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Type 2 Diabetes Management: Putting Theory Into Practice—Introduction

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TYPE 2 DIABETES is the most common metabolic disease, and the number of diabetic individuals is increasing worldwide. It is claimed that we are experiencing a true diabetes pandemic. At present, the number of diabetic patients in the world is estimated to range between 150 and 200 million, but it has been calculated that this number will rapidly increase to reach the extraordinary figure of 300 million diabetic individuals in the next 25 years. There is an urgent need for effective prevention strategies that may reduce the rate of diabetes expansion. Recent trials have shown that changes in lifestyle and, possibly, pharmacological intervention may significantly reduce the rate of conversion to diabetes in predisposed individuals. This approach, however, will require extensive and expensive screening. In the meantime, the number of diabetic patients will continue to rise. This growing number of diabetic patients will be associated with an increase in disease-related cost. In the United States, the direct cost of diabetes increased by 25% and the indirect costs by 50% from 1997 to 2002. These costs are only partially accounted for by the therapy of the metabolic disorder. The majority of the costs are due to the treatment of long-term complications. Thus, prevention of complications is imperative. Epidemiological and prospective studies have demonstrated that intensive treatment of hyperglycemia can effectively reduce the development and/or progression of microvascular disease. In the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), maintenance of hemoglobin A_{1c} (HbA_{1c}) as low as 7% in type 2 and type 1 diabetic patients, respectively, was associated with significant reduction in retinopathy, nephropathy, and neuropathy. However, the number of patients achieving such degree of glycemic control was low before intervention studies provided evidence for the importance of intensive treatment of hyperglycemia, and has remained low ($<$30%) after the results of these trials were published. In the near future, therefore, careful analysis of the treatment-limiting factors to be targeted with more suitable therapeutic strategies will be needed.

If the improvement in glycemic control is effective in reducing the risk of microvascular complications, it seems to be less potent at reducing the risk of myocardial infarction, stroke, and peripheral vascular disease, so that an even greater challenge will be the prevention of cardiovascular events in the diabetic population. Cardiovascular disease (CVD) is the main cause of morbidity, mortality, and diabetes-related costs. In the diabetic population, the relative risk of coronary heart disease (CHD) is 1.5 to 1.7 in male and 1.7 to 4.0 in female diabetic patients. Their 10-year risk for major coronary events approximates the risk of patients without diabetes but with a previous CHD event. According to the World Health Organization (WHO), the prevalence of CVD in diabetic individuals ranges from 26% to 36%. CVD accounts for as much as 75% of hospital admissions for diabetic complications and for 75% of deaths in type 2 diabetes. Life expectancy is 5 to 10 years lower in these patients than in the nondiabetic general population. The relationship between diabetes and cardiovascular events is so stringent that the American Diabetes Association has identified diabetes as a cardiovascular disease while the National Cholesterol Education Program Expert Panel (NCEP) on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) has come to the conclusion that diabetes should be considered a CHD risk equivalent.

This excessive risk of CVD in diabetes is unlikely to be explained by hyperglycemia itself. Rather, it is the common combination of high plasma glucose levels with dyslipidemia, hypertension, endothelial dysfunction, and prothrombotic status that act in concert to confer greater risk. Several intervention trials have indicated that treatment of hypertension, and

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hypercholesterolemia, and use of small doses of aspirin can significantly reduce the risk for myocardial infarction, stroke, and peripheral vascular disease. This has prompted the concept of assessment and treatment of the global CVD risk in diabetes and underlined the need for hypoglycemic agents that may provide added value in preventing vascular damage. More recently, the Steno-2 study has shown that a comprehensive therapeutic approach is indeed associated with positive outcomes. Although effective, this approach is not free of potential problems. Polypharmacy and compliance with polypharmacy may be one of them. Compliance with therapy has been shown to improve by reducing the number of tablets to be administered. New drug formulations that maintain the peculiarities of the active agent while administered as a monodose are thus welcome. The recent introduction of gliclazide modified release (MR), a new once-daily formulation of the sulfonylurea gliclazide that ensures progressive drug release paralleling the 24-hour glycemic profile, while selectively acting on adenosine triphosphate–dependent (K_{ATP}) channels of the pancreatic β cell, offers new opportunities.

The symposium "Type 2 Diabetes Management: Putting Theory Into Practice" offers informative updates and articulates currently available evidence linking diabetes treatment with prevention of cardiovascular disease. T. Wascher reviews the molecular structure, tissue distribution, molecular composition, and role of ATP-sensitive potassium channels in the pancreas and cardiovascular system with regard to tissue selectivity of different sulfonylureas. N. Danchin addresses type 2 diabetes as a risk factor for ischemic heart disease, the pathophysiology of macroangiopathy with specific focus on the role of K_{ATP} channels, and the management including the clinical rationale for β-cell selective sulfonylureas. G. Renier discusses the pathological mechanisms responsible for atherosclerosis in type 2 diabetes, and the importance of employing hypoglycemic agents that may also reduce oxidative stress. O. Pedersen critically describes and reviews the rationale, design, and results of the Steno-2 study, stressing the implication for future treatment in type 2 diabetic patients. D.E. Grobbee addresses the need for a large morbidity/mortality trial such as the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) study providing the rationale for choosing gliclazide MR and perindopril-indapamide combination as reference drugs. Finally, G. Schernthaner reviews the data on efficacy, safety, and other parameters of once-daily formulation of sulfonylureas by comparing their results in terms of efficacy and safety.