PCSK9 inhibitor use by HeFH stakeholders.

Chapter Six: A discussion of the results obtained from chapter four and five. The chapter outlines the significance of these results to current practice and identifies the potential impact of the work.

6.2 Structure of the discussion section

The current section begins with a discussion of the quantitative results (chapter 4) in relation to the overall aim of the thesis. This was followed by a summary of the themes emerging from the qualitative phase of the study (chapter 5). The results from the two phases of the study were then integrated as shown in section 6.2.3. A joint display approach was used to highlight corresponding and contrasting results from the qualitative and quantitative data. The subsequent section (6.3 - Discussion of emerging themes) then discusses the themes developed from both phases of the study.

6.2.1 Quantitative results summary

The quantitative phase of the study addressed research question two and was presented in chapter 4.

The main study aim was to assess the feasibility of predicting HeFH patients who could potentially require PCSK9 inhibitors using CPRD data. With regard to this aim, the following conclusion was drawn:

Despite the potential for identifying HeFH patients who could benefit from PCSK9 inhibitors, the overall model prediction was inadequate to sustain clinically significant results. We therefore conclude that the clinical attributes currently available in CPRD may be insufficient to predict PCSK9 inhibitor requirement among HeFH patients.

The predictive model developed retained three patient clinical attributes (age at diagnosis, maximum LDLC on record and the use of lipid lowering medication) and produced a predictive ability that was greater than chance. These variables were statistically significant to overall LDLC reduction; however the derived predictive model could not distinguish between positive and negative cases sufficiently. Nevertheless, the existence of clinical attributes that are associated with LDLC reduction suggested potential for further research for PCSK9 inhibitor use modelling; these may involve the use of different health databases with clinical attributes outside the scope of CPRD.

With regard to the overall research aim of identifying potential barriers and facilitators to PCSK9 inhibitor use, the study found the following relevant statistics –

63.9% of HeFH patients who did not achieve guideline recommended treatment targets did not meet the LDLC threshold for PCSK9 inhibitor eligibility.
Patient records for clinical attributes relevant to PCSK9 inhibitor use were sparsely recorded e.g. just over half of HeFH patients in the database had at least one record of LDLC.
About 80% of HeFH patients did not meet guideline recommended LDLC treatment targets and could potentially require referral to secondary care.

A summary of the data used for analyses is provided herein. All HeFH patients considered for secondary prevention treatment were eligible for PCSK9 inhibitors (i.e. LDLC > 3.5 mmol/l). This was expected because HeFH patients typically present with markedly elevated LDLC values, a large number of these patients would therefore have LDLC values above 3.5mmo/l.

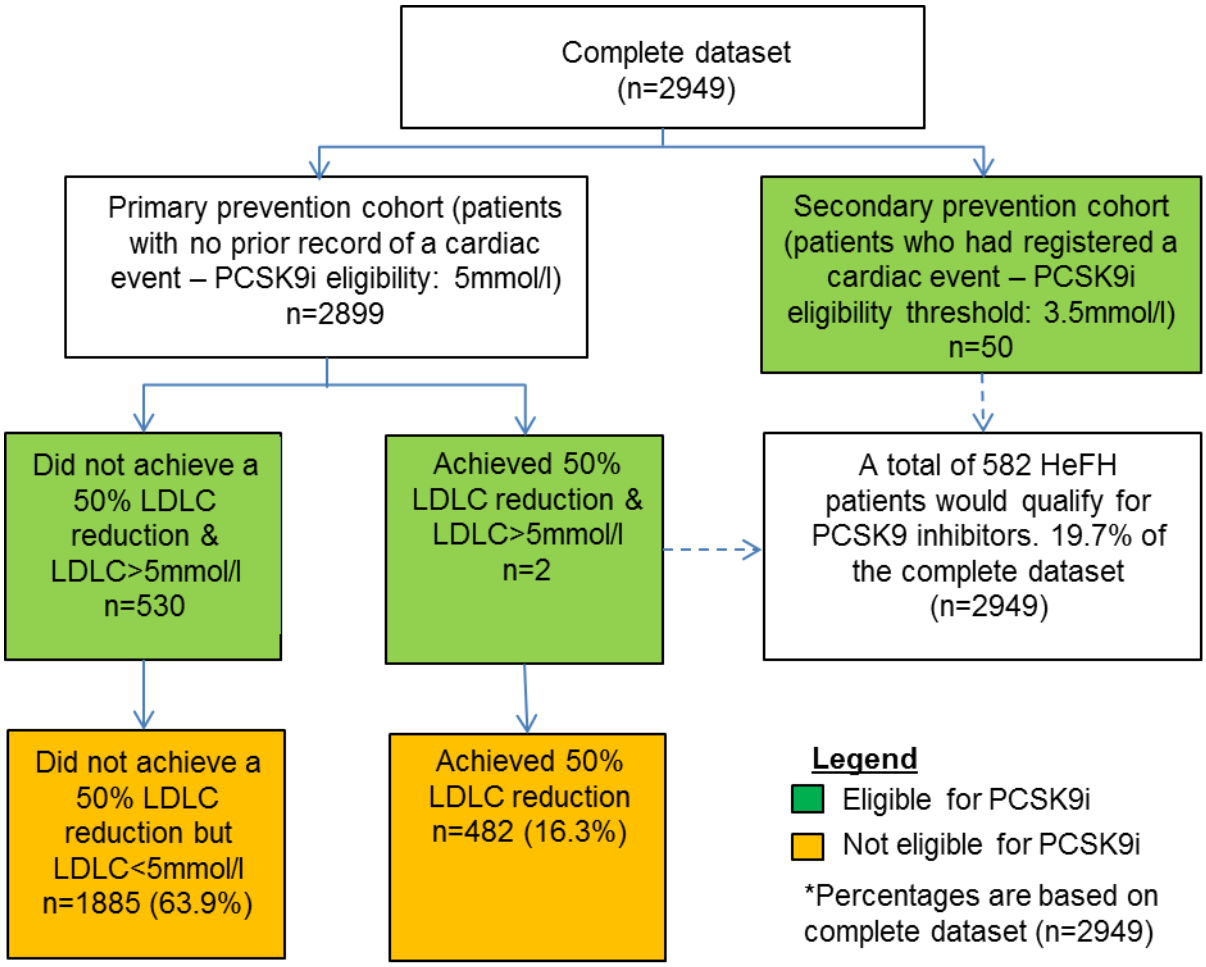

Figure 6.1 Summary of PCSK9 eligibility within the study data set

In the primary prevention cohort 532 patients were found to be eligible for the new class of medication. In total, 582 (19.7%) patients in the study sample would meet the PCSK9 inhibitor eligibility threshold. These results were similar to eligibility studies from past literature; Glueck et al. (2016), Jetty et al. (2017). However, 63.9% (1885) of HeFH patients did not achieve the 50% LDLC reduction target but did not qualify for PCSK9 inhibitors based on the 5mmol/l threshold. This suggested that a proportion of inadequately treated HeFH patients in the UK may not be eligible for

PCSK9 inhibitors based on current NICE guidelines. This potential concern has not been addressed in current literature.

6.2.2 Qualitative results summary

The qualitative phase of the study addressed research question one above and was presented in chapter 5.

The main study objective was to explore the views and opinions of stakeholders in the care of HeFH on the potential barriers and facilitators to PCSK9 inhibitor use. The results were presented as themes emerging from the of participant responses as follows.

Barriers to PCSK9 inhibitor adoption included:

Low referral rates to secondary care

Therapeutic gaps in clinical guidelines

Low levels of knowledge and awareness of HeFH

Inhibitory organisational prescribing policies

Facilitators of PCSK9 inhibitor adoption included:

PCSK9 inhibitor use support from pharmaceutical companies

Patient awareness of disease severity

Negative views on the use of statins

6.2.3 Integration of quantitative and qualitative results

In this section, the quantitative and qualitative data are integrated and explored. The integration of data was primarily conducted at the data analysis and interpretation stages as discussed by Fetters, Curry and Creswell (2013). This section presents a summary of four key complementary results from the qualitative and quantitative phases of the study using a joint display as described by Guetterman, Fetters and Creswell (2015) – table 6.1.

The themes that emerged from the quantitative and qualitative phases of the study were interrelated at numerous levels as shown in figure 6.2 below. For example, the quantitative finding that a majority (~80%) of HeFH patients did not meet guideline recommended treatment targets in primary care and would therefore require referral supported the qualitative theme of low referral rates to secondary care.

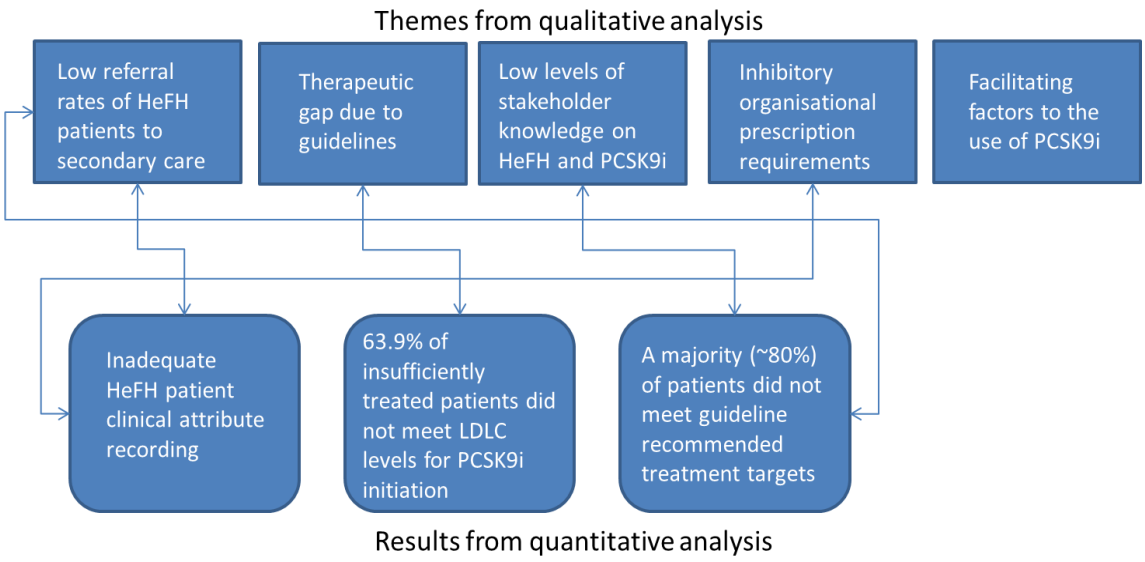

Figure 6.2 Relationships between emerging themes from qualitative and quantitative results

These interactions are elaborated further in table 6.1 below.

Table 6.1 Joint display of corresponding qualitative and quantitative data

Quantitative finding	Qualitative finding	Implication	Effect of integration
The recording of patient clinical attributes was found to be varied. For example, 64.2% (3297) of the total sample size (n=5134) had more than one LDLC measurement on record. Of the total data, 3018 (58.8%) patients had LDLC data that were at least a year apart.	"…there's a blueteq (prescription system section 6.3.1) that has to be filled. They require two LDLs above the threshold which is not in the NICE Guidelines. There are certain other CCGs which want three… The biggest issue with this is that these patients are going to have a high level and so they will be started on it (PCSK9 inhibitors); but it will probably delay everything by six months for them to have two or three blood tests to prove it. " (A3, consultant)	There was agreement that the records for patient attributes were not always sufficient for PCSK9 inhibitor prescription. This suggested that the records of patient clinical attributes may be influencing PCSK9 inhibitor usage in the UK in a manner that is similar to the effect of documentation in the US.	Corroboration
Of 892 HeFH patients that did not register LDLC reduction, 59.2% (528) did not meet the LDLC threshold for PCSK9 inhibitor treatment in the cohort (5mmol/l).	"…it may be that they've got less than 50% reduction but the LDL, they've not got cardiovascular disease and the LDL is less than five, then we've got no other option…" (A5, consultant)	A therapeutic gap may exist in the management of inadequately treated HeFH patients that do not meet LDLC thresholds for the indication of PCSK9 inhibitors.	Corroboration

A proportion of HeFH patients (30.8%) did not register any reduction in LDLC levels. 484 (16.7%) of HeFH patients were found to achieve a 50% LDLC reduction. A further 1523 (52.5%) registered LDLC reduction but not more than 50%.(Although literature on effectiveness of conventional lipid lowering therapy varies, the common result is that a majority of patients do not meet LDLC targets stipulated by guidelines (Pijlman et al. (2011), Versmissen et al. (2008)).	"…so it's probably about 30% of patients achieved target with high intensity statins so a significant number who don't with high intensity statins and those are the kinds of patients who probably benefit from going on to sort of alternative treatment. Some of it's due to compliance, some of it's due to intolerance, some of it's due to you know, I think people's sort of perceptions of FH and things it's not the fatalistic sort of doesn't affect me kind of attitude. But a significant number will not achieve target you know…" (A2, consultant)	Due to low rates in achievement of LDLC targets set by guidelines, more HeFH patients could potentially require referral from primary care; and therefore, consideration for PCSK9 inhibitor use.	Expansion/ Corroboration
In the final study cohort, 10.3% of patients had a record of family history of HeFH; while 5.2% had a family history of high cholesterol on record.	"…particularly the LDLC and maybe their non-HDL, I think if it's greater than 5 or there about and if we get a family history of premature heart attacks or coronary heart disease then we refer." (A11, general practitioner) "…sort of screening patients over 40 and obviously that's just picking out the ones that erm, they've got significant family history that makes you think like that." (A13, prescribing nurse)	Healthcare providers indicated that they relied on the recording of patient history to identify HeFH. However, quantitative results suggest that these patient attributes are not frequently recorded. The potential implication is that under-diagnosis of HeFH in primary care could partially be explained by insufficiencies in	Contradiction

		relevant patient records.	

6.2.4 Answering the research questions

In the context of the current management of HeFH, the qualitative findings highlighted insufficiencies in the identification and referral of HeFH patients to secondary care. They also indicated potential negative effects of strict guidelines and organisational prescription policies in delaying or preventing PCSK9 inhibitor prescription.

The quantitative results suggested low rates of recording of HeFH patient attributes. This finding was supported by qualitative accounts which associated inadequate recording of patient information to delayed identification of HeFH patients in primary are and delayed prescription of PCKS9 inhibitors in secondary care.

The overall result of the integration was a set of themes that depicted barriers to PCSK9 inhibitor use at various points of the HeFH patient treatment journey. Figure 6.3 below shows an illustration of this journey with the emerging barriers highlighted at the typical points that they were encountered.

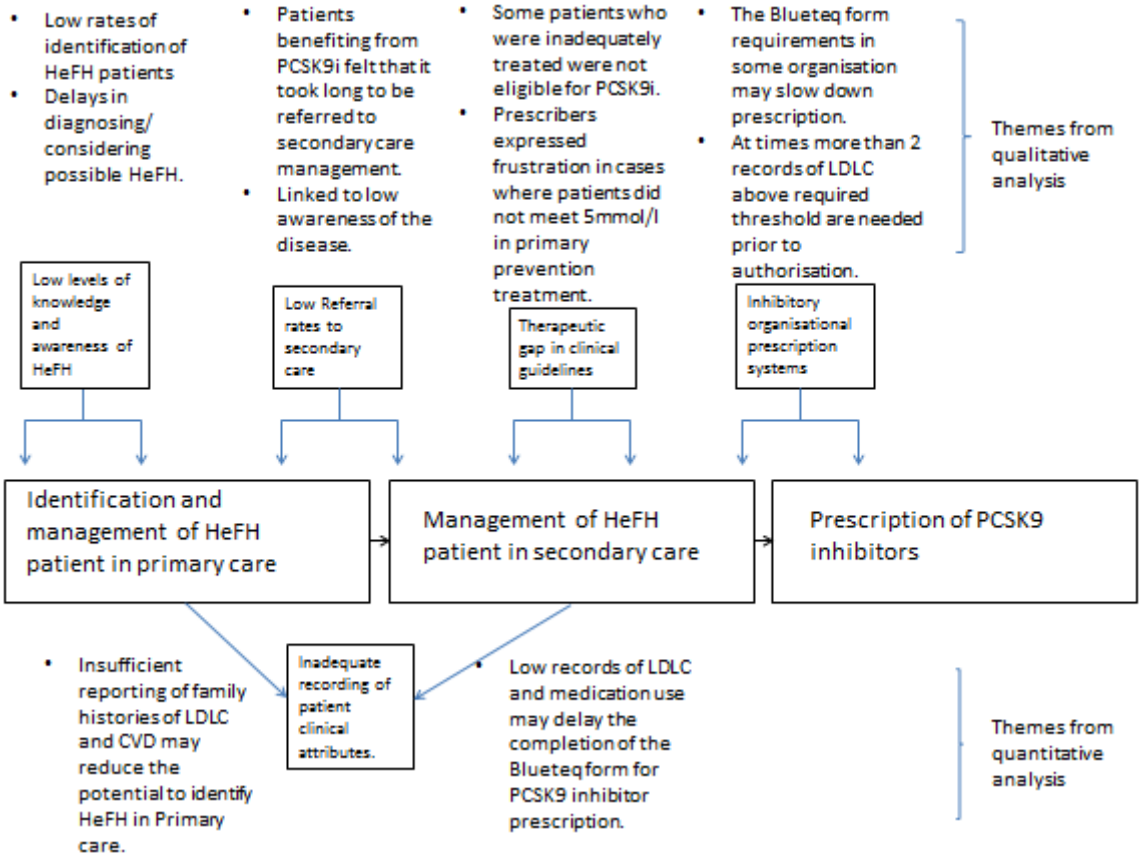

Figure 6.3 HeFH patient journey towards PCSK9 inhibitor use highlighting the current study's emerging themes

6.3 Discussion of emerging themes

This section discusses the themes emerging from both the quantitative and qualitative analyses as shown in figure 6.3 above.

6.3.1 Insufficient recording of HeFH patient clinical attributes

The main finding was that inadequate recording of patient clinical attributes was an influencing factor to the prescription of PCSK9 inhibitors. Stakeholder (lipid consultants and general practitioners) accounts revealed that the unavailability of LDLC records delayed the prescription of PCSK9 inhibitors. Similarly, quantitative analysis showed that patient data was seldom recorded with slightly more than half of the study cohort having at least 1 record of LDLC. The result suggested that a large proportion of HeFH patients could potentially experience delays during the initiation of PCSK9 inhibitors.

The effect of the unavailability of patient clinical records on PCSK9 inhibitor prescription emerged from organisational policies for prescription in the current study. In order to monitor usage of costly medication (such as PCSK9 inhibitors), the Blueteq prescription system is used to regulate the prescription process. Based on interviewee accounts, the Blueteq form for PCSK9 inhibitors includes as part of its requirements, evidence of LDLC records above 5 mmol/l (in primary prevention treatment) and 3.5mmol/l(in secondary prevention treatment), a record of the use of other lipid lowering agents, reasons for unsuccessful treatment. These requirements are always in adherence to NICE LDLC targets and recommendations. However, some CCGs, for example, require two or three LDLC readings above the stipulated thresholds. Although this requirement technically adhered to NICE guidelines, clinicians felt that the additional conditions only served to lengthen the approval process. The addition of these steps to the prescription process appears to act as a barrier to medication provision. This may suggest a potential need for a re-evaluation of how CCGs interpret and implement NICE guidelines on PCSK9 inhibitors as this is not a standard process across NHS trusts.

The reasons for the inadequate documentation of HeFH patient clinical attributes are not addressed in literature; two key reasons for this emerged from the interviewee accounts. Firstly, primary care physicians (GPs and nurses) reported that patients did not actively engage with the treatment process in cases where a cardiovascular disease (CVD) event had not been observed. This meant that patient records and tests were conducted unsystematically as they were dependent on a limited number of patient visits. Secondly, healthcare providers (GPs, nurses, consultants) reported that the identification of HeFH patients was opportunistic rather than through cascade screening. This resulted in cases of HeFH patients being identified with minimal relevant medical histories prior to the prescription of PCSK9 inhibitors.

6.3.2 Therapeutic gap in the provision of PCSK9 inhibitors

Corroborating results between quantitative and qualitative analyses suggested that a therapeutic gap existed in the management of HeFH patients using PCSK9 inhibitors. This was attributed to the absolute targets of LDLC that were stipulated by NICE technology appraisals (TA) 393 and 394 (for alirocumab and evolocumab respectively) for the initiation of PCSK9 inhibitors. Specialist consultants reported that some HeFH patients who were not adequately treated did not meet the LDLC thresholds set by guidelines.

The evidence base for PCSK9 inhibitors does not appear to address these potential gaps in the management of PCSK9 inhibitors extensively. Orringer (2019) discussed the extent to which lipid management guidelines were useful to clinicians. They found that updated guidelines offered an effective evidence base for the management of HeFH. The paper reported the existence of therapeutic gaps in guidelines and recommended the use of literature to support decision making in such instances. The current study identified such a gap in the guidelines in the use of PCSK9 inhibitors.

Specialist consultants reported that some patients had to be managed on less effective lipid lowering agents due to the high LDLC cut-off for PCSK9 inhibitor initiation in guidelines. The specialists in these cases deemed the patient to require PCSK9 inhibitors based on clinical judgement of their treatment history but felt inhibited by the need to comply with NICE guidance. One specialist consultant in this study described the process as a ‘post-code lottery’ for patients in these cases, as patients had to ‘earn’ the right to PCSK9 inhibitor use by waiting until their LDLC level rose to the required levels. These patients expressed frustration as some of them had to wait for a year or more before they could receive the medication.

Suggestions to rectify the matter from clinicians revolved around the lowering of LDLC thresholds, and the general consensus was that the LDLC cut-off points were

high. The explanation for this was that NICE guidelines, though evidence based, also account for cost-effectiveness of medication. This could lead to initial high thresholds for medication eligibility while it the medications are costly. The clinicians in this study understood this; however, they expressed frustration at the lack of options for patients they deemed to require PCSK9 inhibitors. If medication costs are lowered in the future, the requirements for the use of PCSK9 inhibitors may be less restrictive.

6.3.3 Inadequate level of knowledge amongst stakeholders

Both primary care and secondary care health professionals felt that the level of knowledge of HeFH was low, especially in primary care. Consultants and nurses in secondary care admitted that although knowledge levels in secondary care were not ideal, they felt that it was improving. Interviewee accounts included cases of primary care practitioners (GPs and nurses) not being aware of the existence of PCSK9 inhibitors. Such cases were also witnessed by the primary researcher during the conduct of the interviews. Furthermore, a GP admitted to not knowing how serious HeFH was, and the fact that more was expected from primary care with regard to the identification of patients.

"…when they talked about the lipid lecture, that I mentioned, they were not quite emphasising on the severity or the importance of this topic. Now having spoken to you it looks like it needs to be made aware more prominently to primary care, when to refer and what to do so this is quite a serious topic, I think more awareness needs to be created…" (A14, GP)

Cardiologists appeared to be aware of PCSK9 inhibitors and indicated that they would refer patients whose LDLC levels were uncontrolled so that they are considered for the medication. The opinion of consultants in lipid clinics suggested that cardiologist referral rates for HeFH were historically low, but had started to increase. Lipid specialists attributed this increase to the introduction of PCSK9 inhibitors, and the fact that it could only be prescribed at the lipid clinic. This view was

verified by a one cardiologist who stated that they referred HeFH or potential HeFH patients to the lipid clinics only when they felt that they required PCSK9 inhibitors.

GPs and nurses relied on QRISK and general CVD in their encounters with HeFH or potential HeFH patients, some GPs indicated that they would suspect HeFH if LDLC levels were above 7.5mmol/l. Physicians in primary care have the role of identifying HeFH patients from the general public. The use of these tools without HeFH specific guidelines could potentially mask the existence of HeFH. In such cases, HeFH would be managed as normal hypercholesterolemia. Interviews with primary clinicians identified that some physicians mistook HeFH for normal hypercholesterolemia. This result suggested that clinicians required more knowledge on HeFH and PCSK9 inhibitors, particularly clinicians in primary care.

In this study, most HeFH patients on PCSK9 inhibitors were found to be aware of the condition and kept up to date with their LDLC management. Primary care clinicians reported that some patients did not take the disease seriously and were influenced by negative media reports on statin use.

"…I was talking in the pub and me mate's said, he doesn't take them anymore cause he gets this, this and this, so I thought I'm going to do that, so they listen a lot to the media and also what their friends think." (A13, prescribing nurse)

This finding was in agreement with past studies on HeFH patients that found varying levels of engagement in HeFH patients. Watts et al. (2016) suggested that the opinions of HeFH patients on the controllability of the disease and the efficacy of pharmacological therapies were a potential influencing factor of engagement. The current study agrees to some degree with Watts et al. (2016); however, it was found that patients were serious about the disease if they had experienced a CVD event. Some patients felt that they were not informed about the disease severity; they also felt that HeFH was diagnosed by primary care clinicians when it was too late. The

patients' perceptions echo the finding on the level of knowledge of clinicians. The overall results on level of knowledge amongst stakeholders in the care of HeFH suggested that both clinician (in primary care) and patients needed to be educated about the condition and its management.

6.3.4 Low levels of referral of HeFH for secondary care treatment

HeFH patients are under diagnosed and undertreated (Nordestgaard et al., 2013). The current study added to this by identifying that once identified in primary care only a relatively small number of HeFH patients were referred for secondary care treatment and potentially PCSK9 inhibitor initiation. Quantitative data revealed that a majority of HeFH patients in primary care did not meet therapeutic LDLC targets following statin therapy and were potential candidates for referral for specialist management. Through the qualitative interviews, clinicians in secondary care confirmed this finding; the overall feeling was that referral rates for HeFH patients were low. Secondary care clinicians felt that the potential reason for this was the possible management of HeFH as normal hypercholesterolemia; primary care clinicians did not oppose the viewpoint.

"in terms of the knowledge I would probably think some people(GPs) might sort of confuse it with ordinary polygenic hyperlipidaemia and just 'Oh it's raised cholesterol, all I need to do is just do a QRISK and start statin and invite the patient to see the nurse and discuss about healthy lifestyle advice." (A11, GP)

The management of HeFH as normal hypercholesterolemia meant that HeFH patients were treated with lipid lowering agents (mainly statins) as stipulated in CVD prevention treatment guidelines. No further measures were taken to ensure that the disease was not genetic (HeFH). This finding is consistent with studies such as O'Brien et al. (2014) and O'Brien et al (2015) which found that only 42% of 1295 adult familial hypercholesterolemia patients were receiving the guideline

recommended high intensity lipid lowering therapy. Similarly, De Backer et al. (2015), a study of 24 European countries, found that 45% of FH patients with a recorded cardiac event were not receiving high intensity statin treatment. The quantitative phase of the current study found that 36% (1492) of 4116 HeFH patients were not receiving any form of lipid lowering. These results suggested that HeFH patients were not effectively treated despite a formal diagnosis of the condition. Subsequently, lower levels of referral were observed.

Low rates of referral could be attributed to several reasons; a lack of awareness of the disease as discussed in section 6.3.3 above, poor identification of potential HeFH patients, and non-adherence to clinical guidelines among other reasons. For example, a contradiction was found between the qualitative accounts of clinicians and CPRD quantitative data that could negatively affect the identification of HeFH patients. GPs and nurses in primary care relied on patient clinical histories for the identification of HeFH patients; however, quantitative data revealed that these records were limited. This suggested that lack of prior patients records could be a potential hindrance to the identification of HeFH. Without the records of family history CVD or HeFH, a physician who was aware of HeFH identification criteria had a limited chance of suspecting HeFH in cases with elevated but borderline values of LDLC. These cases would therefore be treated as normal hypercholesterolemia. These findings implied that low referral rates to secondary were caused by varying reasons

A GP suggested that nurses could improve the recording of family histories for HeFH patients because they conducted NHS health checks. However, they felt that all clinicians in primary care had a role in recording of medical histories to facilitate identification of HeFH.

"I think where the diagnosis of FH comes from if there's that family history and raised cholesterol… I think because there's this scheme that is called NHS Health checks between the age of 40 and 45, when they come to see the nurse it actually is documented. So I think nurses should be a bit more proactive and find out if truly there's that family history under the age of 60, document it…" (A11, GP)

6.3.5 Facilitators to the use of PCSK9 inhibitors

The final theme constituted the factors that were perceived as facilitators to the use of PCSK9 inhibitors. One factor that was independent of the stakeholders was the influence of pharmaceutical companies. Secondary care clinicians reported that assistance from pharmaceutical companies provided access to HeFH patients. This translated into increased prescription of PCSK9 inhibitors as eligible patients were identified. A research nurse also indicated that provision of training helped to facilitate the process of prescribing PCSK9 inhibitors. Negative views on statins were also found to be a potential facilitator for the use of PCSK9 inhibitors. Clinicians reported patients asking to be taken off statins once their LDLC levels were reduced by PCSK9 inhibitors.

"A lot of people, when they go on the PCSK9 inhibitors, ask if they can then reduce or come off the statin. So, we just have to explain to them, that you know, the studies show that taking them both together is of greater benefit than just taking one or the other…" (A4, research nurse)

One patient noted that they would have preferred to have statins removed from their treatment regimen but had to take them as their condition deteriorated.

"…I think after having a heart and a bypass you seem to make it a bit more tolerant, don't you, you know, like [laughs]. Prevention is better than cure they say but after that really I just go along with it and, to be fair, sometimes if I think they're a bit much I'll miss the odd day out of the statin and then take them where last time I just thought I can't, that I can't handle this, and then I was back to the doctors trying to sort things out." (A12, patient)

Finally, opposite to the theme on lack of awareness, when patients understood the potential severity of the disease in causing cardiac events, their level of engagement with the HeFH treatment pathway was improved. Such patients expressed frustration when PCSK9 inhibitor prescription was delayed while their LDLC levels were still uncontrolled.

6.3.6 Summary of discussion

The Blueteq prescription system was perceived to be a barrier to prescription in cases where multiple records of LDLC measurements that met guideline stipulated targets for PCSK9 inhibitor eligibility were required. Prescribers also stated that current NICE guidelines for the provision of PCSK9 inhibitors were restrictive in some cases. Some patients who were deemed to require PCSK9 inhibitors by lipid consultants based on clinical judgement and history of treatment did not meet the LDLC thresholds for eligibility. Other themes included 'inadequate level of knowledge amongst stakeholders' and 'insufficient patient clinical records'. Both primary care and secondary care practitioners felt that knowledge on HeFH could be improved, especially among primary care clinicians.

"I think especially in primary care in GP surgeries; they don't have as much knowledge of FH and PCSK9…" (A4, research nurse)

"in terms of the knowledge I would probably think some people(GPs) might sort of confuse it with ordinary polygenic hyperlipidaemia and just 'Oh it's raised cholesterol, all I need to do is just do a QRISK and start…" (A11, GP)

Inadequate levels of knowledge and insufficient patient clinical records led to low levels of referral of HeFH patients' to secondary care; preventing consideration for PCSK9 inhibitor use in patients who were not sufficiently treated. Insufficient patient clinical records were found to slow down the pace of PCSK9 inhibitor prescription as these patient data were required prior to prescription approval. The rate of HeFH

patient identification was also reduced by insufficient patient records because clinical attributes such as family history of CVD and HeFH were required to make a diagnosis of HeFH.

6.4 Significance and limitations of the study

6.4.1 Significance of the study

The main significance of this study exists in the identification and delineation of the treatment journey for the 'difficult-to-treat' group of HeFH patients that would require PCSK9 inhibitors. The study also identified specific factors that acted as barriers or facilitators to PCSK9 inhibitor use. In particular, LDLC measurements and records were found to be an important determining factor in the prescription of PCSK9 inhibitors. This provides knowledge on the under-researched area of barriers and facilitators to PCSK9 inhibitor use in the UK and could serve to guide further research.

New findings included the barriers associated with the Blueteq prescription system, and the potential restrictiveness of NICE guidelines. The themes related to low referral rates of HeFH patients to secondary (low level of awareness of HeFH and PCSK9 inhibitors, and inadequate recording of clinical attributes) have been shown to affect HeFH management in past literature. This study confirmed that these factors remain relevant to the provision of PCSK9 inhibitors and described how they affected PCSK9 inhibitor use. The facilitators of PCSK9 inhibitor use also provide insight on the improvement of patient awareness and knowledge of HeFH and PCSK9 inhibitors.

The current study presents a potential contribution to methodological advancements in the study of PCSK9 inhibitor use as no other studies were found to use both quantitative and qualitative methods on the topic. The availability of (or lack of) patient clinical records had been identified as a potential hindrance to the prescription

of PCSK9 inhibitors elsewhere (Cohen et al., 2017). This did not appear to be relevant in the use of PCSK9 inhibitors in the United Kingdom prior to the study. This study showed that value can be drawn from using multiple methods approaches to study barriers to the use of PCSK9 inhibitors. The assessment of the views of multiple stakeholders involved in the use of PCSK9 inhibitors contributed to the development of a treatment path for HeFH patients by corroborating participant accounts. Other studies have previously evaluated the interaction of stakeholders in order to assess the factors influencing healthcare provision (e.g. Raaijmakers et al., 2013); however, no body of work has focused on identifying specific barriers and facilitators to PCSK9 inhibitor use in the UK using this method.

Finally, the current study also provided insight into predictive modelling for a rare disease. In cases where the management of such diseases is difficult the collection of patient data can be lacking. This could possibly be because most patients with rare diseases are treated on a case by case basis in secondary care, and there are usually limited clinical guidelines about disease management. However, the present study showed the potential of continuous feasibility assessments on rare disease data in order to determine whether useful insights can be developed. Similar to the development of diagnostic predictive models in HeFH such as Weng et al. (2015), it may be possible to gradually extend these analyses to other rare diseases and their associated databases.

6.4.2 Limitations of the study

The quantitative sample had a sample size that produced enough power for multiple logistic regression analysis. However, the recording of patient clinical attributes was found to be minimal (~48 of patients did not have an LDLC measurement recorded); this had the potential of limiting the functionality of the developed predictive models.

Admittedly, this finding was relevant to the overall research question; and echoed studies in other countries that identified similarly low levels of patient records (Weng et al. 2015, Cohen et al. 2017). Nevertheless, this showed that CPRD data may not be appropriate for modelling PCSK9 eligibility.

A potential limitation was that the views of pharmacists were not captured in the present study. Lipid consultants reported that the pharmacist did not have a clear role in the management of HeFH patients that were referred to secondary for PCSK9 inhibitor provision. Once PCSK9 inhibitors were prescribed, secondary care nurses provided training on the use of injections and further prescriptions were placed on repeat delivery systems with the exception being when the patient was required to attend the clinic. In the patient journey of receiving statin treatment from the GP practice to referral to secondary care for PCSK9 inhibitor use; it was unclear where the pharmacist was involved in a manner that would have an effect on PCSK9 inhibitor prescription. When asked about pharmacists, consultants strongly expressed that PCSK9 inhibitor use needed to be left to experts. It was indicated that pharmacists were not used in the provision of PCSK9 inhibitors but had been involved in ensuring that prescription had no ill effect (Discussion – chapter 5, section 5.5.3.4.2).

"No, I don't think they actually have a role here because this is actually a clinical decision. It's based on NICE. It's an expensive drug. It's a new drug and even the primary care are not allowed to use it. The PCSK9 is specifically secondary care and that's the way it should be. When it comes to other treatments, yes and no. I've seen places where statins are used by pharmacists. By and large, it's okay but a lot of what I hear is a load of rubbish." (A3, consultant)

"We haven't used them in that way, we've mainly used them to discuss particularly when we started to prescribe PCSK9s and helped us with making sure that we have identified the

correct patients and the system for prescribing which is obviously because we can't, normally if we prescribe, if I prescribe a statin, it's the GP that does the prescribing." (A5, consultant)

The typical lipid clinic was small and consisted of a lipid consultant that ran the clinic a number of times a week. The consultant was assisted by nurses who worked across a few departments. In larger trusts, lipid specialist nurses assisted in the clinic and also run research activity. This could indicate why pharmacists were not part of the clinics. Nevertheless, the inclusion of pharmacists may have served to add their opinions on how they could contribute to the use of PCSK9 inhibitors.

6.5 Implications for the provision of PCSK9 inhibitors

It was found that lack of awareness of PCSK9 inhibitors produced varying effects alongside the reduced knowledge on HeFH. Clinicians in primary care appeared to focus on cardiovascular disease CVD management (using QRISK) when hypercholesterolemia was encountered. This increased the likelihood of HeFH being ignored. The condition was suspected when a CVD event was experienced or due to markedly elevated LDLC levels. The resultant effect was delayed referral to lipid specialists for PCSK9 inhibitor consideration. The general implication outlined by GPs was that it was necessary to improve stakeholder knowledge through the use of healthcare campaigns or educational training programs.

Due to the low prevalence rate of the disease however, awareness campaigns alone may not be sufficient to increase patient referral. The use of a case identification tool implemented into the management system for general hypercholesterolemia or CVD management could help to identify patients who potentially require referral. Similarly, a computer program that could highlight potential HeFH cases could act as an automatic system of disease identification. For instance, Weng et al. (2015) developed a successful detection tool for HeFH based on presenting patient clinical characteristic and suggested integration into a computer system. The finding in the

quantitative phase of this study showed that further research on modelling for PCSK9 inhibitor eligibility may be possible.

Another key finding was that the Blueteq system thresholds for the indication of PCSK9 inhibitors proved difficult to achieve for some patients. These thresholds were determined by NICE guidelines and based on cost-effectiveness estimations. However, some CCGs asked for 2 or 3 LDLC readings above the threshold for PCSK9 inhibitor indication while other only required 1. When patients had not achieved these multiple readings, they were deemed ineligible for PCSK9 inhibitor use. The process of repeatedly taking LDLC measurements to meet these criteria took up to 9 months according to some patients. Although CCG requirements are subject to change, it may be necessary to review these requirements for PCSK9 inhibitor use and the possible effect they could have in delaying treatment.

Low recording rates of HeFH clinical attributes were found to affect the provision of PCSK9 inhibitors in two main ways. The identification of HeFH patients in primary care was hindered by a lack of recording of family histories of the disease or of elevated cholesterol. While in secondary care, prescription requirements demanded evidence of patient data prior to prescription of PCSK9 inhibitors. The overall recommendation was, of course, to increase the rate of recording. However, the root cause of the low levels of HeFH patient data reverts back to the discussion on knowledge and awareness.

6.6 Recommendations for future research

Blueteq prescription systems were found to vary between hospitals. Clinical commissioning groups (CCG) set different policies for the prescription of PCSK9 inhibitors as long as these policies were within NICE guidelines. A recommendation for further research would be a study on the variations in Blueteq requirements for

PCSK9 inhibitors use in different NHS trusts, and how the requirements affected the use of the medication.

Secondly, lipid specialists felt that the current NICE LDLC threshold for PCSK9 inhibitor prescription was too high and acted as a barrier to medication use in some cases. Some patients who were deemed to be inadequately treated could not meet these targets and were therefore not eligible for the medication. An assessment of the effect of these hard targets could prove to reduce the number of cases where patients in need of this new class of medication do not meet the necessary requirements.

In assessing the level of impact that HeFH patient clinical attributes had on the prescription of PCSK9 inhibitors, prediction models were developed. Although the results indicated that the model functionality could not be considered successful using CPRD data, the model showed some potential. This is especially so because the recording of LDLC was found to be low, while clinical attributes such as lipoprotein A (LpA) that have been found to have a link to heart disease and LDLC were not routinely monitored. Further research using other datasets (such as the SAFEHEART study's longitudinal data) may therefore be possible on the modelling for PCSK9 inhibitor eligibility.

6.7 Conclusion

This study focused on exploring the potential factors that could influence the prescription of PCSK9 inhibitors. These were presented as themes that reflected potential barriers and facilitators to the use of PCSK9 inhibitors.

The main finding was that LDLC records were important in the prescription of PCSK9 inhibitors. Both the quantitative data and qualitative accounts found that the recording of HeFH patient clinical attributes was inadequate. In the CPRD dataset, only 52% of HeFH patients had at least 1 LDLC measurement on record. From the qualitative

interviews, it was found that the Blueteq system was used in the approval process for PCSK9 inhibitors. Requirements for PCSK9 inhibitor prescription within Blueteq varied between different organisations with some CCGs requiring 2 or 3 LDLC readings above the recommended threshold for PCSK9 inhibitor indication, while others requested 1. The resultant effect was that some patients who were deemed to require PCSK9 inhibitors by lipid consultants would have to attain multiple readings of LDLC above the required threshold before the medication was approved. Patient accounts indicated that the process of taking repeated LDLC measurements took up to 9 months before PCSK9 inhibitors were approved.

Similarly, evidence from both the quantitative data and qualitative accounts showed that a number of patients who did not achieve 50% LDLC reduction did not meet the 5mmol/l LDLC threshold for PCSK9 inhibitor eligibility. The quantitative data found that ~18% of patients who recorded no LDLC reduction following the usage of lipid lowering medication for a year were not eligible for PCSK9 inhibitor eligibility. Lipid consultants expressed similar concerns and maintained that the LDLC threshold for primary prevention treatment in particular was high and strict.

In primary care, low levels of knowledge on HeFH and PCSK9 inhibitors among clinicians were associated with low referral rates of HeFH patients to secondary care. HCPs in both primary and secondary care agreed that primary care clinicians were less knowledgeable about HeFH than secondary care clinicians. In particular, there was concern that HeFH was potentially treated as hypercholesterolemia or some other forms of polygenic hyperlipidaemia by primary care clinicians. This was expressed as a reliance on the use of the QRISK tool. As the QRISK tool did not account for all risk factors associated with HeFH such as family history of HeFH, the scores could potentially mask HeFH and the elevated levels of cholesterol would be

treated with statins. This had the effect of delaying case identification and referral to secondary care for patients who would eventually require PCSK9 inhibitors.

Finally, the factors that facilitated PCSK9 inhibitor use revolved around the provision of support from pharmaceutical companies, the understanding of disease severity by patients and the negative views on the use of statins by patients. In one case, a lipid consultant confirmed that the use of a specific PCSK9 inhibitor agent was based on interactions with the pharmaceutical companies. In this case, the pharmaceutical company was providing training to nurses on the use of injectable devices in order to improve their capacity for educating patients. Negative views on statins (based on information from the media and peers) and the understanding of disease severity improved the patient's acceptance of the injection formulation of PCSK9 inhibitors. Achievement of LDLC reduction was also indicated as a reason that patients accepted the use of PCSK9 inhibitors.

Overall, the study was able to identify specific barriers and facilitators to the use of PCSK9 inhibitors. The study also highlighted the complexity of the treatment pathway for the difficult-to-treat HeFH patient, who would end up requiring PCSK9 inhibitors. This information has the potential to guide improvements in the care of the disease, and the use of this new class of medication.

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Appendices

Appendix 1 **Consent form**

Consent Form

Title of Project: Potential challenges and incentives to the uptake of PCSK9 inhibitors.

Name of Principal Investigator: Prof Stephen Chapman

Please initial box

1	I confirm that I have read and understand the information sheet (version 1.1, 07/06/2018) for the above study and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time.	☐
3	I agree to take part in this study, which involves an interview that will last about 30 minutes.	☐
4	I agree to the interview being audio recorded and transcribed, and I agree for anonymised short quotes from it to be used.	☐
5	I understand that data collected about me during this study will be anonymised before it is analysed or published.	☐
6	I understand that I can withdraw the information I have provided before it is transcribed (anticipated November 2018). After this period the data will be anonymised and it will not be traceable to participants.	☐
7	I understand that relevant sections of my data collected during the study, may be looked at by individuals from Keele University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 copy for participant, 1 copy for researcher

Appendix 2 **Consent to contact form**

CONSENT TO CONTACT FORM

Title of Project: Potential challenges and incentives to the uptake of PCSK9 inhibitors.

Name and contact details of researcher: Myron Odingo, School of Pharmacy, Keele University, Tel: 01782 734788, m.o.odingo@keele.ac.uk

Please initial box if you agree with the statement

1- I agree that the researcher can contact me to discuss my participation in the above study using my contact details below. ☐

Name of participant _____ Date _____ Signature _____

Telephone:_____ **Mobile:**_____

Email:_____

Preferred method of contact: (Please tick the preferred method)

? **Home telephone** ? **Mobile** ? **Email**

Preferred time to be contacted: (Please tick the preferred time)

? **Morning** ? **Afternoon** ? **Evening**

Many thanks for expressing interest in this study. You will be contacted, as per your stated preferences within 24-48 hours to discuss the research further. As previously explained, there is no obligation to commit to the study at this time and whether you participate or not, this will not affect the care or treatment you receive under normal routine care.

Appendix 3 Participant information sheet

Participant Information Sheet

Study title: Potential challenges and incentives to the uptake of PCSK9 inhibitors.

Invitation

You are being invited to take part in a research study. You do not have to take part; but before you decide, it is important for you to understand why the research study is being done and what it will involve.

Please take time to read the following information carefully and discuss it with others if you wish. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

The aim of this study is to explore the views and opinions of healthcare professionals (for example; consultants, nurses and pharmacists), patients and healthcare commissioners on a new type of medicine (called "PCSK 9 inhibitors") for the treatment of high cholesterol.

This new type of medicine can be used to treat a complicated form of high cholesterol called "familial hypercholesterolemia" (FH). It can also be used in cases where patients with high cholesterol are intolerant to currently available medicines; or when currently available medicines do not offer sufficient treatment.

The intention of the study is to identify the role that this new type of medicine is perceived to play in treating people with high cholesterol. The study will also identify potential barriers and facilitators to the use of these medicines in NHS hospital Trusts. Additionally, the study will explore the general problems that healthcare professionals, patients and healthcare commissioners face in the treatment of high cholesterol.

Why have I been chosen?

We would like to interview you to discuss your opinions and experiences on the current treatments of high cholesterol. We believe that this can help to understand the positive and negative issues that may be associated with medicines use and the treatment of high cholesterol in general. This would help to identify the role that a new type of medicine would have and explore the areas that need improvement in the provision of care for high cholesterol.

Do I have to take part?

No. You are free to decide whether you wish to take part or not. There are no consequences if you do not wish to take part.

If you do decide to take part, you will be asked to fill in and sign two consent forms, (one for yourself and one for the research team) and a 'consent to contact' form. You are free to withdraw from the study at any time and without giving reasons. In the case that you withdraw, the information that you provide will be used if sufficient; otherwise, the data will be securely destroyed. You can request for your data to be withdrawn from the study before the completion of transcription (anticipated to be November 2018). After this date, all data will be anonymous.

Appendix 4 Letter of invitation - patients

Myron Odingo
School of Pharmacy
Keele University, Staffordshire, ST5 5BG, United Kingdom
Telephone: 01782 734788
Email: m.o.odingo@keele.ac.uk

Title of Project: Potential challenges and incentives to the uptake of a new medicine for high cholesterol (PCSK9 inhibitors).

We would like to invite you to participate in an interview on a new type of medicine for the treatment of high cholesterol (PCSK9 inhibitors) as part of research by Keele University.

We are interested in interviewing you in order to explore your views and opinions on the current medicines you are taking, any positive or negative experiences you went through in the process of obtaining treatment and what the introduction of a new type of medicine (PCSK 9 inhibitors) can do to help the process.

The information from your interview will be used to study the potential challenges and incentives to the treatment of high cholesterol. The interview will be conducted by Myron Odingo, a research student from Keele University. The interview will take approximately 30 minutes.

The interviews will be audio-recorded and transcribed. The information you provide will be coded so that they cannot be traced back to the participant by anyone not in the research team. After the transcription, the audio recordings and any linking files will be destroyed. No individual participants will therefore be identified in any way in any report arising from the interview.

If you're interested in participating in this research or have any queries about the project please contact the researcher below so that we can arrange a mutually convenient time and location to conduct the interview.

Yours sincerely,

Myron Odingo.

Appendix 5 Letter of invitation prescribers

Myron Odingo
Room 0.24, Hornbeam, School of Pharmacy
Keele University, Staffordshire, ST5 5BG, United Kingdom
Telephone: 01782 734788
Email: m.o.odingo@keele.ac.uk

Title of Project: Potential challenges and incentives to the uptake of PCSK9 inhibitors.

We would like to invite you to participate in an interview on a new type of medicine for the treatment of high cholesterol (PCSK9 inhibitors) as part of research by Keele University.

Given your role and experience as a prescriber for cholesterol medication, we are interested in exploring your views and opinions on the use of this new type of medicine. We will discuss the treatment and management of high cholesterol and related conditions. We will also discuss your role in the process of identification and diagnosis of such cases and whether the systems and services put in place to assist this process are effective or not.

The information from your interview will be used to study the potential challenges and incentives to the treatment of high cholesterol. The interview will be conducted by Myron Odingo, a research student from Keele University. The interview will take approximately 30 minutes.

The interviews will be audio-recorded and transcribed. The information you provide will be coded so that they cannot be traced back to the participant by anyone not in the research team. After the transcription, the audio recordings and any linking files will be destroyed. No individual participants will therefore be identified in any way in any report arising from the interview.

If you're interested in participating in this research or have any queries about the project please contact the researcher below so that we can arrange a mutually convenient time and location to conduct the interview.

Yours sincerely,

Myron Odingo.

Appendix 6 Topic guide - patients

Topic Guide – Potential challenges and incentives to the uptake of PCSK9 inhibitors.

THEMES TO COVER-TOPIC GUIDE

1. **Introduction.**
    a. Introduction (researcher)
    b. Introduce research
    c. Explain: confidentiality, recording of interview (re-confirm consent when the recorder is running), length (about an hour or two) and nature of discussion (specific topics to address, but conversational in style), reporting and data storage issues
    d. Any questions?

2. **Participant background**
    Aim: To introduce participant and set the context for proceeding discussion.
    a. Name of their condition
    b. How long they have had it
    c. Whether thy have been taking medication for this

3. **Main question.** Please describe the treatment journey you had before receiving treatment?
    Prompts – screening, diagnosis, feelings, effect on life

4. **Main question.** What were your experiences through this journey? Both good and bad.
    Prompts - Timing of diagnosis, provision of medicine, efficacy of medicine, family, friends

Appendix 7 Topic guide - prescribers

Topic Guide – Potential challenges and incentives to the uptake of PCSK9 inhibitors.

THEMES TO COVER-TOPIC GUIDE

1. **Introduction.**
    a. Introduction (researcher)
    b. Introduce research
    c. Explain: confidentiality, recording of interview (re-confirm consent when the recorder is running), length (about an hour or two) and nature of discussion (specific topics to address, but conversational in style), reporting and data storage issues
    d. Any questions?

2. **Participant background**
    Aim: To introduce participant and set the context for proceeding discussion.
    a. Current role/ position / job title
    b. Time in current position
    c. Roles and responsibilities within lipid treatment / experience with lipid medication for patients
    d. Level of personal contact with lipid management therapies, diagnosis services, CDSS??

3. **Main question.** How would you describe the current treatment journey for high cholesterol and related diseases especially familial hypercholesterolemia?
    Prompts: screening, diagnosis, treatment, your role.

4. **Main question.** Could you please discuss any pros and cons of current medications?
    Clarifying questions: effectiveness, side-effects, importance of lifestyle advice for patients with high cholesterol, can anything be done to improve...?

Appendix 8 **NHS rec ethics approval**

NHS
Health Research Authority

North West - Greater Manchester South Research Ethics Committee
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

05 June 2018

Prof Stephen Chapman
Hornbeam 3.0.6
Keele University
Newcastle Under-Lyme
ST5 5BG

Dear Prof Chapman

Study title:	**A study of the views and perceptions of key stakeholders (consultants, prescribing nurses, pharmacists, healthcare commissioners, patients) on the use of Proprotein Convertase Subtilisin/Kexin Type-9 (PCSK9) inhibitors**
REC reference:	**18/NW/0386**
Protocol number:	**Not applicable**
IRAS project ID:	**243411**

The Proportionate Review Sub-committee of the North West - Greater Manchester South Research Ethics Committee reviewed the above application on 28 May 2018.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited

Appendix 9 **HRA approval**

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Stephen Chapman
Hornbeam 3.0.6
Keele University
Newcastle Under-Lyme
ST5 5BG

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

18 June 2018

Dear Professor Chapman

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A study of the views and perceptions of key stakeholders (consultants, prescribing nurses, pharmacists, healthcare commissioners, patients) on the use of Proprotein Convertase Subtilisin/Kexin Type-9 (PCSK9) inhibitors**
IRAS project ID:	**243411**
Protocol number:	**Not applicable**
REC reference:	**18/NW/0386**
Sponsor	**Keele University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

Appendix 10 Search words

Population	Intervention	Comparison	Outcome
familial hypercholesterolaemia	PCSK9 inhibitors	perception*	high cholesterol
FH	proprotein convertase subtilisin kexin	detect*	low density lipoprotein cholesterol
heterozygous familial hypercholesterolemia	alirocumab	opinion*	LDL*
heFH	evolocumab	determin*	high density lipoprotein cholesterol
familial hypercholesterolemia	kexin 9 inhibitors	screen*	HDL*
	proprotein convertase subtilisin/kexin	identif*	cardiovascular
	PCSK9'	affect*	cholesterol
		influen*	
		factor*	
		policy*	
		barrier*	
		guideline*	
S1	S2	S3	S4
62,313	4,832	19,281,778	1,341,421
S1 AND S2	1,118		
S2 AND S3	2,824		
S2 AND S4	4,145		
S1 AND S2 AND S3	749		
S1 AND S2 AND S3 AND S4	742		

Appendix 11 List of codes

Barriers to PCSK9 inhibitor adoption	0	0
Experiences and opinions on medication	0	0
Medication	0	0
Patient in denial of HeFH	2	2
Patient journey of receving medication	13	51
Knowledge of stakeholders	0	0
Clinicians	0	0
Ignorance of ldlc above 5 due to lack of other symptoms	2	4
Knowledge of clinicians on FH	8	42
Knowledge of FH identification pathway	6	11
Specialists' approach to FH patients	3	6
Patients	0	0
Opinions on patient diet and effect on FH	3	4
Patient knowledge on HeFH	7	17
Organisational factors	0	0
Organisational factors that may affect PCSK9 use	5	8
Other healthcare providers involvement in FH treatment	9	33
Patient perceptions on secondary care	2	5
Why implementation of new services is slow	4	9
The effect of clinical guidelines	0	0
Effect of hard LDLC targets set by guidelines	0	0
Determination of LDLC targets	5	6
Patient clinician acceptance of higher ldlc target	2	3
Which ldlc targets are used in practice	5	6
Lack of clear guidance on treating children	2	6
The use of clinical guidelines for lipid managment	7	27
Facilitators to PCSK9 inhibitor adoption	0	0
Influence from pharmaceutical companies	3	7
Patient awareness of disease severity	0	0
Severity of disease	3	5
Precriber engagement with the medication provision pathway	0	0
Views on medication use	0	0
Negative perceptions on statin use	0	0
Efficacy of statins in FH	7	12
Patient perceptions on statins	6	14
Patients refusing statin treatment	5	9
Statin intolerance	7	27
Opinions on polypharmacy	3	5
Positive views on PCSK9 inhibitors	0	0
General perceptions on PCSK9 inhibitors	3	5
HCP views on PCSK9 inhibitors	3	12
Patients perceptions on PCSK9 inhibitors	8	18

Appendix 12 Full list of 81 papers read in full and categorised by theme

Barriers and facilitators
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Appendix 13 Readcodes for familial hypercholesterolemia and pure hypercholesterolemia used in the study

Readcode	Description
C320000	Familial hypercholesterolemia
C320.11	Familial hypercholesterolemia

Appendix 14 How guidelines potentially hinder the use of PSK9 inhibitors

An application of the >50% LDLC reduction guideline to the primary treatment cohort (n=2899) results in 484 (16.7%) of the cases achieving a 50% LDLC reduction, 1523 (52.5%) registering LDLC reduction but not more than 50%, and 892 (30.8%) cases did not register a reduction of LDLC levels.

PCSK9 inhibitors are initiated at different LDLC levels for primary and secondary prevention treatment. In the secondary treatment cohort all patients met the LDLC target of 3.5mmol/l and therefore qualified for PCSK9 inhibitor initiation (n=50). In the primary prevention treatment group, 18.4% of patients (n=532) met the 5mmo/l threshold for PCSK9 inhibitor requirement. Therefore, the total number of patients who were eligible for PCSK9 inhibitors was 582 (19.7% of the total study cohort n=2949). These values are similar to Lee et al. (2017) and Glueck et al. (2016), who studied the eligibility for PCSK9 in the US; US guidelines are based on patients having HeFH or CVD and an LDLC above approximately 3.5mmo/l (190mg/dl).

A cross tabulation of these two sets of results suggests that there potentially exists a gap in the therapeutic management of HeFH patients under the current guidelines.

A cross tabulation between final LDLC value attained and therapeutic effect achieved

		Therapeutic effect group			**Total**
		1 Reduction in LDLC but not by 50%	**2 LDLC reduced by 50%**	**3 No change in LDLC or increase**	
Final LDLC value	**LDLC <5mmo/l**	1357	482	528	2367
	LDLC	166	2	364	532

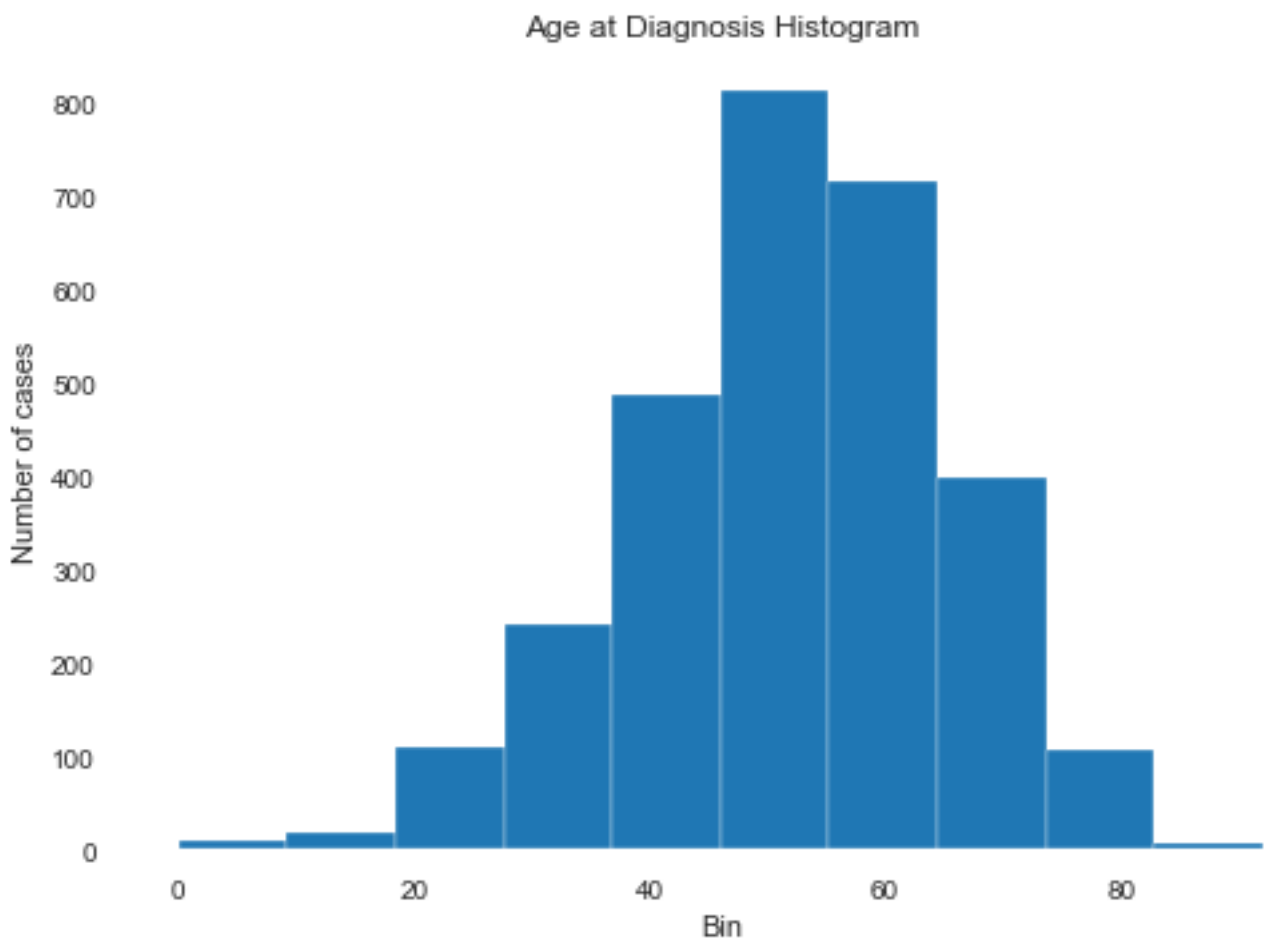
	>5mmo/l				
Total		1523	484	892	2899

It is worth noting that 528 (18.2%) patients registered no change in LDLC lowering but did not meet the requirements for PCSK9 inhibitor initiation. This was because their LDLC levels remained below 5mmol/l. However, in practice this could indicate failure to respond to treatment as guidelines suggest, at least, a 50% LDLC reduction.

The acceptance of a high LDLC value could potentially be explained by past studies which found that patient-physician agreement sometimes meant that guideline stipulated targets were not achieved (Pijlman et al., 2010). This practice is acceptable because CVD specific guidelines (Cohen et al., 2017; NICE CG71) stipulate that in cases where therapeutic LDLC targets cannot be reached, alternative treatment targets can be set by discussion between the clinician and the patients. Nevertheless, there remains a potential therapeutic gap in the management of HeFH patients who are not fully treated yet do not qualify for PCSK9 inhibitors.

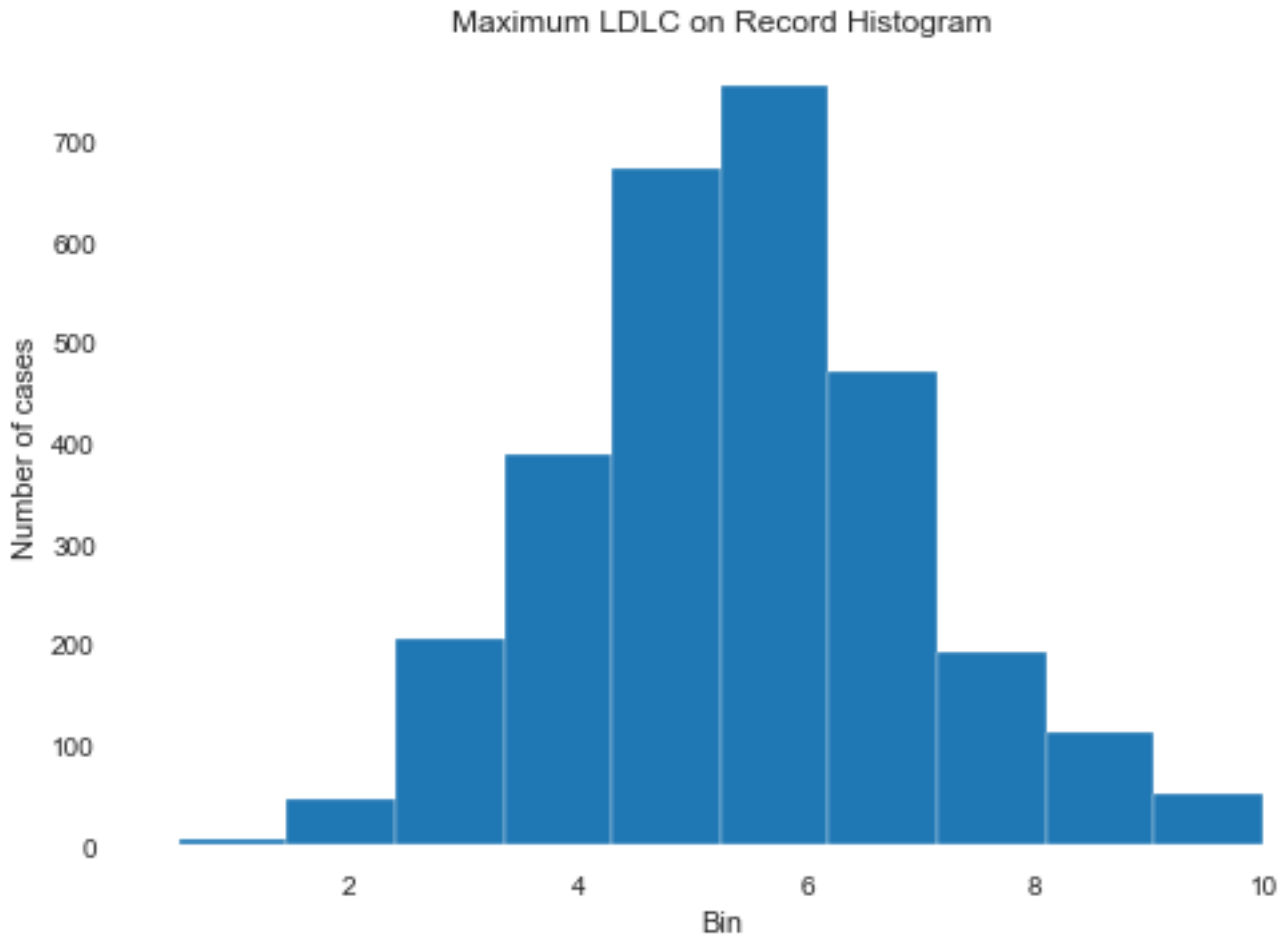
Appendix 15 Tests for normality

FirstOfAgeatdiagnosis	
Mean	52.00138074
Standard Error	0.248623336
Median	53
Mode	57
Standard Deviation	13.38184939
Sample Variance	179.0738931
Kurtosis	0.054316286
Skewness	-0.364080863
Range	92
Minimum	0
Maximum	92
Sum	150648
Count	2897
Confidence Level(95.0%)	0.48749653



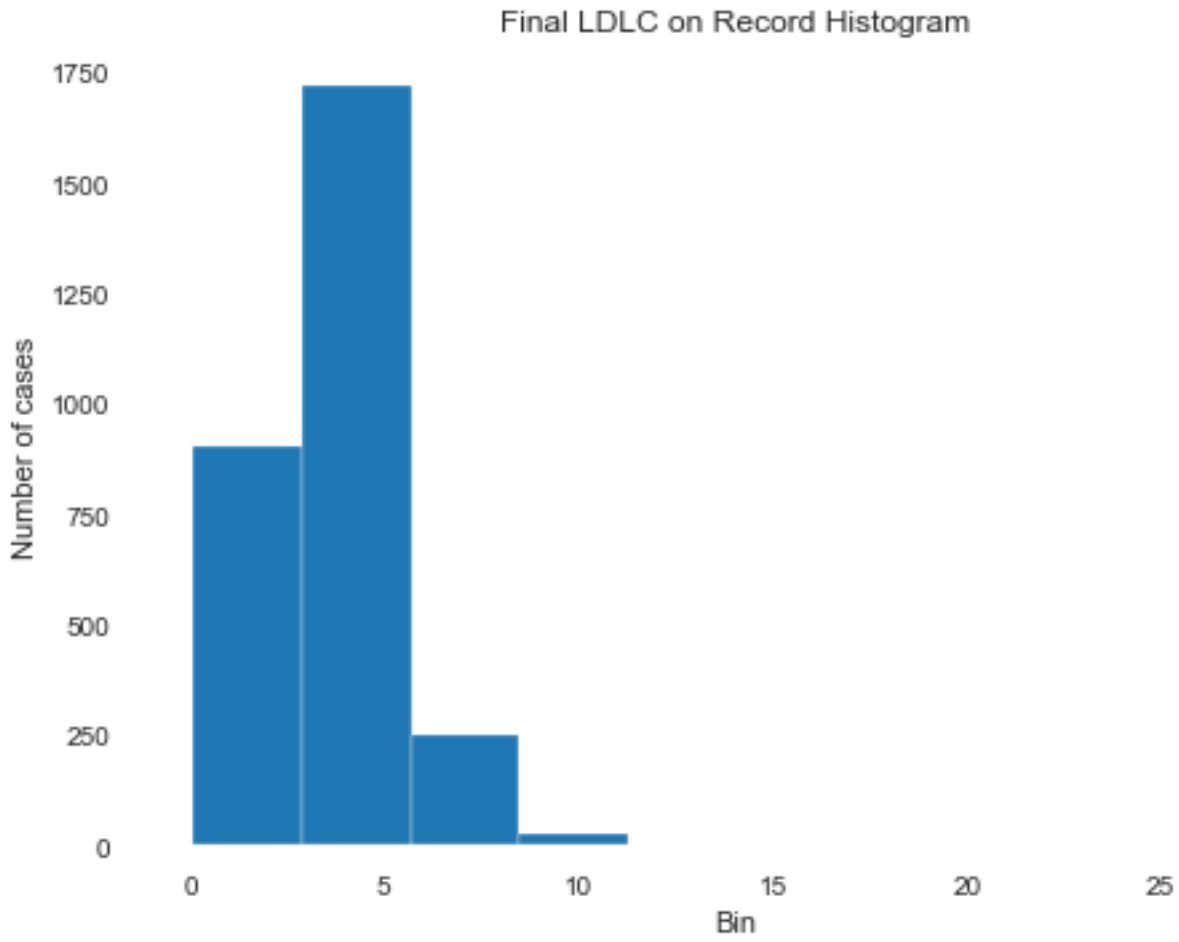
Ldlcmax	
Mean	5.4197378

Standard Error	0.0283863
Median	5.4
Mode	5.5
Standard Deviation	1.5283855
Sample Variance	2.3359623
Kurtosis	0.1190817
Skewness	0.2061561
Range	9.49
Minimum	0.5
Maximum	9.99
Sum	15711.82
Count	2899
Confidence Level(95.0%)	0.0556594



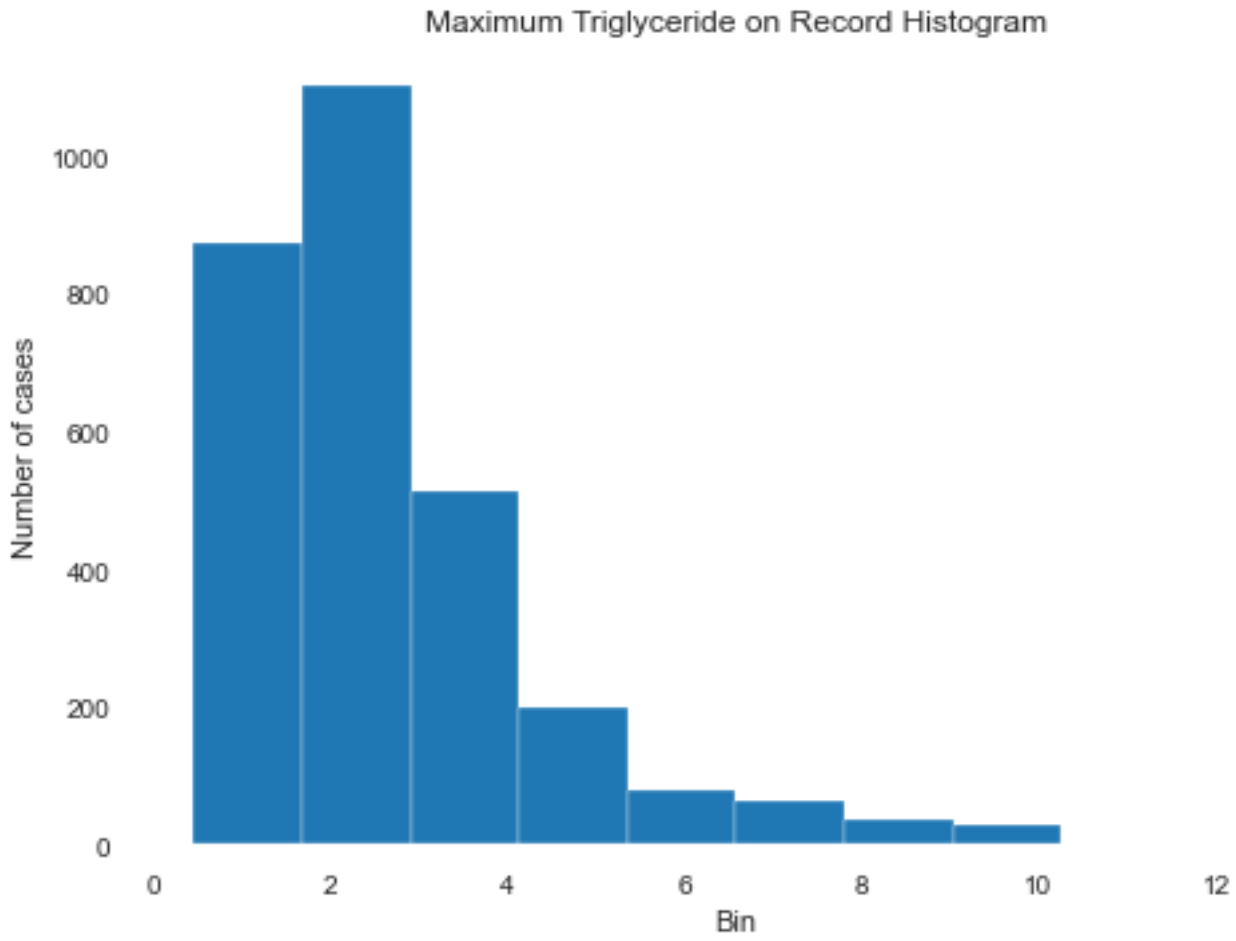
LastOfdata2	
Mean	3.69715764
Standard Error	0.0286025
Median	3.4
Mode	3.3
Standard Deviation	1.54002617
Sample Variance	2.3716806

Kurtosis	28.0509855
Skewness	2.7314077
Range	27.9
Minimum	0.1
Maximum	28
Sum	10718.06
Count	2899
Confidence Level(95.0%)	0.05608329



Triglyceridemax	
Mean	2.67845411
Standard Error	0.03131254
Median	2.22
Mode	2
Standard Deviation	1.68565051
Sample Variance	2.84141763
Kurtosis	3.90079023
Skewness	1.79035318
Range	12.24
Minimum	0.46
Maximum	12.7

Sum	7762.16
Count	2898
Confidence Level(95.0%)	0.06139711



Covariance

	FirstOfAgeatdiagnosis	*Ldlcmax*	*LastOfdata2*	*Triglyceridemax*
FirstOfAgeatdiagnosis	179.0120796			
Ldlcmax	-2.791745214	2.335157		
LastOfdata2	-3.790587374	1.091798	2.370862497	
Triglyceridemax	0.097591292	-0.16645	-0.070720824	2.840437155

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Appendix 16 Logistic regression analysis

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	1907	100.0
	Missing Cases	0	.0
	Total	1907	100.0
Unselected Cases		0	.0
Total		1907	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
1.00	0
2.00	1

Categorical Variables Codings

		Frequency	Parameter coding (1)
MedicineUse Whether the patient took medication or not	1.00	1656	1.000
	2.00	251	.000
FamHistFH	1.00	204	1.000
	2.00	1703	.000
FamHistMI	1.00	102	1.000
	2.00	1805	.000
FamHistHC	1.00	92	1.000
	2.00	1815	.000
Hypothyroidism	1.00	106	1.000
	2.00	1801	.000
KidneyDisease	1.00	1	1.000
	2.00	1906	.000
DiabetesMellitus	1.00	27	1.000
	2.00	1880	.000
LDLCmaximumvalue 1=0-5	1.00	749	1.000
	2.00	1158	.000
Triglyceride	1.00	615	1.000
	2.00	1292	.000
AgeAtDiagnosis	1.00	348	1.000
	2.00	1559	.000
gender	1	762	1.000
	2	1145	.000

Classification Table[a,b]

			Predicted		
			FinalLDLCvalue 1=0-4.9		Percentage
	Observed		1.00	2.00	Correct
Step 0	FinalLDLCvalue 1=0-4.9	1.00	1555	0	100.0
		2.00	352	0	.0
	Overall Percentage				81.5

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-1.486	.059	633.470	1	.000	.226

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	gender(1)	4.525	1	.033
		FamHistFH(1)	6.495	1	.011
		FamHistMI(1)	1.008	1	.315
		FamHistHC(1)	3.738	1	.053
		Hypothyroidism(1)	.021	1	.884
		KidneyDisease(1)	4.420	1	.036
		DiabetesMellitus(1)	3.961	1	.047
		AgeAtDiagnosis(1)	16.730	1	.000
		Triglyceride(1)	.901	1	.342
		1=0-5(1)	255.504	1	.000
		Whether the patient took medication or not(1)	1.222	1	.269
	Overall Statistics		279.604	11	.000

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	341.874	1	.000
	Block	341.874	1	.000
	Model	341.874	1	.000
Step 2	Step	16.667	1	.000
	Block	358.541	2	.000

	Model	358.541	2	.000
Step 3	Step	9.210	1	.002
	Block	367.750	3	.000
	Model	367.750	3	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	1482.257[a]	.164	.267
2	1465.590[b]	.171	.278
3	1456.380[b]	.175	.285

a. Estimation terminated at iteration number 7 because parameter estimates changed by less than .001.

b. Estimation terminated at iteration number 8 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	.000	0	.
2	.323	1	.570
3	1.097	3	.778

Contingency Table for Hosmer and Lemeshow Test

		FinalLDLCvalue 1=0-4.9 = 1.00		FinalLDLCvalue 1=0-4.9 = 2.00		
		Observed	Expected	Observed	Expected	Total
Step 1	1	743	743.000	6	6.000	749
	2	812	812.000	346	346.000	1158
Step 2	1	567	567.689	4	3.311	571
	2	176	175.311	2	2.689	178
	3	812	812.000	346	346.000	1158
Step 3	1	480	480.442	3	2.558	483
	2	242	242.030	3	2.970	245
	3	21	20.528	0	.472	21
	4	637	631.802	221	226.198	858
	5	175	180.198	125	119.802	300

Classification Table[a]

	Observed	Predicted

			FinalLDLCvalue 1=0-4.9		Percentage Correct
			1.00	2.00	
Step 1	FinalLDLCvalue 1=0-4.9	1.00	1555	0	100.0
		2.00	352	0	.0
	Overall Percentage				81.5
Step 2	FinalLDLCvalue 1=0-4.9	1.00	1520	35	97.7
		2.00	314	38	10.8
	Overall Percentage				81.7
Step 3	FinalLDLCvalue 1=0-4.9	1.00	1546	9	99.4
		2.00	349	3	.9
	Overall Percentage				81.2

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	1=0-5(1)	-3.966	.415	91.372	1	.000	.019	.008	.043
	Constant	-.853	.064	176.557	1	.000	.426		
Step 2[b]	1=0-5(1)	-4.222	.424	99.040	1	.000	.015	.006	.034
	Whether the patient took medication or not(1)	-.967	.234	17.117	1	.000	.380	.241	.601
	Constant	.044	.225	.039	1	.844	1.045		
Step 3[c]	AgeAtDiagnosis(1)	.467	.152	9.431	1	.002	1.595	1.184	2.148
	1=0-5(1)	-4.208	.425	98.276	1	.000	.015	.006	.034
	Whether the patient took medication or not(1)	-.995	.235	17.977	1	.000	.370	.233	.586
	Constant	-.032	.227	.020	1	.889	.969		

a. Variable(s) entered on step 1: 1=0-5.

b. Variable(s) entered on step 2: Whether the patient took medication or not.

c. Variable(s) entered on step 3: AgeAtDiagnosis.

Correlation Matrix

		Constant	1=0-5(1)	1=0-5(1)	Whether the patient took medication or not(1)	AgeAtDiagnosis (1)
Step 1	Constant	1.000	-.155			
	1=0-5(1)	-.155	1.000			

Step 2	Constant	1.000		-.239	-.958	
	1=0-5(1)	-.239		1.000	.204	
	Whether the patient took medication or not(1)	-.958		.204	1.000	
Step 3	Constant	1.000		-.239	-.946	-.107
	AgeAtDiagnosis(1)	-.107		.001	-.051	1.000
	1=0-5(1)	-.239		1.000	.205	.001
	Whether the patient took medication or not(1)	-.946		.205	1.000	-.051

Model if Term Removed

Variable		Model Log Likelihood	Change in -2 Log Likelihood	df	Sig. of the Change
Step 1	1=0-5	-912.065	341.874	1	.000
Step 2	1=0-5	-911.435	357.280	1	.000
	Whether the patient took medication or not	-741.128	16.667	1	.000
Step 3	AgeAtDiagnosis	-732.795	9.210	1	.002
	1=0-5	-903.843	351.305	1	.000
	Whether the patient took medication or not	-736.939	17.497	1	.000

Variables not in the Equation

			Score	df	Sig.
Step 1	Variables	gender(1)	.213	1	.645
		FamHistFH(1)	.742	1	.389
		FamHistMI(1)	1.695	1	.193
		FamHistHC(1)	.379	1	.538
		Hypothyroidism(1)	.081	1	.776
		KidneyDisease(1)	2.349	1	.125
		DiabetesMellitus(1)	.972	1	.324
		AgeAtDiagnosis(1)	8.653	1	.003
		Triglyceride(1)	.221	1	.638
		Whether the patient took medication or not(1)	18.235	1	.000
	Overall Statistics		33.993	10	.000
Step 2	Variables	gender(1)	.052	1	.819
		FamHistFH(1)	.998	1	.318
		FamHistMI(1)	2.230	1	.135
		FamHistHC(1)	.712	1	.399
		Hypothyroidism(1)	.106	1	.745

		KidneyDisease(1)	2.517	1	.113
		DiabetesMellitus(1)	1.140	1	.286
		AgeAtDiagnosis(1)	9.523	1	.002
		Triglyceride(1)	.092	1	.761
	Overall Statistics		16.021	9	.066
Step 3	Variables	gender(1)	.527	1	.468
		FamHistFH(1)	.179	1	.673
		FamHistMI(1)	2.141	1	.143
		FamHistHC(1)	.242	1	.622
		Hypothyroidism(1)	.028	1	.868
		KidneyDisease(1)	2.796	1	.094
		DiabetesMellitus(1)	.936	1	.333
		Triglyceride(1)	.014	1	.906
	Overall Statistics		6.688	8	.571

Step number: 1

Observed Groups and Predicted Probabilities

```
    1600 +
+
         I
I
         I
I
F        I
I
R   1200 +                              2
+
E        I                              2
I
Q        I                              2
I
U        I                              2
I
E    800 +                              1
+
N        I1                             1
I
C        I1                             1
I
Y        I1                             1
I
     400 +1                             1
+
         I1                             1
I
         I1                             1
I
         I1                             1
I
```

```
Predicted ---------+---------+---------+---------+---------+---------+-----
----+---------+---------+----------
  Prob:   0       .1        .2        .3        .4        .5        .6
.7        .8        .9         1
  Group:
11111111111111111111111111111111111111111111111112222222222222222222222222
22222222222222222222222
```

Predicted Probability is of Membership for 2.00
The Cut Value is .50
Symbols: 1 - 1.00
2 - 2.00
Each Symbol Represents 100 Cases.

Step number: 2

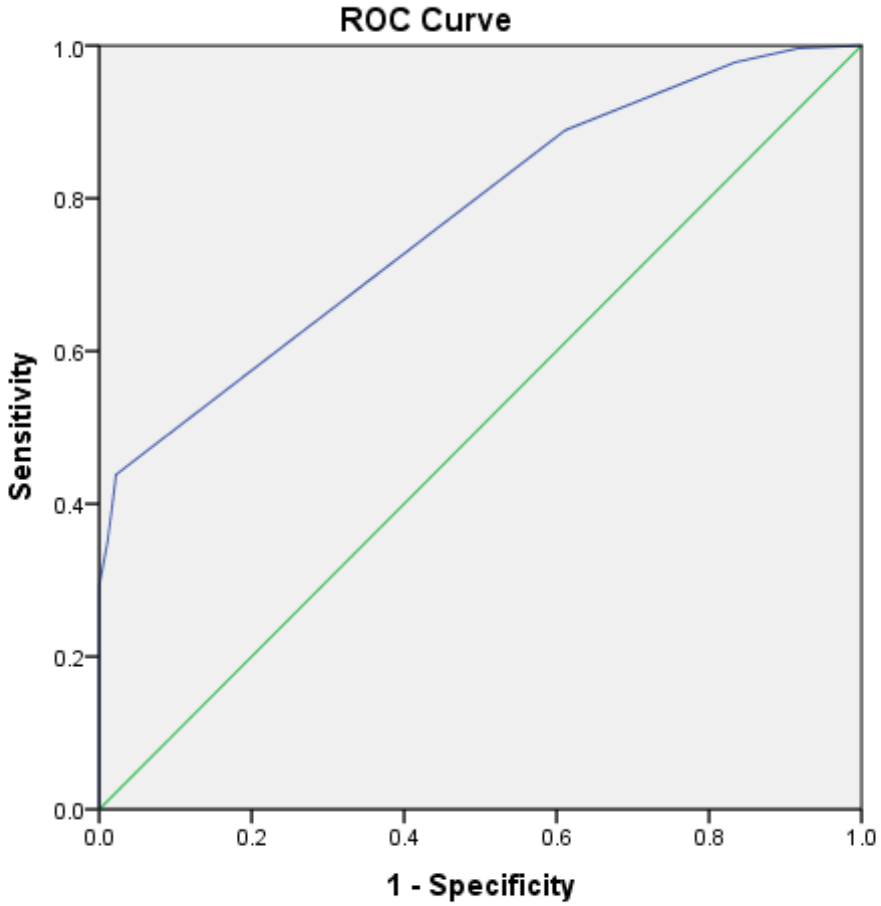
Observed Groups and Predicted Probabilities

```
    1600 +
+
         I
I
         I
I
F        I
I
R   1200 +
+
E        I                          2
I
Q        I                          2
I
U        I                          2
I
E    800 +                          1
+
N        I                          1
I
C        I1                         1
I
Y        I1                         1
I
     400 +1                         1
+
         I1                         1
I
         I11                        1
I
         I11                        1                       2
I
Predicted ---------+---------+---------+---------+---------+---------+-----
----+---------+---------+----------
  Prob:   0       .1        .2        .3        .4        .5        .6
.7        .8        .9         1
  Group:
11111111111111111111111111111111111111111111111112222222222222222222222222
22222222222222222222222
```

```
Predicted Probability is of Membership for 2.00
The Cut Value is .50
Symbols: 1 - 1.00
         2 - 2.00
Each Symbol Represents 100 Cases.
```

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx

Appendix 17 ROC analyses



Area Under the Curve

Test Result Variable(s): predicted_logit

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.772	.017	.000	.739	.805

The test result variable(s): predicted_logit has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Coordinates of the Curve

Test Result Variable(s): predicted_logit

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity

-10.971000	1.000	1.000
-9.737500	.996	.917
-9.240000	.978	.833
-8.742500	.889	.611
-7.136000	.447	.033
-5.529500	.438	.022
-5.032000	.351	.011
-4.534500	.293	.000
-3.301000	.000	.000

The test result variable(s): predicted_logit has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

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Appendix 18 Derivation and validation dataset analyses

Study variables	In-dataset variable name	Variable categories
Treatment effect (outcome variable)	effect2	1: did not work 2: did work
Age at diagnosis	agediag2	1: 0-40 2: more than 40
Gender	gender	1: male 2: female
Maximum low density lipoprotein cholesterol (ldlc) measurement	ldl2	1: 0-5 mmol/L 2: more than 5 mmol/L
Maximum triglyceride measurement	tri3	1: 0-1.7mmol/L 2: more than 1.7 mmol/L
Family history of familial hypercholesterolemia	famfh1	1: yes 2: no
Family history of myocardial infarction	fammi1	1: yes 2: no
Family history of high cholesterol	famhc1	1: yes 2: no
Diagnosis of hypothyroidism	hpy1	1: yes 2: no
Diagnosis of kidney disease	kd1	1: yes 2: no
Diagnosis of diabetes	diab1	1: yes 2: no
Prescribed drug groups	druggroups	1: Took medication 2: Did not take medication

Dataset randomly split by 66% to 34%, derivation and validation cohorts, using SPSS.

	Derivation cohort (number & percentage) 1941(65.8%)	**Validation cohort (number and percentage) 1008(34.2%)**
Treatment outcome		
1:medication worked	307(15.8%)	181(18%)
2:medication did not work	1634(84.2%)	827(82%)
Age at diagnosis		
1:0-40	338(17.4%)	204(20.2%)
2:more than 40	1601(82.5%)	804(79.8%)
Gender		
1:male	789(40.6%)	404(40.1%)
2:female	1152(59.4%)	604(59.9%)
Maximum LDLC measurement		
1:0-5mmol/L	709(36.5%)	359(35.6%)
2:more than 5mmol/L	1232(63.5%)	649(64.4%)
Maximum triglyceride measurement		
1: 0-1.7mmol/L	572(29.5%)	312(31%)
2: more than 1.7 mmol/L	1368(70.5%)	696(69%)
Family history of familial hypercholesterolemia		
1:yes	209(10.8%)	96(9.5%)

2:no	1732(89.2%)	912(90.5%)
Family history of myocardial infarction		
1:yes	107(5.5%)	45(4.5%)
2:no	1834(94.5%)	963(95.5%)
Family history of high cholesterol		
1:yes	104(5.4%)	50(5%)
2:no	1837(94.6%)	958(95%)
Diagnosis of hypothyroidism		
1:yes	116(6%)	63(6.3%)
2:no	1825(94%)	945(93.8%)
Diagnosis of kidney disease		
1:yes	1(0.1%)	0(0%)
2:no	1940(99.9%)	1008(100%)
Diagnosis of diabetes		
1:yes	30(1.5%)	18(1.8%)
2:no	1911(98.5%)	990(98.2%)
Prescribed drug groups		
1: statins	1164(60%)	598(59.3%)
2: statins + ezetimibe	267(13.8%)	156(15.5%)
3: statins + ezetimibe+ fibrates	73(3.8%)	49(4.9%)
4: medication not recorded	262(13.5%)	119(11.8%)
5: combinations of lipid therapies	175(9%)	86(8.5%)

Significance level 0.05

Two tailed hypothesis

Difference Scores Calculations

Treatment 1

N_1: 27
$df_1 = N - 1 = 27 - 1 = 26$
M_1: 862.56
SS_1: 13617512.67
$s^2_1 = SS_1/(N - 1) = 13617512.67/(27-1) = 523750.49$

Treatment 2

N_2: 27
$df_2 = N - 1 = 27 - 1 = 26$
M_2: 448
SS_2: 3635586
$s^2_2 = SS_2/(N - 1) = 3635586/(27-1) = 139830.23$

T-value Calculation

$s^2_p = ((df_1/(df_1 + df_2)) * s^2_1) + ((df_2/(df_2 + df_2)) * s^2_2) = ((26/52) * 523750.49) + ((26/52) * 139830.23) = 331790.36$

$s^2_{M1} = s^2_p/N_1 = 331790.36/27 = 12288.53$
$s^2_{M2} = s^2_p/N_2 = 331790.36/27 = 12288.53$

$t = (M_1 - M_2)/\sqrt{(s^2_{M1} + s^2_{M2})} = 414.56/\sqrt{24577.06} = 2.64$

The *t*-value is 2.64434. The *p*-value is .010796. The result is significant at $p < .05$.

F-Test Two-Sample for Variances

	Variable 1	*Variable 2*
Mean	448	862.5555556
Variance	139830.231	523750.4872
Observations	27	27
df	26	26
F	0.26697871	
P(F<=f) one-tail	0.00062949	
F Critical one-tail	0.51834617	

F is smaller than critical so the samples are the same.

Alpha 0.05