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## Framingham Study Insights on Diabetes and Cardiovascular Disease

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**Featured Article:** Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979;241:2035–8.<sup>3</sup>

This diabetes report extended prior Framingham study findings with more-robust 20-year data for estimating the relative risk of specified atherosclerotic cardiovascular events from prior diabetes. It prospectively compared the cardiovascular impact of diabetes in women vs men, revealing the greater vulnerability in women. The role of diabetes as a contributor to atherosclerotic cardiovascular disease (CVD) was uncertain at the time of the report, with some doubting whether diabetes actually caused coronary disease. This and prior Framingham study reports confirmed prospectively in a general population sample the clinical observations of medical practitioners—that their patients with diabetes had excessive occurrence of peripheral artery disease, coronary disease, and strokes. The report also highlighted the less appreciated fact of a high risk of heart failure in patients with diabetes. The most notable unique feature of the report was that it revealed that the impact of diabetes varied both in relation to specific cardiovascular outcomes and with the sex of the individual. The relative impact was greatest for intermittent claudication and heart failure and least for coronary heart disease, which nevertheless on an absolute scale was the chief adverse cardiovascular outcome. The finding of a greater susceptibility in diabetic women was not unique to Framingham. It was also observed in diabetes clinics elsewhere (1, 2).

Several measures of the impact of diabetes on CVD incidence were used in the 1979 *JAMA* diabetes report. These measures included the absolute rate at which CVD develops in diabetics vs nondiabetics, the relative risk of developing CVD for a diabetic compared with a nondiabetic, and the fraction of CVD that is attributable to diabetes. They reflect the personal, clinical, and public health implications of the abnormality, which

are important dimensions to consider. The findings in this report have been confirmed by more extensive follow-up in the Framingham study and by other prospective epidemiologic investigations in a variety of population samples from the US.

In the Discussion section of the report, the relevance of the findings about diabetes provided a number of insights into things to come. It pointed out the many problems in evaluating the impact of diabetes on CVD, not the least of which is the definition of the diabetic state, which continues to derive chiefly from the blood sugar concentration. It postulated that “some elusive unique feature of diabetes that promotes its cardiovascular sequelae must be sought out and the means to correct it found” and further suggested that “a number of pathogenetic possibilities deserve further attention, including a possible contribution of hyperinsulinemia resulting from peripheral insulin resistance, possible adverse effects of oral hypoglycemic agents, and the influence of diabetic cardiomyopathy.” Increased thrombogenesis that could be responsible for diabetic CVD risk had already been reported, including diminished fibrinolytic activity, increased platelet aggregation and adhesiveness, and raised concentrations of fibrinogen (3, 4).

The Discussion also noted, “hyperlipidemia is frequently associated with diabetes and is often considered a major determinant of its atherosclerotic sequelae.” A previous Framingham study investigation, however, showed that in women diabetes exerted a sizable impact, even when HDL cholesterol and triglycerides were taken into account (5). Finally, the 1979 *JAMA* report noted, “Investigations of the origin of atherosclerosis have thus far disclosed no qualitative difference between lesions found in diabetics and lesions found in nondiabetics.” Many of the above-cited issues about the mechanism responsible for the adverse cardiovascular effect of diabetes are still being researched. Currently, it appears that a reduction in the hazard of type 2 diabetes is better achieved by controlling the cardiovascular risk factors that usually accompany it than by conventional therapy that focuses chiefly on the impaired glucose tolerance per se (6).

This widely cited report emphasized the hazard of generalizing risk factor information from one sex to the other. For many of the risk factors considered, there was a difference between the sexes in the impact on

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<sup>3</sup> This paper has been cited 1860 times since publication.

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subsequent CVD. This difference was particularly notable for cigarette smoking and diabetes. Whereas cigarette smoking was a more harmful influence among men, diabetes was by far more pernicious among women for every cardiovascular end point. Compared with other major risk factors for CVD, type 2 diabetes carries a low attributable risk because it is not as highly prevalent; however, an explosive increase in the prevalence of adiposity, which promotes insulin resistance and the metabolic syndrome, has assigned “prediabetes” a major role in preventive cardiology. Further investigation of the special risks of insulin resistance for cardiovascular events in diabetics of different ethnic groups is clearly needed.

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