Journal of Clinical & Experimental Cardiology

Kruse et al., J Clin Exp Cardiology 2017, 8:9
DOI: 10.4172/2155-9880.1000539

Research Article Open Access

Cardiovascular Disease and its Risk Factors in Patients with Familial Hypercholesterolemia: A Systematic Review

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Abstract

Objectives: Familial hypercholesterolemia (FH) leads to prolonged vascular exposure to high levels of low-density lipoprotein cholesterol and subsequent development of atherosclerotic lesions. This study examines additional risk factors in patients with FH and their impact on cardiovascular disease (CVD) risk.

Methods: A systematic literature review identified publications describing cardiovascular risk in patients with FH (January-October 2016), extending a previous published review (2004-2015). Each article was assessed for bias by two reviewers using the modified Newcastle–Ottawa assessment scale for non-randomized studies. Additional risk factors studied included age, sex, FH mutations, and previous CVD.

Results: Three new studies were identified, conducted in the Netherlands, Spain, and Brazil, and reviewed together with the 14 studies identified in the previous review. The study with the lowest bias, comparing patients with versus without FH, reported odds ratios (ORs) for coronary artery disease (CAD) of 10.3 (95% confidence interval [CI]: 7.8–13.8) and 13.2 (95% CI: 10.0–17.4) in patients treated and untreated with lipid-lowering therapy, respectively. The highest risk increases in mortality were observed in the 30–60-yr age band. Most studies found that men with FH had a ~2.5-fold higher CVD risk compared with women, although the magnitude of the difference varied by study. Patients carrying null-mutations had a 68% higher risk of premature CVD (OR: 1.68; 95% CI: 1.10–2.40), and recurrence of cardiovascular events versus patients carrying defective-mutations. Premature CVD was identified as a risk factor for mortality (standardized mortality ratio: 1.62; 95% CI: 1.32–1.93).

Conclusions: FH-related CVD risk is high, even in treated patients, and represents an important unmet medical need. Alongside classical risk factors (age, blood pressure, body mass index, smoking, lipid levels), FH-causing mutations are important for understanding FH-related CVD risk. Other parameters, such as age at which statin therapy is started, require further research.

Keywords: Familial hypercholesterolaemia; Cardiovascular disease; Risk; Bias; Lipid-modifying therapy

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by autosomal inheritance of genes related to low-density lipoprotein cholesterol (LDL-C) metabolism, resulting in lifelong elevation of LDL-C. It is estimated that 14–34 million people have FH worldwide [1]. Major causes of FH are loss-of-function mutations in the LDL receptor (LDLR) or apolipoprotein B-100 (APOB) genes, and gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 [2]. The prolonged exposure of the vasculature to high levels of LDL-C leads to the development of atherosclerotic lesions in the arteries supplying the coronary, cerebral, and peripheral vascular beds [3]. These lesions in the arterial wall gradually progress in size, occupying an increasing proportion of the arterial lumen over time. When ≥ 70% of the vessel is obstructed, clinical symptoms of ischemia develop [4].

Most acute complications, such as myocardial infarction (MI) and sudden cardiac death, however, occur in vessels that are not severely obstructed. Although the genetic mutation leading to FH is present at birth, the resulting increase in LDL-C often remains asymptomatic until the occurrence of an acute cardiovascular event. Approximately half of patients with FH have no manifestations of coronary disease until they undergo sudden death or nonfatal MI. These events occur at a higher frequency and at an earlier age in patients with FH than in patients without FH or in patients with polygenetic causes of elevated LDL-C [5].

Patients can therefore come to the attention of healthcare professionals via several routes, including clinical manifestation of cardiovascular disease (CVD), an incidental LDL-C measurement, or a screening program. Such programs may target individuals for screening because of a family history in a first degree relative (cascade screening), or may be general, population-level (universal) programs [6]. Early management with aggressive lipid-modifying therapy to reduce LDL-C levels together with modification of other risk factors is effective as a CVD event prevention strategy [7]. As a result, some countries have introduced universal screening programs, while the European Atherosclerosis Society has issued a call for greater awareness of FH [1]. Screening involves clinical criteria for FH alone, or in combination with genetic testing. It should be noted, however, that many patients

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Received September 07, 2017; **Accepted** September 13, 2017; **Published** September 18, 2017

Citation: Kruse G, Kutikova L, Wong B, Villa G, Ray KK, et al. (2017) Cardiovascular Disease and its Risk Factors in Patients with Familial Hypercholesterolemia: A Systematic Review. J Clin Exp Cardiolog 8: 539. doi:10.4172/2155-9880.1000539

who have a clinical phenotype of FH do not have one of the known pathogenic mutations [1].

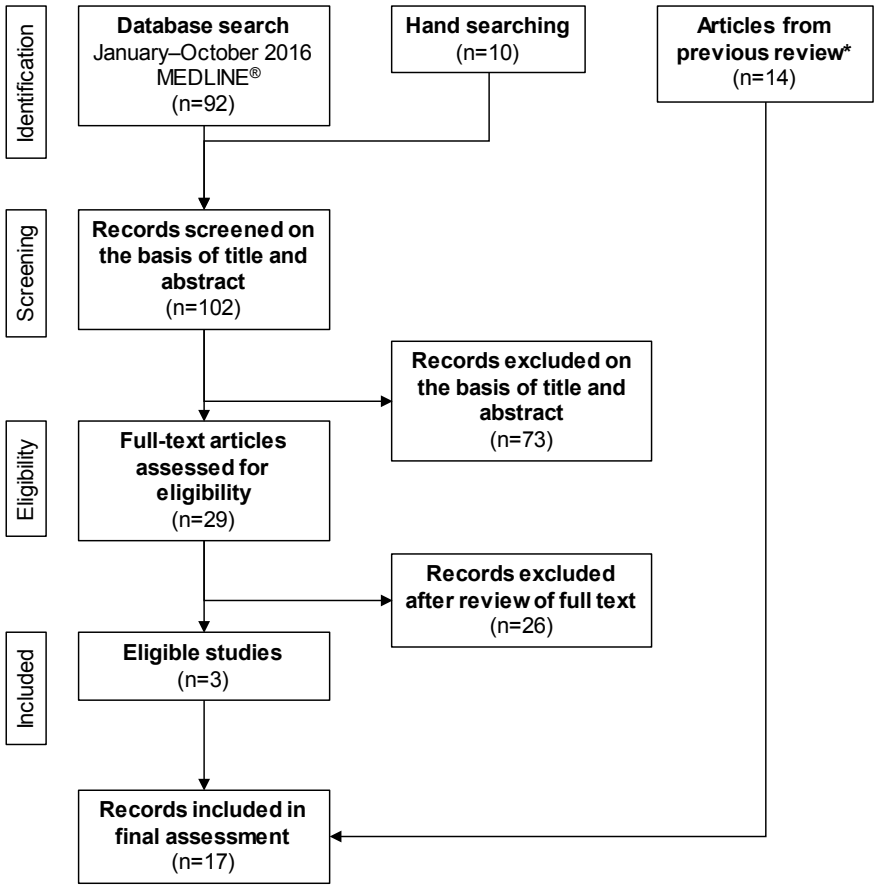
In a previous systematic literature review, the increased risk of CVD in FH populations was assessed, along with the adequacy and availability of the evidence according to a study quality checklist to support health technology assessment decision making. [8]. Recently published studies have incorporated new data sources and calculated new estimates of the increased risk of CVD in patients with FH. In addition to the impact of elevated LDL-C levels, the risk of CVD in patients with and without FH is affected by risk factors such as male sex, age, and specific FH-causing mutation [9]. The impact of these additional risk factors in patients with FH compared with those without is not well understood. In this updated review, we identified all newly published literature and performed the same quality assessment on the new studies. We also reviewed CVD risk factors to expand our understanding of variables such as age, sex, and genetic mutations, and their impact on CVD risk.

Methods

The objective of this systematic review, which was an update to a previous systematic review [8], was to examine the risk of CVD in patients with FH compared with those without the condition, and to investigate the role of additional risk factors in these patients. We also conducted a bias assessment of the studies identified to support healthcare policy decision making. We added 'familial hypercholesterolemia' in addition to 'familial hypercholesterolaemia' to the original search string: "(((Cardiovascular Disease Risk AND (Familial Hypercholesterolaemia OR Familial Hypercholesterolemia) NOT Nursing) AND English [Language]) NOT randomized controlled trials) NOT reviews [Publication Type]". The original search was performed by two reviewers using MEDLINE® for articles published between January 1, 2004, and December 31, 2015, and our update covered articles published in MEDLINE® from January 1, 2016 to October 31, 2016, which were reviewed alongside those previously identified. Publications that included any measure of CVD risk (risk, rates, odds, or ratios of mortality and morbidity) in patients with FH were the outcomes of interest of this review. Studies were excluded if they had no CVD risk estimate in patients with FH; had no information on CVD risk estimates in patients with versus without FH; were not specific to FH (using a prospective definition of FH); or included only a subgroup of patients with FH. Review articles and letters to the editor were also excluded. Bias assessment of the newly identified studies was conducted by the same two reviewers as the search and paper selection, as previously described [8], using the modified Newcastle–Ottawa assessment scale for non-randomized studies. Data on prospectively defined CVD risk factors and population exposure were extracted from all studies, including those previously assessed.

Results

The new literature search identified 92 potential publications from



*Wong et al. (2016) [8]

Figure 1: Flow diagram of the studies included in the systematic review.

PubMed (MEDLINE®) (Figure 1). Review of reference lists from those papers identified nine further references. One additional paper [10], published just after the literature review was performed, was identified as meeting the study criteria during the development of this review and was included in the analysis.

After title and abstract review, 28 articles were identified as likely to contain cardiovascular risk estimates and were retrieved for full-text review. Of these, three studies contained estimates of the rate of increased risk of CVD in FH and were included in the literature review [10-12]. The new studies included CVD risk estimates from Brazil [11], a country not represented in the previous literature review, and new risk estimates from Spain [12] and the Netherlands [10]. The three new studies are summarized in Table 1 along with the 14 studies reviewed previously [10-26].

Study	Country/ ethnicity	Study sample	Genotypes	CVD risk measure	FH risk estimate	Exposure group	Comparison group
Population survey-based studies							
Benn et al. (2012) [13]**	Denmark	Population survey of 69,016 patients in Denmark	*LDLR* W23X, W66G, and W556S, and *APOB* R3500Q mutations	OR, coronary artery disease (mortality and non-fatal)	13.2 (10.6–17.4)	No LMT	Random sample of Danish population
Registry-based studies							
Mabuchi et al. (1989) [14]	Japan	Konazawa Hospital cohort of 527 patients *vs.* Japanese population	None	PMR for CHD (non-fatal)	10.9 (7.95–15.03)	No LMT	Japanese population
Simon Broome (1991) [15]	British	526 registry patients *vs.* population of England and Wales	None	SMR for CHD mortality*	3.74 (1.8–6.89)	Males aged 0–79 yrs LMT treated	Population of England and Wales
					4.13 (1.34–9.64)	Females aged 0–79 yrs LMT treated	
					3.86 (2.1–6.39)	All aged 0–79 yrs LMT treated	
Simon Broome (1999) [16]	British	1185 registry patients (1980–1995) *vs.* population of England and Wales	None	SMR for CHD mortality*	2.6 (1.7–3.8)	Males aged 0–79 yrs LMT treated	Population of England and Wales
Alonso et al. (2008) [17]	Spanish	Spanish register of 811 patients *vs.* Spain population estimate	*LDLR* mutation (null, defective, unknown); *APOE* genotype (E2, E3, E4)	% premature CVD (fatal and non-fatal)	21.9%/2.6%= 8.4× risk	80% of patients receiving LMT	Spanish population
Neil et al. (2008) [18]	British	Simon Broome Registry, 3,413 patients *vs.* England and Wales (1980–1991) population	None	SMR for CHD mortality	1.98 (1.02–3.46)	Age 20–79 yrs, primary prevention LMT treated	Population of England and Wales
					5.15 (3.35–7.64)	Age 20–79 yrs, secondary prevention LMT treated	–
		Simon Broome Registry, 3,413 patients *vs.* England and Wales (1992–2006) population			1.03 (0.75–1.38)	Age 20–79 yrs, primary prevention LMT treated	–
					3.88 (3.18–4.68)	Age 20–79 yrs, secondary prevention LMT treated	–
Versmissen et al. (2008) [19]	Dutch	Dutch lipid clinic patients aged >55 yrs (n=1,950) *vs.* Rotterdam study sub-group	None	HR for MI (Non-fatal)	8.7 (4.77–15.82)	No LMT Not taking statins for >1 month before their MI	Rotterdam study in the elderly, age- and sex- matched sub-group to patients with FH
Besseling et al. (2013) [20]	Dutch	High-severity *vs.* low severity FH group (severity defined based on LDL-C >8 mmol in men aged 36–40, then that percentage applied to the whole Dutch cohort) Does not provide a risk estimate *vs.* non-FH	Required FH mutation (genotypes not reported)	HR for CVD (Non-fatal)	1.25 (1.05–1.51)	Redefined risk severity group LMT treated	Low-severity FH group
Mundal et al. (2014) [21]	Norway	Norway Registry, 4,688 patients (1992–2010) *vs.* Norwegian population	32 mutation types. Most common: *LDLR* (313+1,G>A; C210G, S78X, D200N, W23X, N804K, R395W, P664L) and *APOB* (R3500Q)	SMR for cardiovascular death	2.29 (1.65–3.19)	89.1% receiving LMT	Norwegian population
Perez de Isla et al. (2016) [12]	Spain	From SAFEHEART study, 3,745 patients with 2,752 FH cases	209 different functional mutations in LDLR and APOB genes	CVD (fatal and non-fatal)	3.01 (2.20–4.12)	LMT treated	Unaffected relatives

Study	Country/ ethnicity	Study sample	Genotypes	CVD risk measure	FH risk estimate	Exposure group	Comparison group
Robinson et al. (2016) [10]	Dutch	30,074 patients from genetic cascade program: 4,197 with FH and 25,877 controls	Severe class 1 *LDLR* mutations included; *APOB* and non-class 1 *LDLR* mutations excluded	CVD (non-fatal)	12 (6–25) 16 (9–27) 9 (6–14) 6 (4–9) 4 (2–9) 5 (1–36)	Age 20–30 Age 30–40 Age 40–50 Age 50–60 Age 60–70 Age 70–80 No LMT	Relatives who tested negative for family FH mutation
Hospital-based and family-based studies							
Jensen et al. (1967) [22]	Denmark	Family study of 11 families (1944–1964 *vs.* Danish population)	None	SMR mortality	2.88 (1.73–4.46)	LMT treated	Danish population
Slack et al. (1969) [23]	British	104 patients with clinical FH *vs.* 41 patients with type III, IV or V hyperlipoproteinemia	None	1st heart attack (fatal and non-fatal)	60% increased risk	LMT treated	Type III, IV or V hyperlipoproteinemia
Sijbrands et al. (2000) [24]	Dutch	Family study of 855 first degree relatives *vs.* Dutch population	*LDLR* mutations (null, other); patients with *APOB* B3500 excluded	SMR mortality	1.34 (1.16–1.55)	LMT treated	Dutch population
Sijbrands et al. (2001) [25]	Dutch	Pedigree analysis of 250 descendants of a single pair of ancestors *vs.* Dutch population	*LDLR* (V408M)	SMR mortality	1.32 (1.03–1.67)	LMT treated	Dutch population
Mohrschladt et al. (2004) [26]	Dutch	Leiden lipid clinic patients (n=400), all treated with statins	None	RR IHD mortality	2.6 (0.6–3.3)	No history of CHD LMT treated	Dutch general population
Silva et al. (2016) [11]	Brazil	818 individuals from San Paulo Medical School Hospital with FH mutation, without FH mutation, and relatives	With or without mutation (*LDLR*, *PCSK9*, and *APOB*)	CVD (fatal and non-fatal)	4.0 (1.33–11.98) 2.9 (1.13–7.40)	Positive mutation Positive mutation	Negative mutation Relatives with negative mutations

*Simon Broome SMR results have been expressed as absolute risk increases (SMR/100)

**Only population-based estimate

APOB: Apolipoprotein B; APOE: Apolipoprotein E; CHD: Coronary heart disease; CVD: Cardiovascular disease; FH: Familial hypercholesterolemia; HR: Hazard ratio; IHD: Ischemic heart disease; LDL-C: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein cholesterol receptor; LMT: Llipid-modifying therapy; MI: Myocardial infarction; OR: Odds ratio; PCSK9: Proprotein convertase subtilisin/kexin type 9; PMR: Proportional mortality ratio; RR: Relative risk; SMR: Standardized mortality ratio

Table 1: Studies reporting the risk of CVD in patients with FH. Shaded rows are studies identified in the updated literature search (January–October 2016).

Bias assessment and cardiovascular risk

Results of the bias assessment of the three newly identified studies are shown, along with the 14 studies previously assessed in Table 2 [10-26].

Two of the three studies identified in this updated review were registry-based studies. Perez de Isla et al. (2016) included data from January 2004 to November 2013 from 28 clinics that are part of the SAFEHEART registry in Spain [12]. Of 4,132 individuals examined, 2,752 had molecularly defined FH, and 993 were unaffected relatives. The goal of the study was to analyze atherosclerotic CVD risk in a large FH population compared with unaffected relatives, results showing a 3-fold higher risk of CVD events in patients with FH (odds ratio [OR]: 3.01; 95% confidence interval [CI]: 2.3–4.6). These patients were recruited from lipid clinics, where they might have received more intensive treatment. Furthermore, no comparison with the general Spanish population was made for either patients with FH or their relatives, leading to potential selection bias. Comparing the two groups, several differences were found between patients with FH and unaffected relatives, including a higher prevalence of tobacco use in unaffected relatives and a higher prevalence of a history of premature atherosclerotic CVD and diabetes in patients with FH. Differences between the groups could therefore affect the risk estimate. Use of lipid-modifying therapy (LMT) was also prevalent during the study, with much higher use in patients with FH compared with unaffected relatives, resulting in performance and confounding bias concerns.

Robinson et al. (2016) examined 30,074 patients from the Netherlands (1994 to 2010) to estimate 10-yr risk of non-fatal CVD in patients with FH (n=4,197) [10]. The results showed a CVD event rate of 20–40% for patients aged 40–80 years with a severe LDLR mutation, increasing to very high event rates in patients aged >60 years. Across all time periods, the estimated cardiovascular event rate increased relative risk (RR) by 8-fold in patients with FH compared with relatives without FH. ORs ranged from 2 (95% CI: 1–3) for patients aged 70–80 years to 13 (95% CI: 9–18) for those aged 30–40 years. LMT use was found to have a higher prevalence before genetic FH diagnosis in patients with FH than in controls, and the authors estimated a CVD risk in a pre-statin period to control for this difference. Estimated cardiovascular event rates in the pre-statin period led to a RR more than 10-fold higher in patients with FH than in unaffected relatives, with ORs ranging from 5 (95% CI: 1–36) for patients aged 70–80 years to 16 (95% CI: 9–27) for those aged 30–40 years. This study recruited patients through a Dutch genetic national cascade screening program and excluded index patients to limit selection bias. Selection bias is still a concern, however, because the CVD rate did not

Bias category	Selection				Performance			Detection				Attrition		Confounding		Reporting	Other	High bias count × study
Study	Eligibility criteria explicitly described	Selection of eligible population from the target population	Similarities of exposed and unexposed groups	Exclusion of participants from analysis of the outcome	Ascertainment of exposure and outcome	Temporal sequence	Concurrent interventions or unintended exposures	Blinding of assessors	Valid and reliable measurement of exposure status	Valid and reliable measurement of outcomes	Exposure durations	Missing data across exposed and unexposed groups	Accounting for missing data	Control for confounders	Valid and reliable measurement of confounders	Post hoc analyses	Other biases	
Population-survey-based studies																		
Benn et al (2012) [13]																		0
Registry-based studies																		
Mabuchi et al. (1989) [14]																		6
Simon Broome Registry (1991) [15]																		4
Simon Broome Registry (1999) [16]																		4
Alonso et al. (2008) [17]																		11
Neil et al. (2008) [18]																		4
Versmissen et al.(2008) [19]																		3
Besseling et al. (2014) [20]																		4
Mundal et al. (2014) [21]																		5
Perez de Isla et al. (2016) [12]*																		3
Robinson et al. (2016) [10]*																		2
Hospital-based and family-based studies																		
Jensen et al. (1967) [22]																		3
Slack et al. (1969) [23]																		9
Sijbrands et al. (2000) [24]																		2
Sijbrands et al. (2001) [25]																		2
Mohrschladt et al. (2004) [26]																		3
Silva et al. (2016) [11]*																		4
High bias assessment count × bias type	9	16	11	3	1	0	7	1	1	3	2	1	0	3	3	1	7	

White, low risk of bias; light grey, unclear risk of bias, dark grey, high risk of bias
*Studies identified in the updated literature search (January–October 2016)

Table 2: Results of bias assessment in the 17 included studies.

include fatal CVD events, which probably resulted in an underestimate of CVD risk in the FH population. Furthermore, no comparison was made between the study population and the broader general population.

Hospital- and family-based studies are popular for studying patients with FH because of the relative ease of patient recruitment. Compared with population survey and registry studies, however, these studies have a higher degree of selection bias because patients are identified from a selective and limited population. Hospital- and family-based studies also suffer from selection bias, with comparison groups drawn from different population sources to the study groups.

The third of the three newly identified studies (Silva et al. 2016) was a hospital-based study that studied 818 patients, index cases and relatives, identified prospectively (dates not specified) using a genetic cascading screening program from a laboratory at the University of Sao Paulo Medical School Hospital, Brazil [11]. The risk of fatal and non-fatal cardiovascular events at 1 year of follow-up was assessed by questionnaire 1 year after patients joined the screening program, leading to potential ascertainment bias. ORs for cardiovascular events after 1 year were 4.4 (95% CI: 1.5–13.1) for positive FH mutation versus negative FH mutation and 1.4 (95% CI: 0.5–3.6) for positive FH mutation versus relatives with negative FH mutations. Limited information was provided on how patients were identified and no comparison was made with the general population, making selection bias a concern. One year is also a very short time period to assess meaningful risk estimates of cardiovascular events. Other potential biases to the risk assessment include higher rates of LMT in patients with FH compared with relatives, and the higher intensity of care that molecularly diagnosed FH patients received by being part of the screening program.

Of all 17 studies, the population survey by Benn et al. [13] remained the only one to have no areas of high-risk bias. In that study, the authors examined the prevalence of FH and the risk of CVD for patients with FH among 69,016 individuals from the Danish general population in the Copenhagen General Population Study. The use of probabilistic diagnostic criteria for the determination of FH with a modification of the Dutch Lipid Clinic Criteria, and the use of an internal comparison group, improved the validity of the study. The adjusted OR for coronary artery disease (CAD) in patients with definite or probable FH not receiving LMT was 13.2 (CI: 10.0–17.4) compared with patients without FH. In patients receiving LMT, the adjusted OR for CAD was 10.3 (7.8–13.8).

Risk Factors

Age

Risk of CVD varies by age, and 10 of the 17 studies reported CVD

risk by age bands. The early studies by Jensen et al. (1967) and Slack (1969) report mortality and heart attacks, respectively, by age bands, but the counts were too low to draw significant conclusions [22,23]. The Simon Broome (1991) study was the first to report that RR decreases with age, while absolute risk increases [15]. They reported a standardized mortality ratio (SMR) for coronary heart disease (CHD) of 96.9 (95% CI: 36.7–218.0) for ages 20–30 years, 5.2 (2.2–10.2) for 40–59 years, and 0.4 (1.0–2.4) for 60–74 years. Neil et al. also found a similar trend of declining CHD mortality by age bands when examining patients with FH compared with the general population in England and Wales [18]. They reported an SMR for CHD mortality of 37.5 (95% CI: 7.73–109.59) for ages 20–39 years, 3.42 (1.48–6.74) for 40–59 years, and 0.27 (0.01–1.53) for 60–79 years. Mundal et al. found a similar trend when comparing CVD mortality of patients with FH with the Norwegian population [21]. They reported the highest SMR for CVD mortality in patients aged 20–39 years (SMR: 8.03; 95% CI: 3.34–19.28) and the lowest in those aged >80 years (SMR: 0.76; 95% CI: 0.34–1.70). Sijbrands (2000) found that mortality in patients with FH and first-degree relatives compared with the Dutch population was U shaped, with the highest risk in patients aged 40–54 years [24]. Specifically, they report an SMR of 0.45 (95% CI: 0.17–0.98) for ages 1–19 years, 1.88 (1.36–2.53) for 40–54 years, and 0.96 (0.60–1.46) for 80–103 years. Mohrschladt et al. (2004) found a similar relationship, with the estimated RR for statin-treated patients with FH compared with the general population, highest in patients aged 40–59 years: RR was 7.6 (95% CI: 2.9–20) and 4.3 (1.6–11) for ischemic heart disease (IHD) and prior CVD, respectively [26]. Robinson et al. (2016) also found a similar relationship, with the highest relative CVD risk in patients with FH aged 30–40 years (RR: 6; 95% CI: 9–27). It is possible that the decreasing relative mortality observed in older patients is the result of selection bias, with only the patients with the least severe FH surviving until old age [10].

Sex

Sex is another important risk factor, and most studies reported separate risk estimates for male and female patients with FH. Most studies found that males have a numerically higher CVD risk compared with females, although the actual difference varied by study. For example, Jensen et al. (1967) reported an SMR of 2.88 (95% CI: 1.73–4.46) for males and 1.71 (95% CI: 0.91–2.93) for females [22]. Similarly, Sijbrands et al. (2000) reported SMRs of 1.48 (95% CI: 1.23–1.78) and 1.16 (0.90-1.46) for males and females, respectively [24]. Some studies specifically examined the CVD risk of males versus females: Mohrschladt et al. (2004) reported a risk estimate for CVD in males versus females of 2.4 (95% CI: 1.0–5.7) [26], Versmissen et al. (2008) found that men had a 2.5-fold (95% CI: 2.1–3.1) greater risk of CHD than women [19], and Perez de Isla et al. (2016) found that female sex had an independent protective effect (OR: 0.27; 95% CI: 0.20–0.38) [12]. Slack et al. (1969) found that the cumulative probability of a IHD event by 60 years of age was 85.4% for men and 57.5% for women when comparing FH with hyperlipoproteinemia [23]. They also found that patients with FH develop IHD at a mean age of 42.7 years for men and 48.4 years for women. Similarly, Mabuchi et al. (1989) reported that the mean age of death from cardiac events was significantly younger for men (54 years) than women (68 years) [14], while Alonso et al. (2008) found that the mean age at onset of cardiovascular events was 42.1 years in men and 50.8 years in women [17].

While most of the studies support the finding that men with FH have a higher risk than women with FH, Benn et al. (2012) found no significant difference in risk estimates between men and women with this condition [13], while three studies showed the opposite effect [15,16,21]. Mundal et al. (2014) found a numerically higher risk of CVD mortality in women (SMR: 1.75; 95% CI: 1.19–2.58) than in men (SMR: 1.41; 95% CI: 0.96–2.06) [21]. The two Broome Registry studies also found a higher risk in women with FH versus male patients, but the results were not statistically significant [15,16].

Individual FH mutations

Most of the early studies did not include mutation analysis [14-16,22,23]. Several of the most recent studies analyzed mutations for identification of patients with FH and to report mutation frequency, but did not estimate their impact on CVD risk. Benn et al. (2012) used the Dutch Lipid Clinic Network criteria to categorize Danish patients as having possible, probable, and definite FH [13]. With these criteria, presence of specified LDLR mutations (W23X, W66G, and W556S – which accounted for 36% of LDLR mutations in the Danish population) classified a patient as definite FH. Similarly, Robinson et al. used the Dutch genetic cascade screening program to identify patients with FH. Patients with APOB mutations and non-class 1 LDLR mutations were excluded from the analysis because several mild mutations are particularly prevalent in the Netherlands [10]. Mundal et al. used molecular diagnosis of FH to identify 4,688 patients, and matched them to the Norwegian Cause of Death Registry [21]. Among the 113 deaths observed during follow-up, 32 different mutation types were identified, the most common being in the LDLR gene. Besseling et al. used an FH-screening program in the Netherlands to identify carriers of FH mutations and subsequently analyzed first-degree relatives of those patients [20].

Some of the more recent studies analyzed mutations for two reasons: to allow patient identification and selection based on specific, known FH mutations, and to examine whether specific FH mutations are themselves a risk factor for increased CVD risk. The first study to include molecular genetic analysis was Alonso (2008), in which patients from the Spanish National FH Register were screened for a defect in the LDLR gene [17]. The authors found >204 different point mutations and 16 different large rearrangements along the LDLR gene, with the 10 most frequent mutations found in 31.5% of patients, confirm high genetic heterogeneity in the Spanish FH population. Mutations were classified as receptor-negative (null) or receptor-defective depending on their functional class. Patients carrying null mutations had significantly higher total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio ($P<0.05$), frequency of premature CVD (OR: 1.68; 95% CI: 1.10–2.40; $P<0.01$), and recurrence of cardiovascular events ($P<0.05$) compared with patients carrying defective-mutations.

Two studies by Sijbrands et al. incorporated genetic testing, but in different ways. The earlier study traced 855 first-degree relatives of 113 unrelated patients [24,25]. Patients with hypercholesterolemia and the apoliprotein B3500 mutation, and other primary and secondary hyperlipoproteinemias, were excluded from the study. The authors compared mortality between all 97 first-degree relatives of 14 carriers of null alleles and the 156 relatives of 24 carriers of other types of mutations in LDLR. After controlling for sex and calendar period, mortality risk in relatives of patients with null alleles compared with relatives of those with other types of mutations was not statistically significant (OR: 1.05; 95% CI: 0.63–1.74; $P=0.8$). The second study traced the ancestry of three selected probands with the same mutation (V408M) [25], which had the advantage of not selecting patients on the basis of clinical manifestations of FH, although it did prevent comparisons between mutations. Based on data from the Spanish Familial Hypercholesterolemia Cohort Study, Perez de Isla et al. (2016)

used molecular analysis to define patients with heterozygous FH [12]. They identified 209 different functional mutations in LDLR and APOB genes, although the type of mutation (null or defective) was not independently associated with the existence of CVD (P=0.29).

Homozygous FH

Patients with homozygous FH have higher levels of LDL-C and higher cardiovascular risk compared with heterozygotes, which could affect CVD risk estimates if they are included in some studies and excluded from others. However, homozygous patients are very rare compared with heterozygous patients [1], so they are frequently excluded from these studies. Eleven of the 17 studies explicitly included only heterozygous patients [10,12,15-18,20,21,23-25], while a further five studies did not report whether homozygous patients were included or excluded [11,13,19,22,26]. Mabuchi et al. (1986) included both heterozygous and homozygous patients in their study, but excluded homozygous patients when calculating risk estimates. There is no obvious relationship between exclusion of homozygous patients and risk estimates [14].

Other parameters impacting CVD risk in FH

Inclusion of patients with a history of CVD in studies could potentially affect risk estimates. Of the studies in this review, six did not explicitly discuss previous CVD [14,20-23,25], one excluded patients with a history of CVD [19], and eight included patients with a previous history of CVD but did not estimate its impact on subsequent CVD risk [10,11,13,15-18,26]. In Sijbrands et al. (2000), 62 of 113 families were referred based on the presence of premature cardiovascular symptoms in at least one family member [24]. To understand the impact of this effect on mortality, the authors performed separate analyses on patients with and without premature CAD. The SMR for relatives from families with premature CAD was 1.62 (95% CI: 1.32–1.93; P=0.001) and for relatives from families without premature CAD was 1.10 (95% CI: 0.86–1.34; P=0.4). Perez de Isla et al. (2016) found that history of premature CVD was significantly higher in patients with FH compared with unaffected relatives (P<0.001), although there were no significant differences in the prevalence of familial history of premature CVD [12].

Within the studies reviewed, the durations of FH management and specific treatment were not directly studied. However, successive publications from the Simon Broome registries in the UK have presumably used the same initial cohort of patients augmented with additional recruitment over time [15,16]. Each successive article therefore at least partly includes patients with progressively longer durations of treatment, which could have reduced the reported risk of CVD in patients with FH as seen in those publications.

Restricting outcomes to include only fatal outcomes could lower the estimated risk of CVD estimates compared with studies that include both fatal and non-fatal outcomes, which occur more frequently. Nine studies focused specifically on CVD mortality [14-16,18,21,22,24-26] while seven studies, including Benn et al. (2012), included both fatal and non-fatal cardiovascular events in their risk estimates [11-13,17,19,20,23], and one study focused on non-fatal atherosclerotic CVD [10]. Examining the relationship between fatal/non-fatal CVD risk and FH risk estimates, studies that focused on fatal outcomes tended to have lower risk estimates compared with studies that included both fatal and non-fatal events.

Discussion

This systematic literature review extended a previous review of studies that estimated CVD risk in FH populations, and a formal assessment of study bias was used to determine the least biased literature-based estimate for the increased risk of CVD among patients with FH. Three additional studies were identified in this updated review, one of which included estimates from Brazil [11], a country that was not represented in the previous review, while the other two studies provided new estimates in countries previously included (Spain and the Netherlands) [10,12].

When the three new studies were included with the original 14 papers in the formal bias assessment, the same general trends in sources of bias were found as previously reported [8], and the study by Benn et al. (2012), a population-level survey undertaken in Denmark [13], was confirmed as providing the least biased risk estimate. Such population-based studies are very rare, and no similar studies were identified in the updated literature review, which included two registry studies [10,12] and one hospital-based study [11]. While interest in FH has increased in recent years among the scientific community, issues relating to under-diagnosis [1] still hinder the feasibility of population studies.

The early hospital-based and family-based studies concerning FH were descriptive observations of a new phenomenon within small groups of patients or families in which it was observed that CVD was particularly common. As occurs in much of medicine, these case descriptions were valuable in generating the hypothesis concerning the increased cardiovascular risk associated with FH. Indeed, the magnitude of increase in cardiovascular risk identified in these early reports left little doubt that the increase was genuine. The more recent hospital-based studies included genetic testing for patient identification but retained some of the same biases as the earlier studies. Formal bias assessments of these studies show that they are less useful for specific quantification of the risk.

Registries are a convenient and easily available data source for studying the risk of FH, and registry-derived data were still the most common source of literature-based estimates of increased CVD risk, accounting for 10 of the 17 studies. In all instances, registries were national programs designed to identify as many patients as possible with the highest risk in the most efficient way, and then to manage their risk with the best therapies available for the remainder of the individual's life or as long as possible. Common methods were used to identify patients with early CVD, find index cases, and undertake cascade family screening, and to intensify case finding within specialty settings. Although these methods are efficient and appropriate for registries, they result in higher bias assessments when the purpose is to understand the magnitude of increase in cardiovascular risk. In particular, registries are susceptible to patient selection and ascertainment bias as a result of these recruitment methods, as well bias resulting from comparisons made versus the general population.

The present study expanded the previous systematic review by examining other risk factors in FH populations. Age was one of the most commonly studied risk factors. Consistent with general literature on age, most studies, particularly the registry studies, found that SMR is highest in young patients with FH, usually in the age cohort of 20–39 years old, and declines in older patient cohorts. This is likely to be linked with the increase in cardiovascular risk with age in individuals without FH, and the high early mortality of patients with FH around the age of 50 years. In a few studies, notably hospital-based studies, the highest risk occurred in the patients aged 40–59 years. It is possible that the hospital-based studies, which have a higher degree of selection bias as a result of the limited populations from which they draw, were identifying patient populations that were more likely to be receiving

appropriate management of their condition. This in turn would reduce the severity of FH, leading to longer survival.

Sex was another commonly studied risk factor. Most studies that examined either separate CVD risk estimates for men and women, or estimated CVD risk for males compared with females, found a significantly higher risk for men with FH. Three studies also found that mean age of death and/or cardiovascular events was much earlier for men than for women [14,17,23]. There appeared to be no relationship between these findings and type of study. While most of the evidence supports higher risk in men with FH, Mundal et al. (2014) found a higher risk of CVD mortality in women than in men [21]. The Broome Registry studies observed a similar effect, although it was not statistically significant [15,16], and Benn et al. (2012) found no significant difference in risk estimates between men and women with FH [13]. Given these findings, a better understanding of the impact of sex on CVD risk in patients with FH is needed.

Eight of the studies in this systematic review performed genetic testing, although most of these reported frequency of mutations or associations between mutations and LDL-C measures, rather than calculating a risk estimate. Recent evidence has shown a very high risk of CVD resulting from FH-causing mutations. In a study of patients with severe hypercholesterolemia, Khera et al. (2016) found that patients with LDL-C ≥190 mg/dL and no FH mutation had a 6-fold higher risk of CVD compared with a reference group with LDL-C <130 mg/dL and no mutation [27]. Patients with both LDL-C ≥190 mg/dL and an FH mutation had a 22-fold increased risk. Benn et al. (2016) examined mutations present in 98,099 participants from their general population study [13] and found a very high OR for four mutations – three in LDLR (W23X;W66G;W556S) and one in APOB (R3500Q) – in patients fitting the clinical criteria of definite or probable FH [28], validating the diagnostic criteria used in that study. Additional research is needed to better understand which mutations lead to elevated risk of CVD.

Some of the studies also employed genetic testing to identify patients with FH and controls, which were used for both patient selection and identification of specific mutations. Homozygous patients have much higher levels of LDL-C and higher cardiovascular risk than heterozygotes, which could lead to a higher CVD risk if homozygous patients are included in analyses at variable rates. Homozygous FH is, however, much rarer than heterozygous FH, with a prevalence estimated about 1:1,000,000 compared with 1:500 for heterozygous FH [2]. To minimize the impact, 11 of the studies excluded homozygous FH patients. The remaining studies either did not use genetic testing or did not explicitly state whether homozygous FH were included in the studies. There was no obvious impact of including homozygous patients on the estimate of CVD risk.

Other parameters and study design methodologies that could affect CVD risk estimates include the inclusion of patients with a history of previous CVD, measuring exclusively fatal or non-fatal outcomes, and accounting for FH treatment [1,29]. Patients with previous CVD have a higher risk of subsequent CVD, and exclusion of these patients could lower the risk estimates. Ten studies explicitly included patients with a previous history of CVD and one study explicitly excluded such patients. Perez de Isla et al. (2016) found that history of premature CVD was significantly higher in patients with FH [12], which suggests that excluding these patients would lower CVD risk. There is, however, no obvious pattern to the risk estimates based on this criterion, which could be the result of other risk factors masking the impact of previous CVD. In contrast, eight studies explicitly measured fatal CVD risk, and these studies tended to have lower estimates compared with the studies that also measured non-fatal outcomes. This measurement difference can have a large impact on risk estimates and is important to take into account when comparing studies. The durations of general FH management and of specific treatments were not specifically included as risk factors in any of the studies in the review. As noted above, however, the Simon Broome registries have maintained an initial cohort of patients in the UK and recruited additional patients over time [15,16], which may lead to a reduction in the apparent risk of CVD in successive publications.

Although published too recently to be identified by this systematic literature review update, two quantitative analyses of risk factors in patients with FH are now available [30,31]. In a study of the Spanish SAFEHEART registry, 2,404 adults with FH were followed-up for a mean of 5.5 years [30]. Age, male sex, history of previous atherosclerotic CVD, high blood pressure, increased body mass index, active smoking, and LDL-C and lipoprotein(a) levels were found to be independent predictors of incident atherosclerotic CVD. These parameters were then combined by the authors into a single risk equation (SAFEHEART-RE) to allow stratification of patients with FH. In a Canadian study, predictors of risk were identified in 638 patients with an LDLR mutation [31]. Age, HDL-C, male sex, hypertension, and smoking were found to be independent predictors of CVD risk. Combination of these factors into a single score (Montreal-FH-SCORE) provided significantly better risk prediction than any individual factor, with a high Montreal-FH-SCORE associated with 10.3-fold increased risk of CVD events compared with patients with a lower score.

Limitations of the bias analysis used in the present review are the same as those described for the earlier review of which this is an update [8]. Firstly, it should be noted that non-English language publications were excluded from the review. Furthermore, we have not examined the literature for the increase in risk of other cardiovascular manifestations in patients with FH, and have focused on cardiac morbidity and mortality as the most recognized source of CVD. Most of the articles in this review used 'cardiovascular death' as an endpoint of interest, on the assumption that death was the result of CAD, coronary arterial occlusion, and finally MI. The risk determined from this endpoint is then reported as cardiovascular risk. The effects of accelerated atherosclerosis in FH, however, are not limited to the coronary arteries. Atherosclerosis in cerebral vessels, resulting in stroke, tends to occur at a later age, whereas atherosclerosis in peripheral arteries leading to limb ischemia is less frequently reported overall. Both conditions are less recognized than CVD in association with FH.

Conclusions

This review builds upon a previous literature review [8] by expanding the number of studies that estimate the risk of CVD in patients with FH, including one new geographic region and new study designs, and examines other risk factors in the FH population. Many of the studies have biases in their design that could affect their risk estimates. We found that Benn et al (2012), the only population survey-based study in our review [13], remains the best performer for its lack of bias as a well-conducted study, providing credible estimates of the increased risk in patients with FH. The risk of CVD due to FH is high and represents unmet medical need. Other risk factors, including age, sex, and genetic mutations, also appear to have an impact on CVD risk in the FH population. Further research is needed to assess how these, and other key parameters assessed in recent quantitative studies [30,31] – such as blood pressure, body mass index, smoking, and serum lipid levels – interact with FH to affect CVD risk.

Acknowledgments

The study was funded by Amgen (Europe) GmbH. Dr Kutikova of Amgen is an author on this manuscript. Editing assistance was provided by Dan Booth PhD (Bioscript Medical Ltd, Macclesfield, UK) and funded by Amgen (Europe) GmbH (Zug, Switzerland).

Disclosures

- GK reports no conflict of interest.
- LK, GV are employees of Amgen (Europe) GmbH and own stocks.
- BW received consulting fees from Bayer, Sanofi-Aventis, Takeda, AbbVie, and Amgen. This includes consulting fees from Amgen (Europe) GmbH for the current paper. He is a current employee of Bayer Healthcare.
- KR received research grants from Regeneron, Pfizer, Amgen, and Sanofi; consulting fees from Amgen, Sanofi, Regeneron, MedCo, Cerenis, Lilly, Ionis Pharma, Abbvie; and speaker's bureau from Kowa, AstraZeneca, Pfizer, Takeda, Boehringer Ingelheim, Algorithm, Cipla.
- PM received consulting fees from Amgen and Sanofi.
- EB received consulting fees from Amgen, MSD, Lilly, Sanofi-Aventis, Regeneron, Aegerion, Chiesi, Danone, Unilever, Astra-Zeneca, onis-pharmaceuticals and Rottapharm-MEDA, AKCEA.

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