

**Kannel W B, Castelli W P, Gordon T & McNamara P M.** Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham Study. *Ann. Intern. Med.* 74:1-12, 1971. [Heart Disease Epidemiology Study, Framingham, MA and Natl. Heart & Lung Inst., Natl. Insts. Health, Bethesda, MD]

**The 14-year risk of coronary heart disease (CHD) is described according to cholesterol, Sf 0-20, and Sf 20-400 lipoproteins. Sf 20-400 was not an independent risk factor taking total cholesterol and other risk factors into account, except possibly in women over 50. Sf 0-20 lipoproteins showed a linear independent association with risk but added nothing to the estimate of risk achieved by the total cholesterol alone. [The SC<sup>1</sup>® indicates that this paper has been cited in over 645 publications since 1971.]**

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"The 1971 report from Framingham was an attempt to bridge a growing gap in the rekindled interest in lipoproteins and our further experience with simple lipid measures such as the total cholesterol. To place this report in perspective one needs to recall that interest in the lipoproteins was stimulated in the late-1940s by John Gofman<sup>1</sup> and his associates at University of California, Berkeley. They correctly reasoned that knowledge of how the fats in our blood are transported might provide important insights into how blood lipids are related to cardiovascular disease. Out of their earlier work there came a series of lipoprotein determinations in the analytical ultracentrifuge which culminated in a postulated 'atherogenic index.' This index was a composite of Sf 0-20 beta (low density lipoproteins or LDLs) and Sf 20-400 prebeta (very low density lipoproteins or VLDLs), and emphasized the VLDLs which seemed to them to have a stronger association with coronary heart disease (CHD). The Gofman group's insistence that this was a better test than the serum cholesterol alone provoked a reaction from some of the cardiologists and epidemiologists interested in

lipid atherogenesis who were skeptical as to how much better such an index was compared to the simple total cholesterol. They wanted to justify the added cost and difficulty of the ultracentrifuge lipoprotein analysis. This led to a multicenter trial in the mid-1950s to compare the efficiency of total serum cholesterol versus the atherogenic index in separating coronary cases from controls.<sup>2</sup> The report of this study was clouded by disagreement among the principal investigators who could not reach a consensus and the results were summarized in two versions, one written by each protagonist. The cholesterol proponents claimed a single cholesterol test did just as well; the lipoprotein advocates stuck to their original claim of their superiority.

"In actuality, the simple cholesterol test group won as interest in doing lipoproteins waned in the US until Fredrickson, Levy, and Lees<sup>3</sup> revived such interest in the mid-1960s using their lipoprotein typing system, a much simpler procedure. However, definitive 'typing' also requires preparatory ultracentrifuge analysis. Their lipid studies, correlated with careful family studies, revealed powerful genetic relationships which stimulated great interest. Controversy reemerged as the value of these more detailed lipoprotein analyses were questioned in relation to the simple cholesterol test. Our 1971 paper was an effort to examine some of the trade-offs. It was one of the largest bodies of data showing the impact of cholesterol and lipoproteins on risk using prospective data. The report is now out of date since the revival of interest in high density lipoproteins (HDLs) in the late-1970s. In our most recent paper, in *Circulation*,<sup>4</sup> we examine the new concepts and the evidence seems to clearly indicate that lipoprotein studies add greatly to our estimation of cardiovascular risk, particularly in people over 50, and that most of this added knowledge is contained in the LDL and HDL measures.

"Thus, Gofman's original contention has proved correct. Knowledge of the lipoprotein transport does enhance risk assessment since the serum total cholesterol reflects chiefly the atherogenic LDL-cholesterol component but fails to take into account the protective HDL-cholesterol fraction reflecting removal of cholesterol. His emphasis on VLDL, however, still awaits confirmation."

1. Gofman J W, Lindgren F, Elliott H, Mantz W, Hewitt J, Strbowler B & Herring V. The role of lipids and lipoproteins in atherosclerosis. *Science* 111:166-71; 186, 1950.
2. Committee on Lipoproteins and Atherosclerosis, National Advisory Heart Council. Evaluation of serum lipoproteins and cholesterol measurements as predictors of clinical complications of atherosclerosis: report of a cooperative study of lipoproteins and atherosclerosis. *Circulation* 14:691-725, 1956.
3. Fredrickson D S, Levy R I & Lees R S. Fat transport in lipoproteins: an integrated approach to mechanisms and disorders. *N. Engl. J. Med.* 276:34-44; 94-103; 148-56; 215-25; 273-81, 1967. [Citation Classic. *Current Contents* (3):11, 16 January 1978.]
4. Castelli W P, Abbott R D & McNamara P M. Summary estimates of cholesterol used to predict coronary heart disease. *Circulation* 67:730-4, 1983.