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Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia

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ABSTRACT

High low-density-lipoprotein cholesterol (LDL-C) is routinely described as the main cause of cardiovascular disease (CVD) in familial hypercholesterolemia (FH). However, numerous observations are in conflict with Bradford Hill's criteria for causality: a) degree of atherosclerosis is not associated with LDL-C; b) on average the life span of people with FH is about the same as for other people; c) LDL-C of people with FH without CVD is almost as high as in FH patients of the same age with CVD; and d) questionable benefit or none at all have been achieved in the controlled, randomized cholesterol-lowering trials that have included FH individuals only. Obviously, those individuals with FH who suffer from CVD may have inherited other and more important risk factors of CVD than high LDL-C. In accordance, several studies of FH individuals have shown that various coagulation factors may cause CVD. Equally, some non-FH members of an FH kindred with early CVD, have been found to suffer from early CVD as well. The cholesterol-lowering trials have only been successful by using apheresis, a technique that also removes many coagulation factors, or in an animal experiment by using probucol, which has anticoagulant effects as well.

We conclude that systematic studies of all kinds of risk factors among FH individuals are urgently required, because today millions of people with FH are treated with statins, the benefit of which in FH is unproven, and which have many serious side effects.

We predict that treatment of FH individuals with elevated coagulation factors with anticoagulative drugs is more effective than statin treatment alone.

Background

For several decades LDL-cholesterol has been considered as the cause of early CVD in FH. A strong support of this theory is apparently the discoveries by Goldstein and Brown concerning the regulation of cholesterol metabolism, for which they received the Nobel prize. But what Goldstein and Brown discovered was that individuals with FH have an inherited defect in the gene encoding the LDL receptor, which disrupt the normal control of cholesterol metabolism and leads to high LDL levels in the blood; it was not that high LDL-C was the very cause of CVD. Before we introduce our own hypothesis, it is therefore necessary to demonstrate that the current one does not fit with Bradford Hills criteria [1] for causation.

LDL-C and atherosclerosis

If high LDL-C were the cause of CVD in FH, LDL-C should be associated with degree of atherosclerosis, but several observations are in conflict with this assumption.

In a study of 68 untreated FH individuals haemodynamically significant perivascular diseases, diagnosed by ankle/arm blood pressure ratios and analyses of Doppler-derived blood flow velocities were not associated with LDL-C [2].

In a study including 48 individuals with FH or familial combined hyperlipidemia, no association was seen between LDL-C and degree of atherosclerosis analysed by intravascular ultrasound [3].

In a study of 241 FH individuals no association was found between LDL-C and the number of atherosclerotic plaques identified by

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Table 1
Mean LDL-C, mean HDL-C and mean age in FH individuals with and without CVD in studies published before the introduction of statin treatment. None of the participants had been treated with other cholesterol lowering drugs either.

Authors	n		LDL-C (mmol/l)			HDL-C (mmol/l)			Age		
	CVD +	CVD-	CVD +	CVD-	p	CVD +	CVD-	p	CVD +	CVD-	p
Yamashita et al. 1987[7] Men	23	19	7.65	7.09	ns	1.0	1.2	< 0.01	51.1	45.9	ns
Women	11	13	8.10	7.53	ns	1.0	1.3	< 0.01	56.8	52.5	ns
Seed et al. 1990 [8]	54	61	8.1	8.2	ns	1.19	1.18	ns	47.6	42.0	< 0.05
Hill et al. 1991[9] Men	47	68	7.13	6.51	< 0.05	0.99	1.13	< 0.001	48.2	45.3	ns
Women	26	147	7.25	7.01	ns	1.22	1.29	ns	54.7	49.7	ns
Tato et al. 1993[10]	32	59	8.14	7.68	ns	1.08	1.26	0.002	50.8	54.8	ns

n: numbers; ns: not significant.

ultrasound, neither among those with or without cholesterol-lowering treatment [4], and similar studies on FH individuals without lipid-lowering treatment came up with the same result [5,6].

In a study of the brains of ten young patients (3–32 years) with homozygous FH, six of whom had coronary heart disease (CHD), all of them were free from ischaemic brain lesions and had normal cerebral blood flow [7].

People with FH live on average just as long as people without FH

As many of the patients who die from an acute myocardial infarction before the age of 60 have FH, the general view is that the lifespan of FH people is shorter than normally.

However, this observation is misleading. According to the Simon Broome Register Group [8] CHD mortality for both men and women with FH between age 20–39 was about 100 times higher than in the standard population. This figure may seem alarming, but as mortality in the standard population of that age group in the same time period was only 0.06% for men and 0.01% for women, the actual rate of death was extremely low. During 439 person years of observation only five men with FH between ages 20–39 died from CHD, and during 334 years of observation years only one woman died. Furthermore, after age 59, CHD mortality was the same among FH individuals as in the general population in spite of their higher lipid values.

Similar results appeared from a study by Mundal et al. in which 4688 individuals aged 0–80 with FH verified by molecular genetic methods were followed from 1992 to 2010 [9]. During that time 113 died whereas the expected number in the general population was 133. The mortality benefit cannot have been due to lipid-lowering treatment, because there was no significant difference between the number on such treatment among those who died and those above the age of 18 who survived (88.2% versus 89.1%). In accordance, Sijbrand et al. found that many healthy people with FH, aged over 20 years and who came from a kindred without premature CVD, had a life expectancy similar to the general population [10]. It is also in accord with a systematic review having shown that elderly people (≥60 years) from the general population with the highest LDL-C values live longer than elderly people with low values [11]. That many studies have found that the lifespan of FH subjects is shorter than normal may be because they have only included FH patients with CVD and their relatives. These findings indicate that other factors may cause CVD in FH; either alone or possibly in combination with the high LDL-C values.

Of interest is also another study by Sijbrands et al. [12]. They traced family members of three individuals with genetically determined FH back in time and identified a total of 412 individuals living in previous generations. The coronary and total mortality of these members were compared with the mortality of the general Dutch population. The striking finding was that during the 19th century the mortality rate of these FH people was lower than in the general population. The reason was most likely that the commonest cause of death at that time was infectious diseases, and there is much evidence that high LDL-C protects against infections [13]; most likely due to the fact that LDL is able to inactivate almost all kinds of microorganisms and their toxic products [13,14]. This fact may also explain why non-CVD mortality among the FH individuals in the study by Mundal et al. was lower than in the general population [9].

LDL-C in FH people with and without CVD is almost the same

It is generally believed that the higher the LDL-C, the greater the risk of CVD. As LDL-C in FH may vary considerably, those who suffer from CVD should have higher LDL-C than those who do not, and they should also be younger. However, many studies have found that LDL-C, and the age of those with and without CVD and without lipid lowering treatment do not differ significantly. In most of these studies many of the participants had been on statin treatment for several years, which may introduce a bias. However, no difference was found either in four studies of FH individuals whose LDL-C was analysed before the introduction of statin treatment and before they were offered any lipid-lowering treatment [15–18]. As shown in Table 1 the mean LDL-C and the mean age of those with and without CVD did not differ significantly in five of the six cohorts included in these studies. In contrast, high-density-lipoprotein HDL-C was significantly lower in four of the six cohorts with CVD.

Questionable benefit from the cholesterol-lowering trials

The strongest argument for causality is the placebo-controlled, randomized trial where a lowering of the suspected causal factor results in a lowering of the disease in question. For ethical reasons few such trials have been performed on FH individuals. Instead, a high intensity cholesterol-lowering has been compared with a low intensity lowering. Apart from the use of apheresis, none of these trials have succeeded in improving clinical outcomes including: CHD mortality, total mortality, non-fatal CHD, or CVD events [19–27] (Table 2). Benefit was claimed in the ASAP trial [20], where the arterial intima-media thickness was reduced by 0.031 mm in the group treated with 80 mg atorvastatin. On the other hand, during the same period, it increased by 0.036 mm in the group treated with 40 mg simvastatin. It may be argued that these trials were too short to provide useful information. However, three of them went on for two years and one of them for ten years.

Our hypothesis

The above-mentioned findings contradict the mainstream view that high LDL-C is the major cause of CVD in FH. Additionally, the decrease of CVD risk in older people with FH, supports the idea that factors other than high LDL-C may be the cause of premature CVD in young and middle-age FH individuals, and that these factors are absent among those who survive. These non-lipid factors may be expressed by genes associated with the FH genotypes. If so, some of the members in families with FH, but with normal lipid values, will have inherited these

Table 2
The results from nine randomized, controlled cholesterol-lowering FH trials. None of the results were statistically significant.

	Treatment	n H/L	Trial length; years	CHD mortality; T/C (n) T/C (%)	Total mortality; T/C (n) T/C (%)	Non-fatal CHD; T/C (n) T/C (%)	CVD events; T/C (n) T/C (%)
Koivisto et al.[11]	Ileal bypass vs usual treatment	27/27	10.4	5/4 18.5/14.8	8/8 29.6/29.6	3/3 11.1/11.1	8/7 29.6/25.9
ASAP[12]	80 mg atorvastatin vs 40 mg simvastatin	141/139	2	1/1 0.7/0.7	1/2 0.7/1.4	0/0 0/0	2/2 1.4/1.4
RADIANCE[13]	Torcetrapip + atorvastatin vs atorvastatin	423/427	2	0/1 0/0.2	0/1 0/0.2	3/0 0.7/0	24/11 5.7/2.6
ENHANCE[14]	Ezetimibe + simvastatin vs simvastatin	357/363	2	0/0	0/1 0/0.2	3/2 0.8/0.6	10/7 2.7/1.9
Koren et al.[15]	Evolocumab vs usual care	736/368	1	1/2 0.1/0.5	1/2 0.1/0.5	ni	9/8 1.2/2.2
ODYSSEY FH1[16]	Alirocumab vs placebo	322/163	1.5	0/0	6/0 1.9/0	ni	8/3 2.5/1.8
ODYSSEY FH2[16]	Alirocumab vs placebo	164/81	1.5	0/0	0/0	ni	2/1 1.2/1.2
ODYSSEY LONG-TERM[17]	Alirocumab vs placebo	1530/780	1.5	5#/7# 0.3/0.9	8/10 0.5/1.3	14/18 0.9/2.3	70/40 4.6/5.1
ODYSSEY HIGH[18]	Alirocumab vs placebo	72/35	1.5	0/0	0/0	4/0 5.6/0	10/0 13.9/0
ODYSSEY JAPAN[19]	Alirocumab vs placebo	144/72	1	0/0	0/0	1/1 0.7/1.4	4/2 2.8/2.8
Total		3919/2455					
Mean (%)				0.31/0.61	0.61/0.98	0.92/1.14	3.54/4.01

T: treatment group or group with high-degree LDL-C lowering; C: Control group with low-degree LDL-C lowering or placebo; ni: no information; #: included deaths from unknown cause.

factors and have a greater risk of a suboptimal life span, compared with normal people. This conjecture is supported by the findings by Harlan et al. [28]. They examined nine generations of 1691 related individuals, where a substantial subset of the sample had FH. They analysed the age at death of 40 members of a FH kindred and found that the mean age at death of 13 men with FH was 57.3 years and of 6 men without FH it was 61.8 years. Among 11 women with FH the mean age at death was 65.7 years, whereas it was only 59.3 years among those without FH. Thus, men with FH lived almost as long as their relatives without FH, and women with FH lived six years longer than those without FH. At that time, mean life expectancy in the US was 67 and 75 years for white males and females, respectively, and about 61 and 67 years for non-white males and females, respectively. Heiberg and Slack also found that siblings with and without FH had a similar age of death [29].

The possibility that factors other than raised LDL-C are associated more strongly to the risk of CVD, is supported in many different studies. We have found that the commonest and best documented ones are in-born errors of the coagulation system.

In a study of 17 FH subjects and 26 normal subjects Carvalho et al. found that those with FH had significantly higher sensitivity to aggregating agents ($p < 0.001$)[30].

In another study of FH individuals, Aviram et al. found that their platelets were significantly more reactive to various aggregating agents than platelets obtained from normal individuals. Furthermore, incubating washed platelets from normal individuals with plasma from FH subjects also showed increased response to aggregating agents, whereas washed platelets from FH subjects had a significant decrease of activity [31], providing definitive proof that the increased platelet activation in FH patients is induced by abnormal plasma constituents.

Sugrue et al. found that plasma fibrinogen and factor VIII were significantly higher among FH subjects with CVD, whereas there was no significant difference as regards LDL-C or any other lipid [32].

In a study of nine FH subjects and 10 normal, control subjects matched for sex and age, DiMinno et al. found that in response to adenosine 5-diphosphate, collagen or thrombin, FH platelets from the FH subjects bound about twice as much ^{125}l-fibrinogen as platelets from the controls [33].

In a study of 39 subjects with FH, a third of whom had CVD, Sebestjen et al. found that those with CVD had significantly higher levels of: insulin, insulin resistance, triglycerides, t-PAI-1 antigen and activity and significant lower HDL-C, whereas there were no significant differences as regards, smoking, blood pressure, obesity or LDL-C [34].

Jansen et al. genotyped 1940 FH patients for 65 polymorphisms in 36 candidate genes and found that polymorphism in the prothrombin gene was significantly associated with an increased risk of CVD [35].

In a comparison between 164 FH subjects without CVD and without lipid-lowering therapy and 160 normolipidemic controls matched for age, gender, smoking, and hypertension, Icli et al. found that the mean platelet volume was significantly higher in the FH subjects [36], and as documented by Boos et al. larger platelets are more active, and thereby prone to adhesion and aggregation [37].

Conclusions

It seems clear that in those individuals with FH who suffer premature CVD, the key abnormality is one of coagulopathy. The benefits seen in apheresis supports this conjecture, because apheresis removes not only blood lipids, but also many factors that promote coagulation [38,39]. Our hypothesis is also supported by the finding that HDL-C is higher among those without CVD [7–10], because increased HDL-C is associated with multiple antithrombotic actions [40]. Furthermore, the rabbit model of FH demonstrates significantly higher levels of factor VIII and fibrinogen compared with normal rabbits, and treatment of these rabbits with probucol, which has anticoagulant effects, lowers factor VIII and fibrinogen and prevents atherosclerosis in the absence of a significant reduction of plasma cholesterol [41].

Our findings strongly suggest that other risk factors than high LDL-C may be the key players in increasing CVD risk in FH. As millions of FH subjects all over the world are treated with lipid-lowering drugs with questionable benefit and many serious side effects [42], now it may be the time to test the blood coagulation hypothesis using different anticoagulant approaches.

Conflicts of interest

None.

Contributors

UR wrote the first draft of the manuscript. All authors have made major improvements of the content and the wording.

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