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Abnormal regulation of glycemia ("dysglycemia") has a very long time course, from its earliest stage, labeled pre-diabetes, to the onset of Type 2 diabetes (T2D), to the development of clinically detectable microvascular changes and measurable atherosclerosis, to clinically manifest complications with attendant morbidity and mortality. The Diabetes Prevention Program (DPP) focused on the pre-diabetes stage of dysglycemia and demonstrated powerful beneficial effects of lifestyle intervention (ILS) and metformin (MET), compared with placebo (PLBO), in preventing or delaying the onset of T2D over a 3-year period in a high-risk population (n=3234). The DPP also investigated and described the interventions, phenotypic and genotypic risk factors associated with T2D development, the effects of the interventions in the setting of these risk factors, the health economic implications of T2D prevention, and other outcomes of interest. Based on these results, the DPP lifestyle program has been widely implemented. The 11-year follow-up DPP Outcomes Study (DPPOS) explored the longer-term effects of T2D prevention, bridging the period between pre-diabetes and T2D, and examined outcomes that required more time to develop than the relatively brief 3-years of DPP. DPPOS showed longer term salutary effects of the original interventions on T2D prevention and on cardiovascular disease (CVD) risk factors. Prevention was cost-saving with MET and cost-effective with ILS. Overall, the risk for microvascular disease was significantly greater in subjects who developed T2D and increased with longer duration and higher hemoglobin A1c (A1C). There were no significant differences by treatment group in the prevalence of the aggregate microvascular outcome; however, compared with PLBO and MET, ILS significantly reduced the risk of microvascular disease among women and those who had A1C ≥6.5% at study end. The proposed DPPOS Phase 3 will study the DPPOS cohort for 10 more years, taking advantage of the long term randomized exposure to MET and the densely phenotyped and genotyped DPPOS cohort (n=2778), which includes nearly 1600 patients with known T2D duration and ~1200 who have not developed T2D, to address yet unanswered questions about long-term exposure to MET and ILS initiated during pre-diabetes. DPPOS Phase 3 will examine outcomes that are of increasing public health concern in the aging population with prediabetes and T2D, including the putative benefits of MET on development of CVD and cancer. The main goals of DPPOS Phase 3 are to examine efficiently: 1) the long-term effects of metformin therapy begun in the prediabetic phase on risk for CVD and cancer; 2) the long-term effects by intention-to-treat of ILS and MET on further development of T2D and on traditional and more recently recognized complications of dysglycemia, and of their economic impact; and 3) the clinical course of dysglycemia, evaluated by categorical diagnoses (pre-diabetes vs diabetes) and as a continuum, and their associations with the development of complications, including analyses of interactions with DPP interventions and established and novel risk factors.