

## Chapter 7. Estimate of the FH frequency in Belgium

The prevalence of FH in our country has never been studied and in 1991, we could then really question the “universally” reported frequency of “1/500” in our region (“Le Centre” with 250.000 inhabitants and thus 500 expected FH patients), as we knew only a dozen of FH patients. As population screening of genetic disease is expensive and raises ethical problems, we used the data of the large number of patients recruited in our region to deduce some conclusions about FH frequency.

### **1. Based on genetically ascertained FH patients of our lipid clinics**

As mentioned in Table 5-2 in Chapter 5, 271 patients living in a defined geographical area around our hospital (“Le Centre”) were genetically confirmed as having FH. Given an approximate population size of 250.000 in this area, the prevalence may be estimated to  $271 / 250.000 = 0.0011$  (0.11% ~ 1 / 900)<sup>37</sup>. This estimate was minimal as not all hypercholesterolemic patients were referred to us and as the genetic tests did not allow to confirm all FH. From the family data regarding “HC or early CVD in relatives” collected from the 113 confirmed FH index patients (Table 5-2) living in this region, we estimated to 579 the number of their family members suspected of FH (of whom 271 have been so far confirmed by genetic test). Therefore, the average number of FH relatives by family was thus 5,1 and the prevalence of heFH may approach  $1/431$  ( $579/250.000$ )<sup>38</sup>, which was still an underestimation as we considered only the number of close relative (2° and rarely 3° degree relatives) for which we had the most precise data. Nevertheless, this minimal estimate reached already the theoretical prevalence estimated in Europe and suggests that the true prevalence exceeds largely 1/500 in our region.

It was possible also to estimate the number of FH patients by general practitioners. About 496 GP referred patients to our hospital and amongst them, 138 GP referred patients suspected of FH to our lipid clinics (Fig. 7-1). The number of confirmed FH patients by GP may be estimated on average to 1,96 (271 divided by 138)<sup>39</sup> with 40% of GP having at least 3 FH patients amongst his patients. This was also a minimal estimate because GP did not systematically screen cholesterol in all their patients, especially young adults and because they referred to us only patients for whom they had problems in managing lipids.

Finally if we compared our FH prevalence with those of other rare (more symptomatic) diseases like type I diabetes (N=242), rheumatoid arthritis (N=167) or

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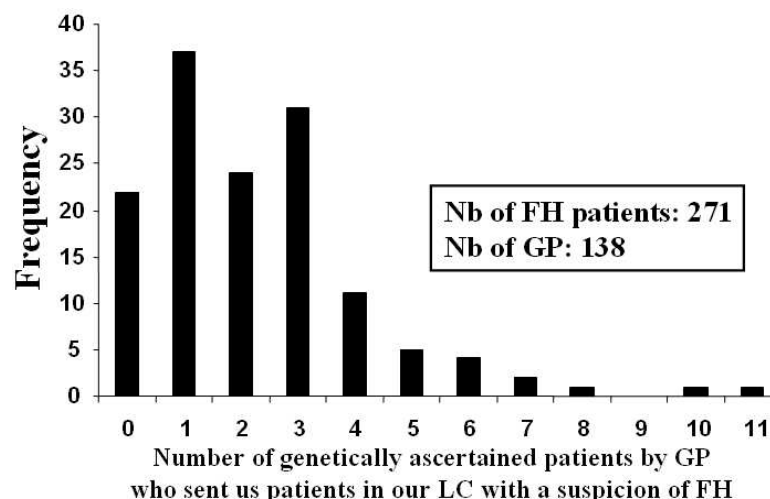
<sup>37</sup> If we take into account of the 15 families of foreign origin (including 30 family members, table 5-2) living in the regions of “Le Centre”, the prevalence was  $301 / 250.000 = 0.0012$  (0.12% ~ 1/830)

<sup>38</sup> Including the 15 families of foreign origin (including 77 family members suspected of FH), the prevalence was  $656 / 250.000 \sim 1/380$ .

<sup>39</sup> Including the 30 patients and relatives of foreign origin and genetically ascertained, this ratio became 2.18 patients by GP.

ulcero-haemorrhagic recto-colitis (N=131)<sup>40</sup>, we could say that FH was more frequent than these diseases (>1-2 FH for each type I diabetes).

**Figure 7-1. Distribution of the number of ascertained FH patients by GP**



The histogram strongly suggests a Poisson distribution (discovery of a FH patient is a rare event). However, the assumption of independence between events is not respected as new cases can easily be found when a patient is found in one family. This may explain the possible distribution bimodality.

## **2. From the number of homozygous FH patients in Belgium**

We diagnosed 5 homozygous FH cases (including two compound heterozygotes for FH and FDB) and heard about 4 other cases (2 in Wallonia and 2 in Flanders). This observed hoFH frequency (9/10.000.000 Belgians) appeared close to the expected prevalence of 1/1000000 found in most countries. However, it was most likely an underestimation given the non proportionality between North and South Belgium: 2/3 of Belgians live in the North but 7 out of 9 hoFH cases live in Wallonia. Is this suggestive that hoFH failed to be recognized in some regions?

## **3. GHHainaut project (“Genetic Hypercholesterolemia in Hainaut”)**

The “GHHainaut study” was a project aimed to promote identification of FH/FDB in the “Province de Hainaut” by GP through a molecular diagnosis service. The hypothesis driving this project was that each GP could find at least one patient with FH. In 1996, 176 GP were asked to collect clinical data and blood samples in families with evidence of inherited HC ([TC]>300 mg/dl). After one year, 174 blood samples from index patients (as well as 73 blood samples of relatives of these IP) were collected by 91 GP (51% participation). After exclusion of 8 index patients who did not comply the selection criteria, 174 index patients (from 86 GP) remained included in the study. Mean TC and mean age in the index cases were  $374 \pm 69$

<sup>40</sup> These numbers were kindly estimated and provided by doctors Philippe Jopart, Christian Docquier, Florence Daumerie and Michael Shapira

mg/dl and  $45.5 \pm 12.3$  years. Of the selected sample, 78% were considered at high probability of having FH because they displayed either tendon xanthoma (only 16% had TX in the IP or in the family), hypercholesterolemic children in the family, or more than 2 hypercholesterolemic first-degree relatives. Genetic screening was conducted in the 174 index cases and confirmed FH in 63 patients (36% of the 174 IP, from 43 GP): 5 with APOB\*R3500Q mutation and 58 with LDLR mutants (27 different mutations). 60 out of 63 mutants were found in patients with the highest suspicion. In phase II, the GP were informed of the results and the 43 GP with a positive IP patients were asked to send blood samples and information about cholesterol screening in the members of the families: 54 blood samples of relatives (including 18 blood samples of relatives initially sent with the blood samples of these index patients) from 29 index patients were sent by 26 GP in the next following year (60% of the recontacted 43 GP). Mutations were found in 42 (77%). Therefore, in this limited period of time, 63 patients and 42 relatives could be found by 91 motivated GP, suggesting that, in a longer period of time, GP should be able to find more than one FH patient.

#### **4. Discussion about these data**

1. In our region, *the prevalence of FH* is probably higher than the theoretical prevalence reported for most European countries (*1/500*). Interestingly, the high frequency of four of our mutations may reflect a possible founding effect and such effect is often associated with higher prevalence in the concerned region. Whether this frequency can be extrapolated to other parts of Belgium is not easy to answer as there may be some geographical heterogeneity in the population. However, if the frequency in Belgium is around 1/500, it means that FH might be considered as a public health problem greater than infection by HIV or type 1 diabetes: about 20.000 Belgians may be affected by this disease. Even if FH requires high statin dosage (equivalent to 2-4 DDD) and combination with other lipid-lowering drug, it contributes thus to a relatively small drug cost<sup>41</sup>. This number also suggests that each GP knows 1 or 2 FH patients (20.000 FH Belgians for 9000 active GP means).

2. In Belgium, we can say that FH is still underdiagnosed. In 1994, less than 10% (less than 50 patients) were truly diagnosed in our specific region (250.000 inhabitants and thus 500 FH individuals). After 10 years of very intensive and proactive effort to raise awareness amongst GP and to screen relatives in the identified families, we are happy to say today that probably more than 50% of the FH population of our region are recognised in our region (271 patients PLUS the many others where FH diagnosis could not be confirmed by genetic tests but was highly suspected). It is likely however that, without such active program, underdiagnosis remains important in most other regions of Belgium, like in most other regions of the world (Neil 2000, Micha 2001). Even if we cannot exclude that some “unrecognised FH” patients are being treated for their high cholesterol level like any other HC patients, we are less confident that they are sufficiently treated and that family screening has been performed. Other arguments for such

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<sup>41</sup> Currently, the total Belgian consumption of statines is estimated to 800.000 DDD per yer (Annemans 2006).

underdiagnosis are the non participation of 86 GP in the GHHainaut project, the slowness to obtain the participation of most relatives in all FH families, but also the disproportion of the prevalence of known homozygous FH between the Flanders and Wallonia.

## Chapter 8. Why is it important to diagnose FH ?

### **1. General view of the question**

When a doctor takes care of a patient with hypercholesterolemia (HC), good clinical practice requires (according to the last European guidelines, De Backer 2004), first to exclude a secondary cause of this HC, second to estimate the global CVD risk and third, if at high risk, to treat him intensively but also to examine all first-degree relatives. In other words, the treatment of high risk patients and the screening for risk factors of his first-degree relatives are mandatory and need to be performed, no matter if the patient is known to have or not a genetic cause for his HC. So the question often asked by practitioners is: “Why do we need to identify precisely the cause of the HC?” Screening for a genetic disease can only be justified if it meets “the principle of proportionality”: the possible benefits should outweigh the possible harms. Here, I summarise some of the reasons why it is (“pro”) or not (“contro”) important, in HC patients, to identify more specifically those with FH.

#### **1.1. “Pro”**

The need to distinguish FH from other causes of HC is based on 3 theoretical reasons that are sufficiently supported by logical or “evidence-based arguments and that translate into clinical practical attitudes in the clinical management for FH-differing from those for NFH-patients.

##### ***1.1.1. Rationales***

1. FH predicts very high risk of CVD, even in the absence of other risk factors because patients are exposed to higher cholesterol levels for longer periods of time (since birth) in FH compared to other causes of HC which start later at adulthood.
2. FH has a specific cause, the defect of LDL receptor pathway, which is only affected by intracellular cholesterol (and also some hormones like estrogens) but not by factors such as caloric restriction, weight loss or physical exercise.
3. FH is dominantly inherited; therefore 50% first-degree relatives (parents, siblings, children), 25% second-degree relatives (aunt/uncle, niece/nephew, grandchildren, grandparents) and 12.5% third-degree relatives may be affected.

##### ***1.1.2. Clinical consequences***

1. The diagnosis must be as clear as possible. Certainly, the demonstration of a functional mutation is the strongest argument for FH. A clear FH diagnosis must be considered as a proof that the patient is at very high risk whatever the presence or absence of other risk factors and thus, an argument to start the treatment at once.
2. The diagnosis must be extended as far as possible in the family. An FH diagnosis in one patient may result in numerous other FH diagnosis for many generations. Such screening, especially in more distant and less available relatives can be only

performed at the conditions of being well motivated and of having a reliable test like DNA testing.

3. The diagnosis must be performed as early as possible, and certainly before 40 years (the usual age at which most individuals start to consult physicians for cholesterol check-up). As shown by others and ourselves (Chapter 6), silent or symptomatic coronary atherosclerosis is often present in 40-year old FH men. The earlier the diagnosis is made; the earlier cholesterol lowering therapy can be initiated with a diet and drug management program. Earlier diagnosis (especially by positive DNA test) at the critical time of childhood (before habits are established) allows earlier education of good dietary and lifestyle principles and may facilitate future compliance for lipid lowering drugs.

4. The treatment must be as early, as specific and as intensive as possible. The lifestyle prescription of aerobic exercise, low calorie intake (like diabetic diet) and weight loss have little impact on the LDL-C<sup>42</sup> in patients with FH in contrast to other causes of high cholesterol like FCHL or PH (especially in presence of hyperinsulinemia, low HDL-C, high blood pressure). Only low saturated fat and low cholesterol diet has an impact on blood cholesterol in FH. Statin is really the drug of first choice in FH and should be prescribed and titrated rapidly to high dosages (Pilote 2005, Prosser 2000). It is cost-effective in FH patients at high CVD risk (Goldman 1993). Since its introduction in 1989, the prognosis of FH has greatly improved (SBRG 1999). As statin reduces risk of CHD in proportion to the degree to which it reduces LDL-C in the general population (Studer 2005) and in FH-patients (Smilde 2001), it is recommended to lower LDL-C as low as possible. Recently, LDL-C targets that differ from the usual recommendations in the general population have been suggested in FH (Chapter 6). Statin can be combined with ezetimibe and/or bile acid chelators. Stanol/stenol preparations that reduce cholesterol absorption are also interesting (not in association with ezetimibe).

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<sup>42</sup> The use of oral contraceptive (OC) in women must be indicated with caution and it is prudent to recommend alternative methods of contraception in FH women of childbearing. There is no published experience of the effect of using OC in FH women, but we may extrapolate to them the conclusions of the observations in the general population that shows that the use of oral contraceptives leads to an increased risk of venous thrombosis, of myocardial infarction, of stroke and of peripheral artery disease (Rosendaal 2003, Tanis 2003). The risk of myocardial infarction and stroke is more pronounced in users who smoke or have hypertension, diabetes and hypercholesterolemia. This last point interests particularly the population of FH women. As plausible explanation for these adverse effects, hormonal contraceptives are known to cause coagulation changes and affects lipoprotein and carbohydrate metabolism. Regarding lipid metabolism, estrogens have a double effect in the liver: they induce LDLr activity but they also increase the synthesis of VLDL (Semenkovich 1987). In Menopausal women, estrogen treatment is thought to lower LDL-C by increasing clearance through hepatic LDL receptors. In oral contraceptives, estrogens increase total cholesterol, VLDL-C, triglycerides (even at a reduced dose of 20 microg EE) and HDL-C and decreases LDL-C. In contrast, progestins decrease levels of total cholesterol, triglycerides, HDL-C and increase LDL-C levels. Therefore, usually, OC increases VLDL-C and total triglycerides with variable effect on HDL-C and LDL-C depending on the associated progestins (depends on the presence or lack of androgenic and/or intrinsic estrogenic behaviour) (Skouby 2005, Machado 2005),

## **1.2. “Contro”**

Genetic information is generally perceived as different and requiring very special attention compared to any other health information. This notion is often called “genetic exceptionalism”. The message that is perceived by the general public is that anything “genetic” would need to be handled with utmost care, and in particular, would need to be protected to any potential misuse. General worries with genetic diagnosis are the possible psychological distress, the induction of fatalism, the social consequences on employment and insurance and the cost of the analysis. These topics have been commented elsewhere (Chapter 3).

## **2. Rationale for our study**

Most of the arguments above focused on the interest of clear diagnosis for family and children screening. However, Belgian medical practice is still mostly focused on individuals rather than on families. That is probably why, very often, GPs were most interested in priority on debating the management of the patient visiting them for their cholesterol. Therefore, one of their frequent questions was: “In term of CVD risk, could we simply consider FH patients as any other hypercholesterolemic patients?”. Although there was the classical theoretical argument that the early presence of HC in FH - at earlier age than any other hypercholesterolemic state - causes the early occurrence of CVD, we did not find any evidence in the literature that clearly demonstrated that FH patients had higher CVD risk than patients with similar severely elevated cholesterol (SHC) and similar family history of early CVD (FHEC). We decided thus to answer this question, by exploring atherosclerosis in 2 groups of patients similar in term of SHC and of FHEC but differing in term of carriage or not of a FH-causing mutation. Atherosclerosis was estimated in various arteries, using carotid and femoral ultrasonographies that measure intima-media thickness, thoracic computed tomography that searches coronary calcification and exercise stress test that screens for silent ischemia. Large observational studies and atherosclerosis regression trials of lipid-modifying pharmacotherapy have established that intima-media thickness of the carotid and femoral arteries, as measured noninvasively by B-mode ultrasound, is a valid surrogate marker for the progression of atherosclerotic disease (de Groot 2004, van Wissen 2003, Wiegman 2004, Nolting 2003). Positive exercise stress test and the presence of coronary calcification (box 8-2) are also strong predictors of CVD mortality.

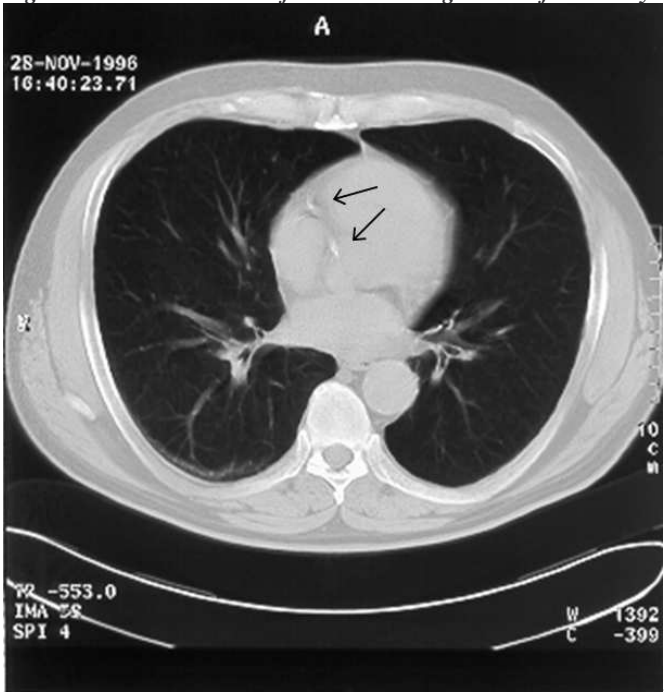
**Box 8-1. Exercise stress test (EST) and coronary calcification as predictive of coronary disease in asymptomatic subjects.**

In general, the relative risk of a subsequent event is increased in patients with a positive EST. Using myocardial infarction and death as endpoints, this has been confirmed for example in the Seattle Heart Watch (Bruce 1980), the Lipid Research Clinics (Gibbons 1983) and the Multiple Risk Factor Intervention Trial (MRFIT) (Rautaharju 1986) studies. The use of EST for prognostic evaluation in high risk patients has also been recognized in the last ACC/AHA guideline for exercise testing (Gibbons 2002). Of course the main limitation is that its positiveness depends on the presence of significant coronary luminal narrowing and that a great proportion of MI are due to rupture of non obstructive atherosclerotic plaques that are not detected by any functional test (Little 1988). Caution must be kept in using EST as a diagnostic tool for CAD. (1) The absence of flow-limiting stenoses (associated with a negative exercise test) does not preclude the occurrence of subsequent myocardial infarction. (2) Mild coronary disease, which is prognostically benign, may be identified in asymptomatic patients and may result to useless invasive investigations. (3) The accuracy of EST in asymptomatic persons has never been defined and probably never will be, because these persons could not systematically undergo angiography (Gibbons 2002).

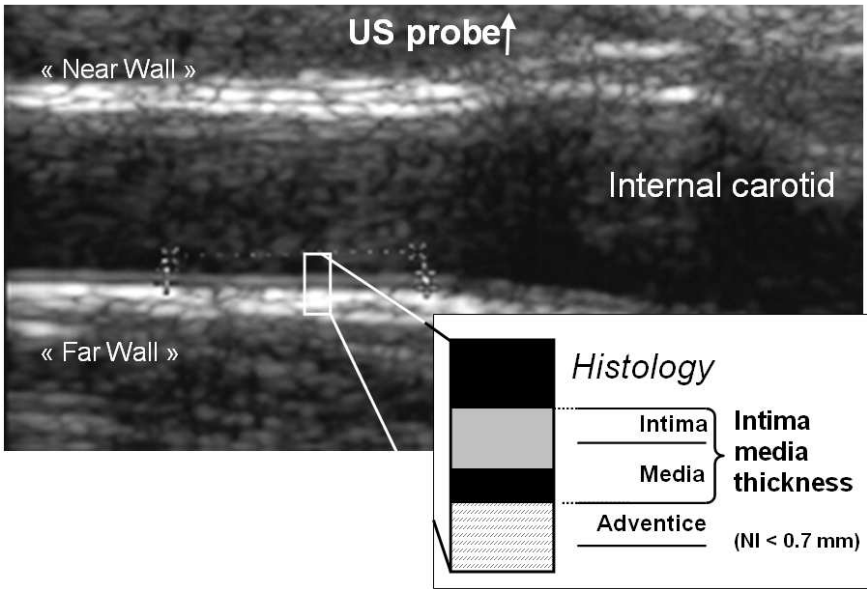
Amongst the techniques used to detect and quantify CC, the electron-beam computed tomography (EBCT) scanners is established as the gold standard (Wexler 1996). The coronary artery calcium score (CACS) measured with this technique is a useful predictor of CAD: several large clinical trials (Ardehali 2007, Budoff 2007) that found clearly incremental predictive value of CACS over the traditional risk factors when used in asymptomatic patients. However, EBCT requires expensive machines and is not useful for other routine clinical CT work. So, except in major cardiothoracic centres, most investigators like us still used more conventional CT scan to identify incidental CC (ICC). ICC detected by conventional CT scan or even simple cinefluorography have been also studied in many studies. The occurrence of ICC is higher in high-risk asymptomatic subjects and related to most known risk factors (DeTrano 1994a). Some follow-up studies showed that the presence of ICC incurs an increased risk of CHD events in asymptomatic high risk subjects at 1 year, independent of standard risk factors (DeTrano 1994b). Compared to EBCT, standard CT underestimates the presence of ICC but probably detects the most dense lesions and areas of stenosis (Margolis 1980 Moore 1989, Mautner 1994). CACS measured by EBCT has a high sensitivity for the presence of CAD but a much lower specificity for obstructive CAD (depending on the magnitude of the CACS) (Ardehali 2007). Using standard CT scan (Becker 1999), it is possible also to quantify a total calcium score (calculated as the sum of each lesion-specific score, calculated as the product of pixel area of density > 130 Hounsfield units multiplied by a factor depending on the peak density of the plaque<sup>43</sup>), but for time reason and problem of software, we could not measure them. However, our diagnostic criteria were based on previously documented methods used in identifying calcification as an incidental finding of CT scans (Moore 1989, Callaway 1997).

<sup>43</sup> This is the Agatston method with factor equals 1 if the peak density is 130-199 HU, 2 if 200-299, 3 if 300-399 and 4 if > 400.

*Figure 8-2. Image of coronary CT scan.*  
*The image illustrated several calcification in the right and left coronary arteries*



*Figure 8-1. Ultrasonography image of internal carotid artery.*



### **3. General discussion of our 2 studies**

#### **3.1. Summary**

Although clinically, non-FH (NFH) patients with these characteristics (SHC & FHEC) could easily be confounded with FH patients, FH patients had greater atherosclerosis than non-FH patients. There was even a “paradox of FH” in the sense that FH-individuals had more severe atherosclerosis than age-, sex-, cholesterol- and FHEC-matched non-FH-individuals whereas they cumulated a relatively lesser number of classical risk factors (Descamps 2001a and 2003b).

#### **3.2. Originality**

These were the first studies that compared the degree of atherosclerosis between FH patients and other HC patients that could be confounded in clinical practice. All other studies had so far compared FH patients with normocholesterolemic patients (see reference in the paper). Another study published the same year (Van Gaal 2001) has also attempted to compare the prevalence of CVD in patients suspected of autosomal dominant HC<sup>44</sup> with or without mutations in the LDLR gene. In this study, the prevalence of CVD was similar in the 24 carriers of LDLR mutations and the 61 non carriers. However several methodological problems may explain such negative results. First, the number of patients is quite small (24 carriers and 61 non carriers compared to 122 carriers and 151 non carriers in our studies). The number of “exposed” subjects is even smaller because the cohort included subjects as young as 9 years where CVD is impossible. Second, 11% of non carriers had tendon xanthomas (TX), which is surprising as it is a hallmark of FH suggesting that a substantial proportion of these non carriers had actually FH not detected by their genetic test. Third, only 8 of 29 patients carried definitively severe mutations (nonsense, frameshift, rearrangement) and 6 had new missense mutations without clear argument about their pathogenicity.

Only three studies including our have evaluated Stress test in FH patients. Prevalence of exercise stress testing in FH patients has been studied previously by comparison with normolipidemic patients (Wojciechowski 1989). In a study which investigated the clinical and biochemical parameters possibly associated with the results of exercise testing in asymptomatic patients with heterozygous FH (Michaelides 2004), fibrinogen levels but not lipid and other classical coronary risk factors predicted exercise-induced myocardial ischaemia. A recent study (Pitsavos 2004) has also demonstrated that exercise tolerance test indices (exercise capacity, heart rate recovery at 1 min and peak pulse pressure levels) were predictors of CHD, after controlling for several potential confounders.

There have been a few publications on ICC or CACS in FH. In patients with homozygous FH, calcification were detected in patients older than 12, including all those with angina (Hoeg 1994, Schmidt 1996). These studies suggested that cholesterol-year score was the best predictor of coronary calcifications and that coronary calcifications were not observed until cholesterol-year exceeded 10000

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<sup>44</sup> Defined by the following criteria: TC >250 mg/dL, LDL-C >180 mg/dL and a minimum of 2 additional first-degree relatives with HC. Exclusion if secondary causes of HC, if TG >400 mg dL/L and/or if FDB.

mg-year. Other studies in HeFH patients demonstrated significantly greater CACS by EBCT compared to controls or subjects with moderately elevated cholesterol and CAD. (Hoffmann 2001) and even evidenced coronary calcifications in young (7 out of 29 patients aged 11-23 years) FH cohort (Gidding 2001).

### **3.3. Implication of our studies**

All these patients with SHC and FHEC had quite important atherosclerosis when compared to subjects without any CVD risk factor<sup>45</sup>, but the identification of FH adds two new useful pieces of information.

1) All FH patients with such conditions should be considered at high risk. All risk factors are important to treat but they are not necessary to justify LDL-C treatment. Family screening needs to be performed extensively.

2) All no FH patients with such conditions should also be considered at high risk. The fact that they do not carry a LDLR/APOB mutation should encourage the practitioner to search intensively other potentially inherited risk factors (insulin resistance, homocysteine ...). Taking care of these other risk factors may be as important as correcting their LDL-C levels. Of course, as recommended by the last European guidelines, family screening of risk factors is mandatory.

In some of my conferences to GP, I presented an illustration of the practical importance to know the genetic status of a HC patient by a clinical exercise (Box 8-1: "Which case (A or B) requests most care in term of CVD prevention?").

### **3.4. Limitations of our studies (see also in papers)**

They concerned the fact that the patients were recruited in lipid clinics and that atherosclerosis was measured by surrogate endpoints and not by clinical endpoints. Also, we did not have a control group of "normal" subjects without HC and/or FHEC, because it was not in our purpose to compare the degree of atherosclerosis relative to a group of "normal" subjects and, because, in our lipid clinics, there is no rationale to perform extensive analysis of atherosclerosis in patients without risk factors.

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<sup>45</sup> In "normal subjects, IMT is below 0.7 mm (Chambless 1997) and coronary calcification/positive stress test is absent. Our lowest values found in our lipid clinics' patients since 1992 is 0.4 mm. The mean value of a small cohort of 6 young physicians and technicians aged 25-36 years was 0.48±0.09 mm.

**Box 8-1. An illustrative little story (based on our paper).**

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------|
| Two 45-year-old men, “A” and “B” come to visit the doctor X because high cholesterol levels (both have exactly CT at 320 mg/dl). They know that their father died at age 50 of MI. Let us say “A” is FH and “B” does not have FH. Patient “A” and “B” are not smokers and have the following features. No had XT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |                                     |
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| Blood pressure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 120 / 70 mmHg                         | 150 / 85 mmHg                       |
| Weight, Height, BMI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 75 kg, 1,75 m, 24.4 kg/m <sup>2</sup> | 95 kg, 1,75 m, 31 kg/m <sup>2</sup> |
| TC, LDL-C, HDL-C, TG (mg/dl)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 320 - 240 – 40 – 200                  | 320 – 220- 40- 300                  |
| Glycemia :                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 74 mg/dl                              | 110 mg/dl                           |
| <p><b>Who has the highest CHD risk?</b> Based on their risk factors (male gender, no smoking, no diabetes and the value of blood pressure and TC) and the CHD prediction Chart, their risk at 10 years is 5 – 10 % for A and 10- 20% for B (more exactly 11% and 15% using the Framingham equation). As both had family history of early CHD, the risk is increased (x2) to 10-20 % for A and 20-40% for B. As B was obese, had glucose intolerance and high triglycerides, his risk must be even higher than 40%. So the conclusion is that patient B is at higher risk than A and many doctors may react by treating B in priority.</p> <p><b>The actual risk...</b> could be in fact evaluated by examining intima-media complexes or coronary calcification as it was done in our papers, where we observed more severe atherosclerosis in FH patients (even when controlling for all other CHD risk factors). The 15 % risk predicted in patient A also contrasts with the epidemiologic data that shows a 35% 10 year-mortality risk of FH-men in their fifth decades.</p> <p><b>What is wrong in the reasoning of the doctor?</b> <u>First</u> the CHART does not consider the level of LDL-C (A &gt; B). <u>Second</u>, the doctor is more impressed by what he sees (overweight, high TG, higher BP) than by what the underlying cause of HC (the genetic disease “FH”).</p> <p>This is not an uncommon situation. First, patient “B” has features resembling the common syndrome known as syndrome X which is present in 30% individuals at age 40-50 and often observed in family with history of early CHD. Second, borderline risk (5-20%) is the range of CHD risk where lies most of middle age FH men, when using “CHART”. As a matter of fact, in our study most FH men were in this range of predicted risk: 25/67 were in the range of risk 10-23% and 38/67 in the range 5%-23%.</p> |                                       |                                     |