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## Nomogram to Diagnose Familial Combined Hyperlipidemia on the Basis of Results of a 5-Year Follow-Up Study

Mario J. Veerkamp, MD; Jacqueline de Graaf, MD, PhD; Jan C.M. Hendriks, PhD; Pierre N.M. Demacker, PhD; Anton F.H. Stalenhoef, MD, PhD

**Background**—Familial combined hyperlipidemia (FCH) is traditionally diagnosed by total plasma cholesterol and/or triglyceride levels above the 90th percentile adjusted for age and gender. In a recent study, we showed that the diagnosis of FCH on the basis of these diagnostic criteria was inconsistent in 26% of the subjects over a 5-year period. This result emphasizes the need for reevaluation of the diagnostic criteria for FCH.

**Methods and Results**—A total of 32 families (299 subjects) were studied in 1994 and 1999. A subject was defined “truly” FCH when diagnosed FCH in 1994 and/or 1999 on the basis of traditional plasma lipid criteria. Additional lipid and lipoprotein parameters, including apolipoprotein B (apoB) and small, dense LDL, were measured at both time points. In total, 121 subjects (40%) were defined as truly FCH. Multivariate analysis revealed that absolute apoB values combined with triglyceride and total cholesterol levels adjusted for age and gender best predicted truly FCH. A nomogram including these parameters is provided to simply and accurately calculate the probability to be affected by FCH. Furthermore, it is shown that when percentiles of triglyceride and total cholesterol adjusted for age and gender are not available in a population, the definition of FCH can be established on the basis of hypertriglyceridemia ( $>1.5$  mmol/L) and hyper-apoB ( $>1200$  mg/L).

**Conclusions**—The diagnosis of FCH is best predicted by absolute apoB levels combined with triglyceride and total cholesterol levels adjusted for age and gender and can accurately be calculated by a nomogram. This definition is also a good predictor of cardiovascular risk in FCH. (*Circulation*. 2004;109:2980-2985.)

**Key Words:** apolipoproteins ■ diagnosis ■ follow-up studies ■ hyperlipoproteinemia

Familial combined hyperlipidemia (FCH) was first described in 1973 as a common familial disorder characterized by multiple lipoprotein phenotypes and increased risk of premature cardiovascular disease (CVD).<sup>1</sup> In the 30 years since it was described, the genetic basis for FCH has remained elusive; indeed, even the mode of inheritance remains controversial. Obviously, no genetic hypothesis can be reliably tested when there is no consistent phenotype to establish the diagnosis of FCH.

FCH is characterized by several phenotypes, including increased total cholesterol (TC), increased triglycerides (TG), decreased HDL cholesterol (HDL-C), increased apolipoprotein B (apoB), and the presence of small, dense LDL. Not all research groups use the same criteria to establish the diagnosis of FCH.<sup>2,3</sup> There are even more fundamental problems. Among the most important is that the lipid phenotype can vary substantially within any individual. Recently, we showed in a 5-year follow-up study (1994 to 1999) of 32 families that the diagnosis of FCH on the basis of plasma TC and/or TG level  $>90$ th percentile (pTC or pTG  $>90$ th) adjusted for age and gender is consistent in only 74% of the

subjects.<sup>4</sup> Most importantly, 26% of the subjects with FCH in 1994 had a sporadic normolipidemic pattern in 1999 defined by pTC and pTG levels  $<90$ th corrected for age and gender. Thus, the classic lipid phenotypes are variable not only among family members but also within individuals. This has previously been suspected but has now been convincingly demonstrated by our data and by recent data of McNeely et al.<sup>5</sup>

Although the genetic origin of FCH has remained obscure, much has been learned about its pathophysiology. The characteristic abnormality is an increased production of VLDL with or without impaired clearance of TG-rich lipoproteins in most patients<sup>6</sup> that results in the generation of increased numbers of small, dense LDL particles. This suggests that just as a variable lipid phenotype is the hallmark of FCH within a family, an elevated plasma apoB might be the common hallmark of FCH within an individual. Indeed, this was a principal finding of our previous study,<sup>4</sup> which demonstrated that subjects affected FCH in 1994 and/or 1999 had significantly higher apoB levels and an increased amount of small, dense LDL compared with nonaffected subjects, even when they presented a normolipidemic phenotype.

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**TABLE 1. Subjects in 32 Families Defined as Affected By FCH or Normolipidemic Relatives in 1994 and 1999**

1994	1999, n (%)		
	FCH	NL	Total
FCH	69 (74)*	24 (26)*	93 (31)
NL	28 (14)*	178 (86)	206 (69)
Total	97 (32)	202 (68)	299 (100)

NL indicates normolipidemic relatives defined by pTC and pTG <90th. FCH was based on pTC and/or pTG levels >90th.

\*Subjects classified as truly FCH defined by affected FCH based on pTC and/or pTG >90th in 1994 and/or 1999. In total, 121 subjects (40%) of the study population were defined as truly FCH.

Together with less variability in time, measurements of apoB and small, dense LDL in plasma could potentially lead to more consistent diagnostic criteria for FCH with a better discriminant power to separate affected from nonaffected relatives compared with TC and TG levels alone.

The objective of the present study is to evaluate several diagnostic features of FCH and to provide a nomogram that can simply and accurately predict FCH in clinical practice.

## Methods

### Study Population

The study population consisted of kindreds and probands of families with known FCH who were recruited in 1994 and followed up in 1999 as recently described elsewhere.<sup>4</sup> At both time points of investigation, all subjects completed a questionnaire about medical history, especially cardiovascular status. Body mass index was determined in all subjects. After withdrawal of lipid-lowering medication for 4 weeks and after an overnight fast, venous blood was drawn by venipuncture. Subjects were classified as affected by FCH when plasma pTC and/or pTG >90th on the basis of the PROCAM study.<sup>7</sup> These percentiles are adjusted for age and gender. Nonaffected relatives were defined by TC and TG levels <90th percentile (pTC and pTG <90th). The ethics committee of the University Medical Center Nijmegen approved the study protocol.

In total, 32 families, including 299 subjects, were studied in both 1994 and 1999. In 1994, 93 of the 299 subjects (31%) were affected by FCH. The diagnosis of FCH in 1999 was consistent with the diagnosis in 1994 in only 69 of the 93 subjects (74%). Most importantly, however, 24 subjects (26%) with FCH in 1994 showed a normolipidemic pattern in 1999, and 28 (14%) of the normolipidemic subjects, ie, pTC and pTG <90th, in 1994 were affected in 1999. Of the 206 nonaffected relatives in 1994, 178 (86%) remained nonaffected in 1999.<sup>4</sup> In the present study, we define all subjects who were diagnosed with FCH in 1994 and/or 1999, on the basis of the traditional lipid criteria (pTC and/or pTG >90th), as affected by FCH. Thus, this definition also includes the subjects with FCH in 1994 who show a normolipidemic pattern in 1999 (Table 1). We refer to these affected FCH subjects as "truly" FCH.

### Plasma Lipid, Lipoprotein, and Apolipoprotein Analyses

Plasma TC and TG concentrations were determined by enzymatic, commercially available reagents (Boehringer-Mannheim, catalog No. 237574, and Sera Pak, Miles, catalog No. 6639, respectively). HDL-C was determined by the polyethylene glycol 6000 method.<sup>8</sup> LDL cholesterol (LDL-C) was calculated by subtraction of VLDL cholesterol and HDL-C from plasma TC. Total plasma apoB concentrations were determined by immunonephelometry.<sup>9</sup> Coefficient of variation estimates of the analytical and biological variation of apoB in our laboratory were <7%.

LDL subfractions were separated by single spin density gradient ultracentrifugation.<sup>10</sup> Each individual LDL subfraction profile was defined by a continuous variable K, as described in detail previously.<sup>11</sup> A negative value ( $K < 0$ ) reflects a more dense LDL subfraction profile; a positive K value ( $K > 0$ ) indicates a more buoyant profile.

### Statistical Analyses

The Mann-Whitney test was used to test differences at baseline between truly FCH subjects and their unaffected relatives for statistical significance in the case of quantitative variables; the 2-tailed Fisher's exact test was used in the case of qualitative variables.

Univariate logistic regression was used to evaluate the prognostic ability of the variables separately to discriminate between truly FCH subjects and their unaffected relatives. Because the apoB level, K value, and TC and TG levels in particular were expected to be nonlinearly related in the logistic model, reasonable cutoff values for these variables to discriminate between truly FCH subjects and their unaffected relatives were constructed. At this point, the condition of equal "costs" of misclassification of cases and noncases was used. In other words, the optimal cutoff value for a particular variable was chosen so that the sum of the sensitivity and the specificity to discriminate truly FCH subjects from their unaffected relatives was maximal. Crude ORs with 95% CIs are presented.

Multivariate logistic regression analysis with selection procedures was used to determine the variables that were sufficient and complete to contribute independently to the prediction of truly FCH. Because forward selection procedures do not identify other important variables, probability values for entry into the model were considered to find close alternatives to the variables selected. Adjusted ORs with 95% CIs are presented. With the multivariable prognostic model, a boundary value of the probability to be truly FCH, given the values of the prognostic variables only, was constructed, again under the condition of equal costs of misclassification of cases and noncases. In case of a 2-variable prognostic model, a straight line dissociated cases (ie, truly FCH with high probability) and noncases. In case of a  $\geq 3$ -variable prognostic model, a nomogram was constructed.

Finally, univariate logistic regression was used to evaluate the prognostic ability of variables separately to identify patients with CVD compared with normal subjects. Statistical analysis was performed by using procedures available in SAS (software package 2000, SAS Institute Inc).

## Results

In total, 32 families, or 299 subjects, were studied in both 1994 and 1999. One hundred twenty-one subjects were defined as truly FCH on the basis of plasma pTC and/or pTG >90th adjusted for age and gender in 1994 and/or 1999 (Table 1). Thus, 40% of the study population was truly FCH, whereas 31% in 1994 and 32% in 1999 were affected by FCH. Table 2 shows the anthropometric measurements, lipid and (apo) lipoprotein concentrations, and values of K, reflecting LDL heterogeneity, in truly FCH subjects and nonaffected relatives in 1994. Truly FCH subjects were significantly older and had a higher body mass index than normolipidemic relatives. As expected, among subjects with FCH, CVD was more prevalent. By definition, the truly FCH group had higher TC and TG concentrations. The truly FCH group also exhibited significantly higher concentrations of LDL-C and lower concentrations of HDL-C. Furthermore, significantly higher levels of apoB and lower values of the parameter K, reflecting small, dense LDL, were found in the truly FCH group compared with unaffected relatives.

Crude ORs to predict truly FCH are given in Table 3. All variables except gender contributed independently to the diagnosis of truly FCH.

**TABLE 2. Anthropometric Measurements, Lipid and (Apo)lipoprotein Concentrations, and Value of K in Truly FCH Subjects and Normolipidemic Relatives in 1994**

	Truly FCH (n=121)	Normolipidemic Relatives (n=178)
Age, y	48 (19–73)*	34 (13–71)
BMI, kg/m <sup>2</sup>	26 (18–37)*	23 (15–35)
CVD, n (%)	18 (15)†	5 (3)
TC, mmol/L	6.9 (3.7–9.0)*	5.2 (2.4–7.5)
TG, mmol/L	2.4 (0.2–15.0)*	1.0 (0.3–2.9)
LDL-C, mmol/L	4.48 (1.67–6.63)*	3.47 (1.25–5.71)
HDL-C, mmol/L	0.98 (0.53–2.56)*	1.25 (0.55–2.47)
ApoB, mg/L	1374 (604–2640)*	914 (467–1640)
K value	−0.23 (−0.58–0.59)*	0.03 (−0.48–0.41)

BMI indicates body mass index. Values are median (minimum–maximum). Values of K <0 reflect small, dense LDL.

\* $P < 0.001$ , Mann-Whitney test, † $P < 0.001$ , Fisher's exact test.

Receiver-operating curve analysis shows that the K value, reflecting LDL heterogeneity, and apoB levels are nearly as good at predicting truly FCH as the traditional lipid criteria, including TC and TG levels. Next, the variables were dichotomized by determining the optimal cutoff values of apoB, TC, TG, and K for prediction of truly FCH (Table 4). In our cohort, cutoff values of apoB >1200 mg/L, K <−0.10, TG levels >1.5 mmol/L (pTG ≥6), and TC levels >6.0 mmol/L (pTC ≥7) were found.

To evaluate which (combination of) phenotype(s) best predicted truly FCH, we included all the variables presented in Table 3 in a multivariate logistic regression model. This analysis revealed that the absolute apoB value in combination with pTG and pTC best predicted truly FCH with an  $R^2 = 69\%$ . pTG was the strongest independent predictor of truly FCH ( $R^2 = 58\%$ ); when percentiles are not available, TG

**TABLE 3. Crude ORs to Predict Truly FCH With Univariate Logistic Regression**

Independent Variables	OR	95% CI	$R^2$ , %	AUC, %
Gender (M vs F)	1.13	0.71–1.79	1	52
Age (y)	1.20	1.11–1.30	7	65
BMI (kg/m <sup>2</sup> )	1.41	1.29–1.55	31	79
TC absolute (mmol/L)	3.08	2.36–4.02	40	82
pTC	2.32	1.88–2.85	37	79
TC >6.0 mmol/L	7.19	4.29–12.07	25	73
TG absolute (mmol/L)	11.51	6.43–20.61	58	89
pTG	3.24	2.48–4.24	54	87
TG >1.5 mmol/L	15.19	8.53–27.03	41	80
ApoB absolute (per 100 mg/L)	1.76	1.54–2.01	49	86
ApoB >1200 mg/L	12.31	6.99–21.69	37	78
K value absolute (per 0.1)	0.60	0.51–0.69	27	78
K value <−0.1	9.62	5.50–16.82	31	76

AUC indicates area under the curve as a measure of predictive discrimination (eg, 50% is equivalent to random guessing and 100% is the perfect prediction); BMI, body mass index.

concentrations >1.5 mmol/L can be used to predict truly FCH. When TG levels in percentiles were included in the model, the K value did not provide additional information. In the next step of the regression analysis, apoB was the second most important predictor of FCH. Including apoB levels with pTG in the model improved  $R^2$  to 68%. Finally, pTC contributed significantly to truly FCH, although the  $R^2$  did not increase substantially. The  $R^2$  (ie, the amount of variation) for the combination of these 3 variables was 69%.

By logistic regression, the probability of classification of affected FCH on the basis of absolute apoB values and pTG and pTC was assessed at 60%. In Figure 1, the 2 most informative variables in predicting truly FCH, including apoB and pTG levels, are plotted for all individuals. The optimal cutoff value to predict truly FCH on the basis of the combination of absolute apoB with pTG is 0.52. The shaded area indicates high probability of predicting truly FCH using the observed apoB and pTG values. This figure shows that the prediction area makes a fairly good distinction between truly FCH subjects and nonaffected subjects.

Finally, a nomogram was constructed to calculate the probability of affected by FCH (Figure 2). For each of the 3 variables (pTG, pTC, and absolute apoB levels), the corresponding number of points is read from the scale below. These are then summed to give a total point score, which can be translated into a probability of being affected by FCH by using the 2 scales at the bottom. The optimal cutoff point for the probability of affected FCH was determined under the condition of equal costs of misclassification according to sensitivity and specificity. When having a probability of >60% the subject is defined as affected by FCH when at least 1 other family member also exhibits the FCH phenotype and at least 1 individual in the family has premature CVD. For example, a subject with a pTG of 7 (between 91% and 95%, 8 points), a pTC of 6 (between 76% and 90%, 2.8 points), and an apoB level of 1600 mg/L (4.3 points) will receive a total of 15.1 points. The probability of being affected by FCH is then 0.92. Thus, according to this test, this individual subject (if a member of a FCH family) is being affected by FCH.

### Diagnosis of FCH as a Predictor for CVD

In 1999, 41 subjects (14%) had a history of CVD. To define the ability of the different FCH definitions to predict CVD, sensitivity and specificity were determined. FCH diagnosis based on traditional lipid criteria, including pTC and/or pTG >90th adjusted for age and gender, showed a sensitivity and specificity to predict CVD of 45% and 27% respectively. The proposed new FCH diagnosis based on pTG, pTC, and absolute apoB had a sensitivity and specificity for CVD risk prediction of 59% and 72%, respectively. In the literature, the diagnosis of FCH has also recently been defined as hyper-TG (TG >1.5 mmol/L) and hyper-apoB (apoB >1200 mg/L). In our cohort, the diagnosis of FCH on the basis of these criteria (hyper-TG plus hyper-apoB) had corresponding values of sensitivity and specificity to predict FCH (64% and 72%, respectively). Thus, both new definitions of FCH improved CVD risk prediction compared with the FCH diagnosis based on traditional lipid criteria.



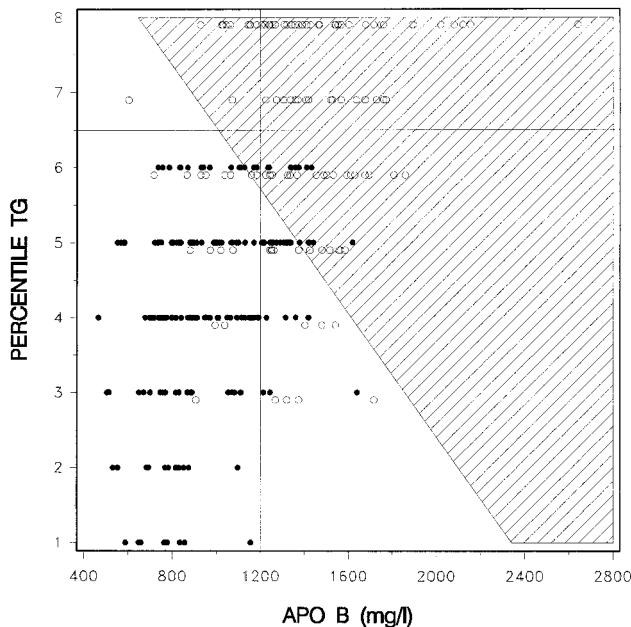
**TABLE 4. Optimal Cutoff Values With Receiver-Operating Curve Parameters for ApoB, K, Absolute TG and TC, pTG, and pTC for Prediction of Truly FCH With Univariate Logistic Regression Under the Condition of Equal Cost of Misclassification**

	Cutoff Point	Probability	Maximum J	Sensitivity	Specificity
ApoB (mg/L)	>1200	0.44	0.55	0.77	0.79
K value	<-0.10	0.40	0.51	0.77	0.74
TG (mmol/L)	>1.5	0.35	0.59	0.81	0.78
TC (mmol/L)	>6.0	0.42	0.46	0.70	0.75
pTG	≥6	0.58	0.61	0.77	0.84
pTC	≥7	0.74	0.51	0.51	1.00

The predictive value of the nomogram for CVD analyzed as a quantitative trait shows that the median probability of being affected by FCH is >3.5 times higher in patients with CVD (median, 0.71; 95% CI, 0.54 to 0.80) compared with patients without CVD (median, 0.20; 95% CI, 0.28 to 0.38) ( $P<0.001$ ,  $t$  test using angular transformed data).

**Discussion**

We propose a new definition of FCH based on absolute apoB levels and TG and TC levels, both adjusted for age and gender. A nomogram is provided to simply and reliably read the probability to be affected by FCH in clinical practice (Figure 2). This nomogram has been constructed using data



**Figure 1.** Probability of classification of affected by truly FCH on the basis of absolute apoB concentration and TG levels adjusted for age and gender. Shaded area indicates probability of truly FCH of >0.52 on the basis of absolute apoB concentration and TG levels adjusted for age and gender. This area was optimal to discriminate those truly FCH from unaffected subjects under condition of equal costs of misclassification. For ease of presentation, unaffected subjects are shifted upward, truly FCH subjects are shifted downward, and cutoff point of pTG (90th percentile) is presented at 6.5. For pTG and pTC, 1=0% to 5%; 2=6% to 10%; 3=11% to 25%; 4=26% to 50%; 5=51% to 75%; 6=76% to 90%; 7=91% to 95%; 8=96% to 100%. ○ indicates truly FCH subjects; ●, unaffected subjects.

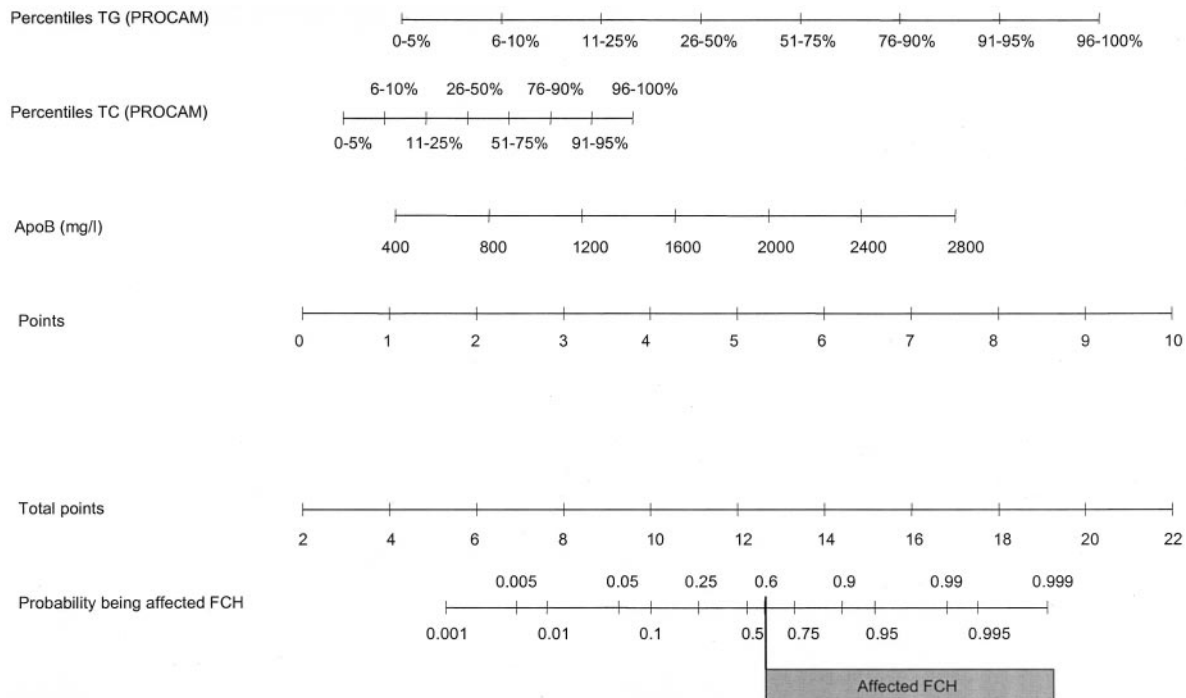
from our large FCH cohort including 299 subjects with 5-year follow-up. This new definition of FCH also reflects increased CVD risk in contrast to the traditional criteria of FCH.

Until now, different research groups used different definitions of FCH.<sup>1-3</sup> In a recent follow-up study, we showed that for the diagnosis FCH, only plasma TC and TG levels adjusted for age and gender are insufficient.<sup>4</sup> Furthermore, the FCH phenotype based on TC and/or TG levels alone is physiologically incoherent.<sup>12</sup> When the traditional lipid phenotype is variable and insufficient, accurate clinical diagnosis in individual subjects is not possible. Equally important, genetic characterization becomes problematic, and biologically correct hypotheses may be falsely rejected because of inaccurate diagnosis. For all these reasons, it is necessary to create unequivocal standardized diagnostic criteria of FCH. The present study shows that absolute apoB levels combined with pTG and pTC are most informative to predict FCH.

**ApoB as a Diagnostic Feature of FCH**

In our previous study, subjects with FCH had significantly higher apoB concentrations compared with nonaffected relatives, even when they had a sporadic normolipidemic phenotype.<sup>4</sup> Additionally, in the follow-up study of McNeely et al,<sup>5</sup> apoB levels were highest among individuals who were consistently affected by FCH, intermediate among those who switched phenotypes, and lowest among individuals who were consistently normolipidemic. In addition, several other studies have shown that apoB is an important phenotypic measure in FCH.<sup>4,13-16</sup> ApoB fits with the most important pathophysiological feature of FCH, increased VLDL secretion and impaired clearance of postprandial lipoproteins, resulting in hypertriglyceridemia, elevated plasma apoB, and small, dense LDL. Another practical advantage of including apoB level as a new diagnostic criterion of FCH is diagnosing FCH at a younger age. A number of studies have shown that in teenaged children, apoB may be elevated, whereas lipids are not.<sup>2,17</sup> A limitation in using apoB as a diagnostic criterion for FCH is the need for an apoB measurement standardized according to the WHO-IFCC standardization program. ApoB can be measured with the same precision and accuracy as the lipoprotein lipids.<sup>18</sup> All these data encourage the inclusion of apoB in the phenotypic definition of FCH.

The present study shows in a large FCH cohort with 5-year follow-up that the optimal cutoff point for apoB to predict FCH is >1200 mg/L. Subjects with an apoB level >1200



**Figure 2.** Nomogram to calculate probability of being affected by FCH using absolute apoB and TG-TC values adjusted for both age and gender. In each of 3 variables, points are calculated by reading from point scale. Total point score is then translated into probability of affected FCH using 2 bottom scales. For example, subject with pTG between 91% and 95%, pTC between 76% and 90%, and apoB level of 1600 mg/L will receive total of 15.1 points (ie, 8+2.8+4.3) according to 4 top lines. Probability of being affected by FCH with total points of 15.1 is then 0.92, according to 2 bottom lines. This subject, therefore, is affected by FCH when also at least 1 other family member exhibits the FCH phenotype and at least 1 individual in the family has premature CVD.

mg/L have an increased probability to be affected by FCH (OR, 12.3; 95% CI, 6.99 to 21.69) compared with subjects with an apoB level <1200 mg/L. The level of apoB >1200 mg/L has been suggested in previous studies. It corresponds to roughly the 75th percentile in men (results of the Framingham Offspring study),<sup>19</sup> and subjects with apoB concentrations >1200 mg/L were significantly more likely to have CVD than subjects with apoB levels <1200 mg/L.<sup>20</sup> Thus, our data now show convincingly that the measurement of apoB concentration is imperative for the diagnosis of FCH.

### Small, Dense LDL and TG Levels as Diagnostic Features of FCH

Small, dense LDL, reflected by the K parameter, is also an important feature in FCH.<sup>16,21–23</sup> We previously showed that subjects with FCH had significantly lower levels of K, reflecting atherogenic small, dense LDL, compared with nonaffected relatives, even when they had a sporadic normolipidemic phenotype.<sup>4</sup> However, this was not shown in the follow-up study of McNeely et al,<sup>5</sup> maybe because different methods were used to determine small, dense LDL. The present study shows that the optimal cutoff point for K to predict FCH is <−0.10, reflecting small, dense LDL.

However, although small, dense LDL is an important feature of FCH, it is of interest that in multivariate analysis, K, reflecting LDL heterogeneity, did not provide additional information in predicting FCH after inclusion of TG, which is the most important predictor of truly FCH, most likely because of the strong correlation between LDL heterogeneity

and TG levels ( $r = -0.68$ ). Serum TG concentration has been suggested to be the most important predictor of LDL size in FCH patients.<sup>23</sup> In both earlier studies<sup>9,24</sup> and this study, we have confirmed that plasma TG levels >1.5 mmol/L distinguish optimally between atherogenic small, dense LDL and a large, buoyant LDL subfraction profile.

### Hyper-TG and Hyper-ApoB as Diagnostic Features of FCH

In an international forum on FCH in 2001, a proposal to redefine FCH was made that was based on hyper-TG and hyper-apoB.<sup>12</sup> The cutoff points proposed were >1200 mg/L for apoB and >1.5 mmol/L for plasma TG. The choice of these cutoff points was tentative and based on the reports mentioned earlier. We show here for the first time that cutoff points of >1200 mg/L for apoB and >1.5 mmol/L for TG are justified on the basis of our large FCH cohort with 5-year follow-up.

Comparing the absolute apoB value combined with pTG and pTC as diagnostic criteria for FCH with hyper-TG and hyper-apoB reveals that the diagnosis based on these combined values better predicted truly FCH ( $R^2 = 69\%$  versus 50%, respectively).

The disadvantage of using percentiles of lipid levels in the definition of FCH is that these levels vary substantially across the world and therefore will affect decisions on cutoff levels. Lipid levels are changing, and up-to-date, accurate information on lipid levels and threshold values is not available in many populations. An advantage of using percentiles is the

correction for age and gender, but assignment of percentiles still depends on the population.

To take into account the great interindividual variability in apoB and TG levels, we recommend using apoB and TG levels as quantitative traits instead of a dichotomy, ie, apoB >1200 mg/L and TG >1.5 mmol/L. Much information is lost because we do not know whether an individual is close to or far from the threshold. Moreover, where family data are used, quantitative traits of relatives are often more informative than their affected status. As a clinical tool, a nomogram was constructed to simply and reliably calculate the probability of FCH in an individual subject on the basis of quantitative apoB, pTG, and pTC values. In case pTC and pTG are not available, we show that it is acceptable to define FCH by TG levels >1.5 mmol/L and apoB values >1200 mg/L.

Finally, we found that our new definition of FCH is of value in predicting CVD risk. Subjects fulfilling the new FCH definition have an increased risk of CVD (OR, 3.8; 95% CI, 7.0 to 21.7). Subjects fulfilling the definition of hyper-TG and hyper-apoB have a comparable OR (4.6; 95% CI, 2.3 to 9.2) in contrast to the diagnosis of FCH based on traditional lipid criteria (pTC and/or pTG >90th), which had an OR of only 0.3 (95% CI, 0.2 to 0.6). Similar results have been reported for intima-media thickness, a surrogate end point of CVD.<sup>25</sup>

Using the proposed new diagnostic criteria included in a nomogram will make it easier to identify patients and test relatives to diagnose FCH. Still, the diagnostic phenotype has to be present in >1 family member, and ≥1 individual in the family must have premature CVD to diagnose FCH. Confirmation of the relevance of this new definition of FCH in other large FCH cohorts is warranted to confirm the unequivocal diagnostic criteria for FCH.

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