Putting Into Perspective the Hazards of Untreated Familial Hypercholesterolemia

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I
n this issue of JAMA, Kjaergaard et al1 describe a 21-year

follow-up of 118 heterozygous carriers of low-density lipoprotein (LDL) receptor (LDLR) mutations causing heterozy-
gous familial hypercholesterolemia (FH) together with 102 of

their noncarrier relatives. These FH patients and their relatives

had been identified between 1992 and 1994 through

cascade screening, starting from LDLR mutation-carrying probands in 32 families. Lipid-lowering treatment with statins

was recommended to all mutation-carrying FH participants.

Primary outcomes were tracked in the Danish National Patient

Registry and included death from any cause, myocardial infarction, coronary revascularization, ischemic stroke, trans-
sient ischemic attack, and peripheral artery disease. FH

patients and unaffected relatives with occurrence of any of

these outcomes prior to the baseline were excluded from the

analysis. A set of controls were matched 10:1 by birth year

and sex from the Danish Civil Registration System.

Despite the vast majority of the FH patients being treated

with statins, probably for most of the follow-up period, risk of

the primary outcome remained elevated with a hazard ratio

1.65 (95% CI 1.17–2.33). Not unexpectedly, the risk specific-

ally for coronary events was considerably higher among the

FH patients (hazard ratio 5.91, 95% CI 3.83–9.10), while no

significant excess risk was seen for stroke or total mortality.

Indeed, total mortality was somewhat less in FH patients and

considerably less in their unaffected relatives, perhaps

because of the increased attention to healthy lifestyle these

families often display. The strengths of the study include the

long-term and comprehensive follow-up together with care-

fully defined FH cases and unaffected relatives. Limitations

are the relatively small size of the cohort as well as

incomplete information about lipid-lowering therapy (only

available after 2004) and standard coronary risk factors.

This study comes on the heels of new recognition of a

much higher prevalence of FH than previously appreciated,

making it the most common, serious monogenic disorder in

humans. New, objective screening projects in large US

populations, with genetic testing done without regard to lipid

levels, place the prevalence of FH mutation carriers (with

mutations in LDLR, APOB, and PCSK9) in 3 different studies at

1 in 204,2 1 in 211,3 and 1 in 224: more than double older

estimates of 1 in 500. Similar estimates for prevalence of FH

are reported for European populations.5–8 Yet, FH remains

seriously underdiagnosed and inadequately treated.

Risk of premature coronary disease among untreated FH

remains of major interest for public health planning and to

better appreciate the need for early identification and

treatment. Accurate estimates of cumulative risk for

coronary artery disease (CAD) by age and sex in untreated

FH as compared with non-FH subjects are also of interest

for purposes of calculating the likelihood of having FH in a

newly developed algorithm for clinical diagnosis of FH.9 The

estimates of cardiovascular disease and CAD incidence

and associated hazard ratios by Kjaergaard et al herein1 are

hampered by incompletely documented effects of prior

treatment. The same may be said of the several other

recent overall estimates of risk associated with genetically

defined FH.2–4 None of the overall estimates of risk in FH

mutation carriers versus noncarriers in these studies should

be taken as risk associated with untreated FH. Perhaps

the best estimate of risk of CAD in untreated FH in these

studies comes from Khera et al,3 who calculated a hazard

ratio of 22.3 (P<0.0001) for CAD among FH mutation

carriers with LDL cholesterol (LDL-C) ≥190 mg/dL (com-
pared with a reference group of noncarriers with LDL-C <130 mg/dL). Interestingly, in this study FH mutation

carriers had 2- to 3-fold higher risk compared with noncarriers at the same current LDL-C levels. Evidence was

presented that FH mutation carriers had experienced longer
exposure to higher LDL-C levels, suggesting a cause for the increased risk in FH. For this reason, without a genetic or reliable clinical diagnosis of FH, even large data sets from pooled prospective studies would be expected to underestimate the risk of FH when only LDL-C cut points are utilized to determine risk.\(^10\)

Perhaps the largest study estimating CAD risk in FH patients and the effects of lipid-lowering was performed among 1950 previously untreated FH patients identified by 1990 by the Dutch Lipid Network group.\(^11\) Of these, 413 FH patients (mean age 41.7) were started on statins while 1537 (mean age 38.2) continued off treatment. Remarkably, after 12.5 years of follow-up, \(\approx67\%\) of the untreated group had developed coronary disease. Use of statins led to an adjusted 82\% risk reduction \((P<0.001)\).

Older estimates of CAD risk attributable to FH from the pre-statin era provide important insights. The severe consequences of not treating FH sufficiently early with appropriate medication, as happens all too often, should be considered paramount when planning a clinical approach to FH. In addition, as noted above, estimates for age- and sex-specific cumulative risk for CAD in FH and non-FH subjects are used in a new algorithm for clinical diagnosis of FH.\(^9\) To estimate CAD risks in untreated FH compared with the general population, data were utilized from previously published estimates of cumulative CAD risk for FH patients (excluding angina only) and their unaffected relatives\(^12,13\) supplemented by lifetime cumulative estimates for CAD in the general population.\(^14,15\) Adjustment downward for reported coronary disease in very young women in the general population was made because of the frequent (>50\%) finding of nonatherosclerotic disease in this subgroup (because of microvascular disease, arteritis, embolic and thrombotic events such as those associated with birth control and smoking, and fibromuscular dysplasia with spontaneous dissection, all of which are much more common in young women than men).\(^16–18\)

The resulting smoothed logistic curves are shown in the Figure. Relative risks for CAD in FH as compared to non-FH exceed 25 in young men. Even higher relative risk estimates for CAD death, greater than 40- to 100-fold, were reported for young, untreated FH in the Simon-Broome Registry before the statin era.\(^19–21\) The diminishing relative risk with age, as general population rates rise, is consistent with other reports, even among partially treated FH as shown in a large Norwegian registry of genetically verified FH.\(^22\) Note that the cumulative risk for a CAD event in untreated FH reaches \(\approx20\%\) by age 42 in men and by age 50 in women. Therefore, untreated FH may be considered a “coronary risk equivalent” by age 32 in men and age 40 in women. The much lower apparent risks reported by Kjaergaard et al\(^1\) herein may therefore be considered a qualified success attributable to the extensive use of statins motivated by the early screening efforts among these FH patients. Nevertheless, the 5-fold residual risk for coronary disease should serve as a strong impetus for aggressive finding and treatment of FH patients at an early age.

**Disclosures**

None.
References


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