Combined Pharmacologic/Nonpharmacologic Intervention in Individuals at High Risk of Developing Type 2 Diabetes

Pro pharmacologic therapy

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The prevalence of type 2 diabetes continues to grow, and it is predicted that, unless effective prevention and control measures are implemented, the global prevalence of the disease will exceed 366 million by 2030 (1). Type 2 diabetes is associated with considerable morbidity, excess mortality, and substantial costs (2–4). A recent statement issued by the American Diabetes Association estimates that in the U.S., the cost of diabetes in 2007 was $174 million. However, the actual national burden is likely to exceed this figure because it does not include the social costs of intangibles such as care provided by nonpaid caregivers. Overall costs are expected to increase further because of the projected rise in the proportion of the population over the age of 65 years. Therefore, if successful, early intervention to delay or prevent the development of diabetes offers enormous potential benefit to individuals, health care systems, and society.

Current diagnostic criteria for overt diabetes include a fasting plasma glucose concentration of ≥126 mg/dl or a 2-h postchallenge plasma glucose concentration of ≥200 mg/dl during a 75-g oral glucose tolerance test (5). The term “prediabetes” has recently been adopted to describe conditions in which blood glucose levels are elevated, but not above the American Diabetes Association–defined level for diabetes; it includes the presence of impaired fasting glucose or impaired glucose tolerance (compared with normal glucose tolerance compared with normal control subjects) (11). A crude analysis of data from the Framingham Heart Study showed a 65% increase in risk of developing chronic kidney disease in subjects with impaired fasting glucose or impaired glucose tolerance (compared with normal subjects), and a further analysis revealed that this was accounted for largely by the increase in vascular risk factors seen in these subjects (12). The U.K. Prospective Diabetes Study (13) demonstrated that intensive glycemic control substantially decreased the risk of microvascular complications in patients with newly diagnosed type 2 diabetes, and it is likely that similar treatment benefits might be gained in patients with pre-diabetes.

Thus, it is clear that pre-diabetes is not a benign state and that early and adequate intervention is indicated to prevent the development of complications and progression to overt diabetes. There is now substantial evidence that progression to type 2 diabetes can be delayed or prevented through lifestyle and pharmacologic interventions (14).

PHARMACOLOGIC INTERVENTION IN INDIVIDUALS AT HIGH RISK OF DEVELOPING DIABETES — A number of studies have documented beneficial effects of lifestyle intervention, including weight-reducing diets and moderate-intensity exercise, in preventing the development of type 2 diabetes in high-risk subjects. The Malmo study (15) was one of the first lifestyle intervention studies and involved men with impaired glucose tolerance and early-stage type 2 diabetes. After a mean follow-up of 6 years, glucose tolerance was normalized in >50% of subjects with impaired glucose tolerance at the start of the study, and >50% of subjects with diabetes reverted to a pre-diabetic state. Similar findings were obtained in the Da Qing study, which examined the effects of diet and/or exercise in a Chinese population with impaired glucose tolerance over a 6-year follow-up period (16). All interventions were associated with a significant reduction in the risk of diabetes, ranging from 36% in the diet-only group to 39% in the combined diet plus exercise group and 47% in the exercise-only group. The results of these early studies were subsequently confirmed by two well-designed studies: the Finnish Diabetes Prevention Study and the DPP (7,17). After ~3 years of follow-up, in each of these studies, there was a 58% relative
risk reduction in the incidence of diabetes in the lifestyle intervention group compared with control subjects.

The trials discussed above provide convincing evidence that intensive lifestyle interventions can reduce the risk of progression from impaired glucose tolerance to overt diabetes. However, there are important reasons why similar success rates cannot be anticipated in routine clinical practice. First, the individuals participating in the trials had access to considerable support from health professionals. For example, both the Finnish Diabetes Prevention Study and the DPP involved multidisciplinary teams, including a physician, dietitian, nurse, psychologist, and physiotherapist, providing expertise in the areas of nutrition, behavioral change, and physical activity. This level of individual education and coaching is not likely to be available in a real-life setting. Second, not all high-risk individuals will be willing or able to accept and implement the lifestyle changes that are required to achieve meaningful health benefits. It is well known that the long-term success rate of diet and lifestyle programs for weight reduction is very low. Year on year, average population weight and waist circumference continue to increase, regardless of diets, TV public awareness campaigns, and personal trainers. Indeed, given the dangers associated with weight cycling and repeated failure, it has been proposed that it is neither ethical nor scientific to support the continued use of dieting for the management of obesity (18). Although the effects of exercise intervention for weight control appear to be more promising, there are only minimal follow-up data for the first couple of years postintervention and virtually none after 5 years (18). The limited amount of evidence that is available on long-term follow-up of traditional diet and exercise intervention studies for weight loss suggests almost complete relapse after 3–5 years (18). One might think that patients with a potentially life-threatening health condition would be more likely to adopt and maintain a healthier lifestyle, but this does not appear to be true. A recently published study has shown that dietary quality tends to be poor, even in patients who have been diagnosed with coronary heart disease within the past year (19), and in another study in patients with coronary heart disease, concordance with a recommended cholesterol-lowering diet was only moderate (20). In the latter study, only one-third of the patients achieved the recommended fat intake and only one-quarter achieved the recommended saturated fat intake. Moreover, concordance was found to be unaffected by disease severity or previous myocardial infarction and was slightly worse in patients who were obese or who had diabetes. The long-term maintenance of healthy behaviors clearly presents a major challenge for health care providers and their patients, and it seems unlikely that dietary and lifestyle interventions will be more successful in individuals with impaired glucose tolerance than in other patient populations. Therefore, there is a need for safe and effective pharmacologic therapies that can be used in combination with lifestyle modification programs for the prevention of diabetes (14).

Current clinical practice guidelines advocate the use of metformin in combination with lifestyle modification as first-line treatment for patients who have been diagnosed with type 2 diabetes (21). Metformin has also been investigated for the prevention of diabetes. The BIGPRO (BGIguanides and the Prevention of the Risk of Obesity) study was designed to investigate whether metformin, used in combination with lifestyle modification, could modify the metabolic abnormalities associated with insulin resistance in subjects without diabetes but with central adiposity (high waist-to-hip ratio) (22). Compared with placebo, metformin plus lifestyle modification was associated with significant weight loss, better maintenance of fasting blood glucose, total and LDL cholesterol levels, and a greater decrease of fasting plasma insulin concentration. The authors concluded that metformin would be a suitable candidate for long-term intervention treatment for the prevention of diabetes. More recently, the DPP demonstrated that intervention with metformin decreased the development of diabetes in adults with impaired glucose tolerance by 31% (7). However, the combination of lifestyle modification plus metformin was not studied. Regardless of their diverse effects upon weight, other drugs that have been investigated in clinical trials for the prevention of diabetes include acarbose, orlistat, troglitazone, rosiglitazone, and pioglitazone (Table 1 shows a summary of key adequately powered studies).

In the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial, treatment with the α-glucosidase inhibitor acarbose reduced progression to diabetes by ~25% after 3.3 years (23). Although treatment with acarbose results in weight loss in some patients, the weight-reducing effect in this trial was negligible. However, in the XENOS (XENical in the Prevention of Diabetes in Obese Subjects) study, the weight-reducing agent orlistat (a gastrointestinal lipase inhibitor) plus lifestyle changes resulted in greater weight loss as well as a greater reduction in the incidence of type 2 diabetes compared with lifestyle intervention alone (24). A reduction in the incidence of diabetes was only seen in subjects with impaired glucose tolerance.

Table 1—Summary of key studies of pharmacologic interventions for the prevention of diabetes

| Treatment | n | Intervention | Duration (years) | Relative risk reduction (%) |
|-----------|---|-------------|-----------------|--------------------------|
| DPP       |   | Metformin   | 2.8             | 31                       |
| Knowler et al. 2002, DPP Research Group 2005 | 2,151 | Troglitazone* | 0.9             | 75                       |
| TRIPOD    |   | Troglitazone | 2.5             | 55                       |
| Buchanan et al. 2002 | 236 | Troglitazone | 2.5             | 55                       |
| XENDOS    |   | Orlistat    | 4.0             | 37                       |
| Torgerson et al. 2004 | 3,305 | Orlistat | 4.0             | 37                       |
| STOP-NIDDM|   | Acarbose    | 3.2             | 36                       |
| Chiasson et al. 2002 | 1,368 | Acarbose | 3.2             | 36                       |
| DREAM     |   | Rosiglitazone | 3.0             | 60                       |
| DREAM Trial Investigators 2006 | 5,269 | Rosiglitazone | 3.0             | 60                       |

*Treatment withdrawn after ~1 year because of hepatotoxicity.
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study. Hispanic women with a history of gestational diabetes (a condition that is known to predispose to subsequent development of diabetes) received troglitazone and were followed up for an average of 2.5 years before the drug was withdrawn due to adverse effects on liver function (26). In this study, treatment with troglitazone was associated with a 5% risk reduction of developing diabetes. Women who completed the TRIPOD study were subsequently invited to participate in the PIPOD (Pioglitazone In the Prevention Of Diabetes) study, which also showed relatively low rates of diabetes after 3 years of treatment with this currently available thiazolidinedione agent (27). The possibility of a class effect of thiazolidinediones for diabetes prevention was further supported by the results of the DREAM (Diabetes REduction Assessment with Ramipril and Rosiglitazone Medication) study, which showed a 60% reduction in the risk of diabetes or death in subjects with pre-diabetes who were treated with rosiglitazone (median duration of treatment was 3 years) (28).

Pharmacologic interventions that are effective in the prevention of diabetes are likely to act through a number of mechanisms, in addition to weight control or reduction. It has been shown that the onset of type 2 diabetes is preceded by a marked deterioration of pancreatic β-cell function (29). An analysis of data from autopsy files of subjects who were obese, and with or without type 2 diabetes or impaired fasting glucose, showed a curvilinear relationship between pancreatic β-cell mass and fasting blood glucose concentrations (30). The development of pharmacologic agents that can preserve pancreatic β-cell function is an exciting area for current and future research.

A preclinical study in diabetic rats has demonstrated that rosiglitazone prevents the loss of pancreatic β-cell mass by maintaining β-cell proliferation and preventing net β-cell death (31). Preservation of pancreatic β-cell function has also been shown in clinical trials of thiazolidinedione drugs. In the TRIPOD study, treatment with troglitazone was associated with preservation of β-cell function in Hispanic women who were at high risk of developing diabetes (26), and similar effects were seen with pioglitazone in the PIPOD study, providing support for a class effect of thiazolidinedione drugs on pancreatic β-cell function (27).

ADOPT (A Diabetes Outcome Progression Trial) compared rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed type 2 diabetes. The primary outcome was the time to monotherapy failure. At 5 years, a lower cumulative incidence of monotherapy failure was seen with rosiglitazone (15%) compared with metformin (21%) or glyburide (34%) (32). If the findings of the TRIPOD and PIPOD studies do indeed indicate a class effect of the thiazolidinediones on pancreatic β-cell function, it may be that the sustained benefit seen with rosiglitazone in the ADOPT study was due to preservation of pancreatic β-cell function. Newer classes of drugs, such as the incretin mimetics and inhibitors of dipeptidyl peptidase-4 activity, may also prove to be effective in preserving pancreatic β-cell function (33). The ability of these agents to delay or prevent the development of diabetes in high-risk individuals may be confirmed in future clinical trials. Thus, the inability of lifestyle alone to reverse the progressive β-cell defect that drives the appearance of type 2 diabetes may be reversed to a variable extent by some pharmacologic therapies. It is this ability that suggests that those therapies will inevitably be included in diabetes prevention programs.

The majority of health economic studies published to date indicate that currently available pharmacologic interventions for the prevention of diabetes are highly cost-effective (34). An analysis of the total costs to the health system and society in the DPP indicated that costs were ~25% higher for lifestyle intervention compared with metformin ($4,603 metformin vs. $5,809 lifestyle) (35); however, both types of intervention were associated with only modest incremental cost compared with placebo. A further analysis of DPP data projected costs, health outcomes, and cost-effectiveness of metformin or lifestyle intervention over a lifetime compared with placebo (36). The authors concluded that, compared with placebo, both metformin and lifestyle interventions provided clinically meaningful health benefits at an attractive cost. Both interventions were found to be cost-effective in all age-groups, except for metformin in participants aged >65 years. The long-term health economic implications of implementing DPP-like interventions in France, Germany, Switzerland, U.K., and Australia have been evaluated using economic modeling (37). The results clearly illustrate that the cost-effectiveness of such an intervention depends on a number of variables related to local constraints and that, to provide information that is relevant for the health care payer, any program must be tailored to the specific setting. As the clinical data for new pharmacologic agents become available, appropriate health economic analyses will also be required.

CONCLUSIONS — The majority of individuals with pre-diabetes (i.e., with elevated fasting glucose levels and/or impaired glucose tolerance) will go on to develop overt diabetes, with its associated complications and increased morbidity and mortality. Moreover, the microvascular disease typically associated with diabetes is also observed in individuals with impaired glucose tolerance. Therefore, early and adequate intervention is indicated to prevent the development of complications and progression to diabetes. A number of well-designed studies have provided evidence that intensive lifestyle intervention programs can significantly reduce the risk of progression from impaired glucose tolerance to overt diabetes. The implementation and maintenance of the required behavioral changes in a “real life” setting is more challenging, however, and similarly high success rates cannot be anticipated in routine clinical practice. The findings of published studies of the use of lifestyle interventions for weight loss and the reduction of cardiovascular risk indicate that the majority of individuals will fail to adhere to recommended dietary interventions, and there is little reason to suppose that concordance will be any higher in patients with impaired glucose tolerance. Therefore, there is a need for safe and effective pharmacologic therapies that can be used in combination with lifestyle modification programs for the prevention of diabetes.

Drugs that have been shown to reduce the relative risk of progression to diabetes include metformin; the thiazolidinediones troglitazone, rosiglitazone, and pioglitazone; the α-glucosidase inhibitor acarbose; and the gastrointestinal lipase inhibitor orlistat. Pharmacologic interventions that are effective in the prevention of diabetes are likely to act through a number of mechanisms, in addition to weight control or reduction. An exciting area for current and future clinical development is the use of drug treatments that may preserve pancreatic β-cell function.

Data from a number of clinical studies have shown that the use of both pharmacologic and lifestyle interventions to delay
progression to type 2 diabetes, if successful, can result in substantial improvements in health and economic outcomes, thereby providing benefits for patients, health care payers, and society as a whole. The risks and benefits for the individual patient should be considered when choosing the most appropriate treatment strategy, which should then be reviewed and adjusted as needed to ensure the best possible outcomes.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
2. Alberti KGMM. The costs of non-insulin-dependent diabetes mellitus. Diabet Med 1997;14:7–9
3. De Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M. Cause-specific mortality in type 2 diabetes: the Verona diabetes study. Diabetes Care 1999;22:756–761
4. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. Diabetes Care 2008;31:596–615
5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006;29 (Suppl. 1):S43–S48
6. World Health Organization/International Diabetes Federation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a World Health Organization/International Diabetes Federation Consultation. Geneva, Switzerland, WHO Document Production Services, 2006, p. 1–46
7. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
8. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. Diabetes 2003;52:2867–2873
9. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. Diabet Med 2007;24:137–144
10. Cohen JA, Jeffers BW, Faldut D, Marcoux M, Schrier RW. Risks for sensorimotor peripheral neuropathy in non-insulin dependent diabetes mellitus (NIDDM). Muscle Nerve 1998;21:72–80
11. Franklin GM, Kahn LB, Bender J, Marshall JA, Hamman RF. Sensory neuropathy in non-insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study. Am J Epidemiol 1990;131:633–643
12. Fox CS, Larson MG, Leip EP, Meigs JB, Wilson PWF, Levy D. Glycemic status and development of kidney disease: the Framingham Heart Study. Diabetes Care 2005;28:2436–2440
13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
14. Chia JY, Lindgarde F. Prevention of type 2 diabetes: fact or fiction. Expert Opin Pharmacother 2007;8:3147–3158
15. Eriksson KS, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmö feasibility study. Diabetologia 1991;34:891–898
16. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang WP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537–544
17. Tuomilehto J, Lindstrom J, Eriksson J, Valle T, Hamalainen H. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
18. Miller WC. How effective are traditional dietary and exercise interventions for weight loss? Med Sci Sports Exerc: 1999;31:1129–1134
19. Ma Y, Olenzdek BC, Pagoto SL, Merriam PA, Chiriboga DE, Griffith JA, Bodenlos J, Wang Y, Ockene IS. Dietary quality 1 year after diagnosis of coronary heart disease. J Am Diet Assoc 2008;108:240–246
20. Erkiklal AT, Sarkkinen ES, Koukkunen H, Rintala JA, Hamman RF. Sensory neuropathy in non-insulin dependent diabetes mellitus. Muscle Nerve 1998;21:72–80
21. American Diabetes Association. Standards of medical care in diabetes: 2007. Diabetes Care 2007;30(Suppl. 1):S4–S41
22. Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F, Cohen JM, Grandmottet P, Vague P, Safar ME, Eschwege E. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution: BIGPRO Study Group. Diabetes Care 1996;19:920–926
23. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karsak A, Laakso M. STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–2077
24. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155–161
25. Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes 2005;54:1150–1156
26. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Gico J, Ochoa C, Tan S, Berkowitz K, Hodin HN, Azen SP. Prevention of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002;51:2796–2803
27. Xiang AH, Peters RK, Kjos SL, Marroquin A, Gico J, Ochoa C, Kawaakubo M, Buchanan TA. Effects of pioglitazone on pancreatic β-cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes 2006;55:517–522
28. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dincag N, Hanefeld M, Hoowgerf B, Laakso M, Mohan V, Shaw J, Zimman B, Holman RR. DREAM (Diabetes Reduciton Assessment with ramipril and rosiglitazone Medication) Trial Investigators: effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glycolucose: a randomised controlled trial. Lancet 2006;368:1096–1105
29. Lyssenko V, Almgren P, Anevkis D, Perfelt R, Lahki H, Nissén M, Isomaa B, Forsen B, Homström N, Saloranta C, Taskinen MR, Group L, Tuomi T. Botnia study group: predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. Diabetes 2005;54:166–174
30. Ritzel RA, Butler AE, Rizza RA, Veldhus JD, Butler PC. Relationship between β-cell mass and fasting blood glucose concentration in humans. Diabetes Care 2006;29:717–718
31. Finegood DT, McArthur MD, Kojwang D, Thomas MJ, Topp BG, Leonard T, Buckingam RE. β-Cell mass dynamics in Zucker diabetic fatty rats: rosiglitazone prevents the rise in net β-cell death. Diabetes 2001;50:1021–1029
32. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitiz BG, Lachin JM, O'Neill MC, Zimman B, Viberti G. ADOPT Study Group: glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
33. Wajchenberg BL. Beta-cell failure in diabetes and preservation by clinical treatment. Endocr Rev 2007;28:187–218
34. Alberti KGMM, Zimmet P, Shaw J. International Diabetes Federation: a consensus on type 2 diabetes prevention. Diabet
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35. Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. Diabetes Care 2003;26:36–47

36. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE. Diabetes Prevention Program Research Group: the cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med 2005;142:323–332

37. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland and the United Kingdom. Clin Ther 2004;26:304–321