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Putting Into Perspective the Hazards of Untreated Familial Hypercholesterolemia

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In this issue of *JAHA*, Kjaergaard et al[1] describe a 21-year follow-up of 118 heterozygous carriers of low-density lipoprotein (LDL) receptor (*LDLR*) mutations causing heterozygous 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, transient 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 specifically 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 carefully 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 222[4]: 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 herein[1] 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 (compared 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

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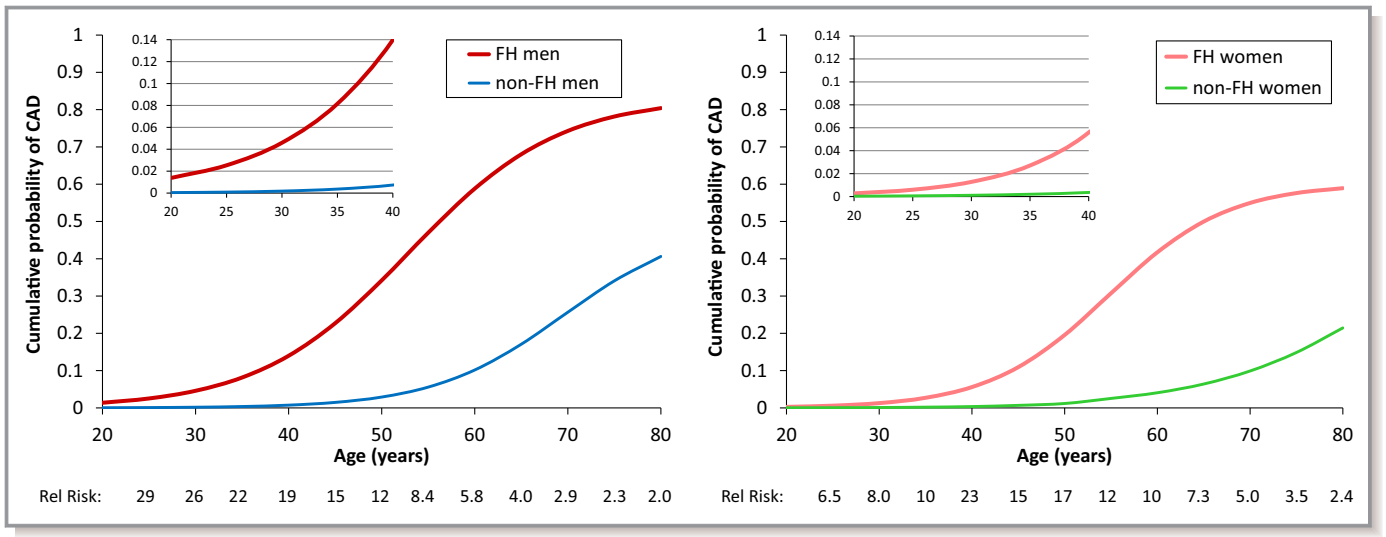

Figure. Cumulative probability of developing coronary artery disease (CAD) in men (left) and women (right) with heterozygous familial hypercholesterolemia (FH) as compared with unaffected relatives or the general population (non-FH). Relative risk (Rel Risk), as the ratio of cumulative CAD risk in FH divided by non-FH, is shown below each curve.

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, ≈67% 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 ≈20% 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.

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