

# Primary Prevention of Cardiovascular Disease in Pre-Diabetes

## The glass is half full and half empty

The modern incarnation of the term “pre-diabetes” occurred during a press conference hosted by the Department of Health and Human Services (HHS) and the American Diabetes Association (ADA) on 27 March 2002 to announce the results of the Diabetes Prevention Program (DPP):

*“HHS and the ADA are using the new term ‘pre-diabetes’ to describe an increasingly common condition in which blood glucose levels are higher than normal but not yet diabetic—known in medicine as impaired glucose tolerance or impaired fasting glucose. . . . Most people with this condition go on to develop type 2 diabetes within 10 years.”*

Pre-diabetes and type 2 diabetes often cosegregate with hypertension and dyslipidemia (low serum HDL cholesterol and high triglyceride levels) as manifestations of the metabolic syndrome (1), which affects 47 million people in the U.S. (2). Components of the metabolic syndrome can be identified in pre-diabetic subjects several years before the diagnosis of type 2 diabetes. Epidemiological studies, including the Paris Prospective Study (3), have shown that pre-diabetes confers an increased risk of cardiovascular disease (CVD). Patients who progress to type 2 diabetes exhibit additional risk for atherosclerotic disorders, which manifest as a two- to fourfold increase in the prevalence of CVD, stroke, and peripheral vascular diseases, compared with nondiabetic subjects (4). The risk of first myocardial infarction in diabetic patients is similar to that of recurrent myocardial infarction in nondiabetic patients who have had a previous event (5). Sadly, the prognosis following myocardial infarction or percutaneous angioplasty (6) is worse for diabetic than for nondiabetic individuals. These tragic disparities underscore the importance of primary prevention of CVD.

In this issue of *Diabetes Care*, The DPP Research Group (7) reports on the effects

of intensive lifestyle intervention, metformin, and placebo on CVD risk factors among subjects with impaired glucose tolerance (IGT). Compared with the placebo and metformin arms, subjects assigned to intensive lifestyle intervention showed decreased blood pressure, increased HDL cholesterol levels, and lower triglyceride levels during ~3 years of follow-up. Intensive lifestyle modification was also associated with a reduction in the more atherogenic small, dense LDL particles. Consonant with the foregoing findings, there was a reduced need for antihypertensive and hypolipemic medications among subjects assigned to the intensive lifestyle arm. It is reassuring that no fatalities were attributable to exercise in this largely previously sedentary cohort.

The demonstration that type 2 diabetes is preventable (8,9) raises hope for the possibility of concomitant prevention of the CVD morbidity and mortality associated with pre-diabetes. In the STOP-NIDDM trial (10), prevention of diabetes by acarbose treatment was associated with a reduction in the incidence of CVD risk markers. The present report (7) does not confirm a similar experience with another drug, metformin. Diabetes prevention through intensive lifestyle intervention reduced the need for antihypertensive medications in the DPP: the prevalence of hypertension at baseline was ~30% in the three comparison groups. After 3 years of follow-up, the prevalence increased to ~40% in the placebo and metformin arms but remained at ~30% in the intensive lifestyle group. Assuming that all patients with hypertension were ascertained at baseline, the stable 30% prevalence of hypertension in the lifestyle arm represents a crude risk reduction of 33% compared with placebo. This is a profound finding in a study that was not primarily designed to prevent hypertension.

The term “prehypertension” has recently been coined to describe individuals

with systolic blood pressure between 120 and 139 mmHg and diastolic blood pressure between 80 and 89 mmHg. It would be of interest to determine whether the attenuation of hypertension observed in the intensive lifestyle arm was due to reversion from prehypertension to normotension, prevention of progression from prehypertension to hypertension, or prevention of direct transition from normotension to hypertension. Furthermore, the goal of  $\geq 7\%$  weight loss in the intensive lifestyle arm was pursued through physical activity (150 min/week) and dietary modification (low fat, low calorie,  $-700$  kcal/day). Although maintenance of the weight loss goal proved elusive for the majority of study subjects by the end of the 3rd year, accrual of self-reported physical activity minutes stayed at the target of  $\geq 150$  min/week. Thus, it remains unclear whether physical activity per se or caloric restriction or weight loss accounted for the reduction in the prevalence rate of hypertension. Clearly, further studies are needed to define the specific components of the lifestyle intervention that impact progression from normal blood pressure to prehypertension and from thence to hypertension. The present report from the DPP strengthens the evidence on the potency of lifestyle intervention in the management of hypertension and provides new data on primary prevention of hypertension. Given the public health scourge of hypertension, the importance of these findings cannot be overstated.

The scant CVD event accrual was an obvious barrier to detecting any differences among the treatment and placebo groups. The characteristics of the study cohort (impaired glucose tolerance, older age, 30% hypertensive, and 44% with dyslipidemia) would have predicted a much higher rate of CVD events. However, the cohort had an astonishingly low (<4%) prevalence of documented CVD at baseline. (Subjects with unstable angina

or recent antecedent CVD events were excluded from participation.) By contrast, pharmacological trials that target individuals with prior CVD events often accrue sufficient events that enable a clear separation between comparison groups within a few years (11). Despite the limitation imposed by small numbers, the absence of even a hint of a trend toward clinical event reduction in the intensive lifestyle arm, despite potent changes in CVD risk markers, is noteworthy. Could this mean some risk factors are not modifiable by lifestyle intervention? For instance, the mean LDL cholesterol level remained unchanged, despite 3 years of intensive lifestyle intervention. It is, therefore, unlikely that lifestyle measures alone would reduce this major CVD risk factor to maximally protective levels (11).

Furthermore, cigarette smoking, proinflammatory cytokines, adhesion molecules, matrix metalloproteinases, fibrinolysis, endothelial function, homocysteinemia, etc., are factors that could display differential sensitivities to lifestyle intervention. Unfortunately, the present report does not provide information on baseline smoking history or the numerous nontraditional risk markers. Of course, CVD risk factors do not automatically lead to myocardial infarction or stroke. Time is a necessary cofactor that permits the transmutation of risk markers to clinical events. The ongoing DPP Outcomes Study will have that element of time and may shed light on the role of lifestyle intervention (or metformin) in the prevention of CVD in pre-diabetic subjects. The present report (7) demonstrates that lifestyle modification prevented or ameliorated hypertension and

dyslipidemia in such subjects. If sustained, these benefits could well translate to a reduction of CVD events, but we don't know that, at least not yet.

SAMUEL DAGOGO-JACK, MD, FRCP

From the Department of Medicine and General Clinical Research Center, Division of Endocrinology, Diabetes & Metabolism, University of Tennessee Health Science Center, Memphis, Tennessee.

Address correspondence and reprint requests to Samuel Dagogo-Jack, MD, 956 Court Ave., Memphis, TN 38163. E-mail: sdj@utm.edu.

S.D.-J. is a DPP investigator, but not a member of the CVD Writing Group.

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