CHAPTER 38

PREVENTION OF TYPE 2 DIABETES

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SUMMARY

This chapter reviews randomized clinical trials of the prevention of type 2 diabetes, from small early trials of drugs available in the 1960s to more recent studies, some very large, of additional drugs and of lifestyle interventions designed to produce weight loss and increase physical activity. Most studies show that type 2 diabetes can be prevented or delayed to varying extents by a variety of drugs used to treat type 2 diabetes and by lifestyle interventions. Whether these interventions affect only hyperglycemia during the time the interventions are provided or also affect other health outcomes, such as mortality rates and the development of diabetes complications, is largely unknown.

INTRODUCTION

The ability to prevent or delay type 2 diabetes by modifying some of its risk factors has been hypothesized for several decades, as reviewed in the 1980s and 1990s (1,2). The long and often gradual time-course of increasing glycemia prior to the diagnosis of diabetes suggested that interventions during this phase preceding diabetes might be effective. For example, obesity and sedentary behavior are potentially modifiable through behavioral intervention. Although the dietary components (as opposed to total caloric intake) that increase risk of type 2 diabetes are controversial, dietary interventions focusing on reducing calories from fat to achieve weight loss (3,4) and increasing dietary fiber (4) have been successful. In addition, diabetes drugs might prevent or slow increases in glycemia, thus preventing the onset of diabetes. More recently, drugs or surgery directed at weight loss, rather than glycemia *per se*, have been used to prevent type 2 diabetes. A small number of randomized comparative effectiveness trials have been aimed at determining the most effective interventions for preventing or delaying type 2 diabetes, usually in adults at particularly high risk of developing diabetes.

Some randomized controlled trials (RCTs) tested lifestyle weight-loss interventions; some used drugs; and some used both. All reported benefit, to varying degrees, of most interventions, although the extent to which studies without beneficial effects have not been published is unknown. Three key questions remain: (1) How should persons be selected for intervention? (2) What is the preferred intervention or combination of interventions for specified populations or individuals? (3) Are there long-term benefits beyond preventing or delaying progression of hyperglycemia to diabetes diagnostic levels?

Virtually all prevention research has targeted "high-risk" persons rather than the general population. This has been done for the practical reason of having adequate power to test interventions with sample sizes and follow times that were affordable. Most RCTs have enrolled persons with impaired glucose tolerance (IGT) during an oral glucose tolerance test (OGTT). Other high-risk characteristics have included overweight or obesity and elevated fasting plasma glucose (FPG). It would be logistically easier to screen for high-risk persons with FPG than with the OGTT required for identifying IGT, yet the authors are aware of only one major RCT that used FPG as its major eligibility criterion (5) and none that recruited high-risk persons based on glycosylated hemoglobin (A1c) or nonglycemic risk factors alone.

This chapter reviews RCTs with type 2 diabetes as a primary or secondary outcome or with other outcomes associated with diabetes. Most reported as their primary outcome the development of diabetes defined by the FPG and OGTT. Some weight-loss studies reported diabetes as a secondary outcome, either as diagnosed clinically outside the study or by measures of glycemia performed in the study. A few such RCTs assessed other health outcomes, such as diabetes microvascular complications, cardiovascular disease (CVD), disability, mortality, or health care costs. It is, of course, these outcomes that are of major concern to individuals and health care systems. There are also potential benefits of intervention(s) aimed at diabetes prevention among those persons who develop diabetes despite the intervention (as many do). It is conceivable that their diabetes may have a less aggressive course because of long-lasting intervention effects, such as

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improved beta cell function, lower body weight, and lower levels of microvascular or macrovascular risk factors.

Major challenges, however, have been noted in implementing the results of RCTs in clinical practice, i.e., outside the setting of RCTs in which relatively motivated persons are enrolled and more resources are generally available than in practice. In addition to the problem of limited resources, implementation programs are difficult to evaluate because randomized comparison groups are usually absent. Such programs, therefore, are usually evaluated by methods other than RCTs.

In this chapter, RCTs that seek to prevent or delay type 2 diabetes using behavioral or drug interventions are reviewed and discussed. This is an update of parts of a review article by some of the authors published in 2008 (6). This review does not include all relevant RCTs, but attempts to include those with the most historical interest and those having the greatest impact on the field. The role of genetics in type 2 diabetes prevention and of treatment effects on long-term outcomes beyond diabetes itself are also discussed. Nonrandomized prevention activities, bariatric surgery, the economic aspects of diabetes prevention, physiologic studies of the potential mechanisms of diabetes prevention, or RCTs that aim to prevent or delay type 1 diabetes (reviewed in Chapter 37 *Prevention of Type 1 Diabetes*) are outside the scope of this chapter.

HISTORY OF PREVENTION RCTS: RESULTS WITH TYPE 2 DIABETES AS THE PRIMARY OR SECONDARY OUTCOME

The history of RCTs in diabetes prevention began in the 1960s and extends to the present. It can be broadly divided into three phases: (1) early small trials of drugs used in treating diabetes; (2) RCTs of lifestyle (primarily weight loss) interventions, alone or in combination with or compared with drug intervention; and (3) more recent, larger sized RCTs of drug interventions. All trials enrolled adults with risk factors for diabetes, primarily IGT, rather than representatives of the population at large. The early studies enrolled persons identified as being at risk based on some level of post-challenge hyperglycemia. The later drug studies compared drugs with placebo, each combined with a lifestyle intervention because of previously demonstrated benefits of lifestyle intervention. The lifestyle interventions in these drug studies were not well described, and it is unknown whether they were as intensive or effective as the lifestyle interventions in studies where such interventions were directly tested.

The history of these RCTs is summarized in the text and Table 38.1 in chronological order of publication of their primary results. This is followed by a section on RCTs that included genetics components and descriptions of studies that had long-term follow-up for health conditions other than diabetes, such as microvascular and macrovascular complications and mortality rates.

EARLY U.K. AND SWEDISH PREVENTION STUDIES USING DRUGS (1979–1982)

The modern history of type 2 diabetes prevention began with three RCTs of drug therapy that were reported in the 1970s and 1980s. They began before the current definitions were established for impaired fasting glucose (IFG) and IGT. These trials examined drugs then in common use to treat type 2 diabetes.

In the Whitehall study, 204 men with IGT were randomly assigned either the biguanide phenformin or placebo (7). The study definition of IGT was complicated, making it difficult to compare with other studies. It required a screening blood glucose 6.1–11.0 mmol/L (110–199 mg/dL)[1] followed by a 50 g OGTT performed in the afternoon with peak blood glucose >10 mmol/L (180 mg/dL) and at least one of the following: 2-hour blood glucose 6.7–11.0 mmol/L (120–199 mg/dL), two values >10.0 mmol/L (180 mg/dL), or mean 2-hour glucose from the screening test and the OGTT >6.7 mmol/L (120 mg/dL). In the 181 patients who completed 5 years of follow-up, the cumulative incidence of diabetes was 14% in the phenformin-treated patients and 16% in placebo-treated patients, with a cumulative incidence rate ratio (drug vs. placebo) of 0.9 (95% confidence interval [CI] 0.4–1.8).

In the Bedford study, 241 men and women with IGT were randomly assigned either the sulfonylurea tolbutamide or placebo and to two dietary groups in a 2-by-2 factorial design (8). IGT was defined by a 50 g OGTT with the 2-hour plasma postload capillary glucose of 6.7–11.1 mmol/L (120–199 mg/dL), inclusive. The study drugs were tolbutamide 0.5 g twice daily or matching placebo. One diet group was taught to restrict carbohydrate intake to 120 g per day. The other group received only brief advice to limit table sugar. During 10 years, 15% of subjects worsened to diabetes, but there were no effects of either the drug or diet interventions.

The third major study of this era was conducted in 147 men with IGT in Malmöhus County, Sweden (9,10). Diabetes and IGT were classified by an OGTT with a load of 30 g glucose per square meter of body surface area among men with glycosuria on initial screening. Diabetes was diagnosed if the 1-hour postload capillary blood glucose was ≥11.1 mmol/L (*200 mg/dL*), the 2-hour glucose was ≥8.6 mmol/L (*155 mg/dL*), and the 3-hour glucose was ≥5.8 mmol/L (*105 mg/dL*).

[1] Glucose concentrations are quoted as written in the original papers in mg/dL, mmol/L, or both. If only one unit was used, a conversion to the other is provided in italics.

TABLE 38.1. Summary of Randomized Clinical Trials for Type 2 Diabetes Prevention in Chronological Order of First Publication of Results

STUDY, LOCATION (REFERENCE)	ELIGIBILITY*	NUMBER OF SUBJECTS RANDOMIZED	INTERVENTION† AND EFFECT SIZE (95% CI)‡ COMPARED WITH THE REFERENCE GROUP (REF.)	EXTENDED FOLLOW-UP RESULTS§
Whitehall, U.K. (7)	IGT	204	5-year cumulative incidence: Phenformin: CIRR 0.9 (0.4–1.8)‡	NR
Bedford, U.K. (8)	IGT	241	Tolbutamide vs. placebo and two dietary groups in a 2x2 factorial design The study reported no effects of either treatment.	NR
Malmöhus County, Sweden (9,10)	Men with IGT	147	10-year cumulative incidence: Tolbutamide: No diabetes among 23 highly adherent participants, but by intention-to-treat analysis, CIRR 0.8 (0.3–2.0)	Mortality was determined after intervention ended through national vital statistics. Tolbutamide was associated with lower mortality from myocardial infarction and all causes, but not significantly (10).
Da Qing study, China (11)	IGT	577 (cluster randomized by 33 clinics)	6-year diabetes incidence by treatment group Ref.: Cumulative Incidence (%) 67.7; CIRD‡ (%) Ref.; Rate per 100 p-yr 15.7; HR‡ Ref. Diet: 43.8; -23.9; 10.0; 0.64 Exercise: 41.1; -26.6; 8.3; 0.53 Both: 46.0; -21.7; 9.6; 0.61	With all three active intervention groups combined for follow-up, treatment maintained an effect on diabetes incidence and was associated with less retinopathy (no effect on nephropathy) and lower mortality in women, but not men (13,58).
Orlistat: Pooled analysis of three trials, international (14)	Most had NGT, BMI 30–43 kg/m^2	675	2-year diabetes incidence: Orlistat: CIRR 0.39, but adherence low owing to side effects	NR
Xendos study, international (15)	NGT or IGT BMI ≥30 kg/m^2	3,305	4-year diabetes incidence: Orlistat: HR 0.63 (0.46–0.86) Among those with IGT: HR 0.55, but adherence low owing to side effects	NR
Diabetes Prevention Study (DPS), Finland (4)	IGT and BMI ≥25 kg/m^2	522	3.2-year diabetes incidence: Lifestyle: HR 0.4 (0.3–0.7)	Treatment effects on diabetes incidence were maintained to some degree with 13-year follow-up (16).
Diabetes Prevention Program (DPP), U.S. (3,21)	FPG ≥95–<126 mg/dL, IGT, and BMI ≥24 kg/m^2	3,234 (+585 in troglitazone substudy)	Diabetes incidence, mean 2.8-year follow-up: Metformin: HR 0.69 (0.52–0.83) Lifestyle: HR 0.42 (0.34–0.52) Troglitazone, mean 0.9-year follow-up: HR 0.25 (p<0.001)	Treatment effects on weight loss and diabetes incidence were maintained to some degree after intervention stopped (23). Lifestyle intervention decreased a composite microvascular outcome in women, but not men (24).
Troglitazone in Prevention of Diabetes (TRIPOD) study, U.S. (27)	Women with previous gestational diabetes (70% with IGT)	266	30-month diabetes incidence: Troglitazone: HR 0.45 (0.25–0.83)	NR
Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), international (28)	FPG 5.6–7.7 mmol/L and IGT	1,429	3.3-year diabetes incidence: Acarbose: HR 0.75 (0.63–0.90)	Reduction in cardiovascular events with small numbers of cases (55).
Kosaka, Japan (30)	IGT	458	Lifestyle: 4-year CIRR 0.33 (p=0.04)	NR
Indian Diabetes Prevention Programme (IDDP), India (31)	IGT	531	3-year diabetes incidence by treatment group Ref.: Cumulative Incidence (%) 55.0; CIRD (%) Ref.; CIRR (95% CI) Ref. Lifestyle: 39.3; 15.7; 0.715 (0.625–0.795) Metformin: 40.5; 14.5; 0.736 (0.649–0.809) Both: 39.5; 15.5; 0.718 (0.630–0.797)	NR

Table 38.1 continues on the next page.

TABLE 38.1. (continued)

STUDY, LOCATION (REFERENCE)	ELIGIBILITY*	NUMBER OF SUBJECTS RANDOMIZED	INTERVENTION† AND EFFECT SIZE (95% CI)‡ COMPARED WITH THE REFERENCE GROUP (REF.)	EXTENDED FOLLOW-UP RESULTS§
Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study, international (33,34)	FPG ≥110–<126 mg/dL, IGT, or both	5,269	3-year diabetes incidence: Ramipril: HR 0.91 (0.80–1.03) Rosiglitazone: HR 0.38 (0.33–0.44) 2x2 factorial design with no interaction	NR
Voglibose trial, Japan (35)	IGT	1,780	48-week diabetes incidence: Voglibose: HR 0.60 (0.43–0.82)	NR
Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) trial, international (36,37)	IGT, FPG ≥95–<126 mg/dL, and cardiovascular risk factor or disease	9,306	Valsartan: HR 0.86 (0.80–0.92) Nateglinide: HR 1.07 (1.00–1.15) 2x2 factorial design with no interaction	Cardiovascular events reported in the main study, with no significant treatment effects (36,37).
Canadian Normoglycemia Outcomes Evaluation (CANOE) trial, Canada (38)	IGT	207	4-year diabetes incidence: Metformin and rosiglitazone combined: HR 0.34 (0.20–0.59)	NR
Actos Now for the Prevention of Diabetes (ACT NOW) trial, U.S. (39)	IGT and IFG	602	2.4-year diabetes incidence: Pioglitazone: HR 0.28 (0.16–0.49)	11-month median follow-up. No effect of pioglitazone on incidence after discontinuation.
Zensharen trial, Japan (5)	IFG; not diabetic by OGTT	641	3-year diabetes incidence: Lifestyle: HR 0.56 (0.36–0.87) (HR 0.24 [0.12–0.48] in the subset with IFG and A1c ≥6.0%)	NR
SEQUEL study, international (41)	Subset of a weight-loss trial with prediabetes or the metabolic syndrome	475	108-week diabetes incidence: Phentermine and topiramide: Lower dose: HR 0.30 Higher dose: HR 0.21	NR
SCALE trial, international (42)	Subset of a weight-loss trial with prediabetes and BMI ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia or hypertension	2,254	3-year diabetes incidence: Liraglutide: HR 0.21 (0.13–0.34) HR 0.34 (0.22–0.53) in worst-case sensitivity analysis for lost to follow-up	NR
Acarbose Cardiovascular Evaluation (ACE) trial, China (43)	IGT and established coronary heart disease	6,522	Diabetes incidence, median 5-year follow-up: Acarbose: HR 0.82 (0.71–0.94)	Cardiovascular events reported in the main study, with no significant treatment effects (43).

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NR, not reported; OGTT, oral glucose tolerance test; p-yr, person-year.

* In all cases, persons meeting diabetes diagnostic criteria at baseline were excluded. Definitions of IGT varied over time, so they were not the same in all trials (see the text for details).

† Lifestyle interventions consisted of some combination of diet and physical activity changes (see text for details). In studies only testing drugs, some degree of lifestyle intervention was given to all study subjects, but its nature was generally poorly described in publications.

‡ Hazard ratio (HR) is the ratio of incidence rates (in cases/person-year of follow-up). Cumulative incidence rate ratio (CIRR) is the ratio of cumulative incidence rates over the duration of the main study (excluding extended follow-up). Cumulative incidence rate difference (CIRD) is the difference in cumulative incidence rates over the duration of the main study. Most studies did not report all three of these effect measures. When studies reported effects as rate reductions, they were converted to rate ratios for this table for uniformity. If 95% CIs were not given, p-values are shown if reported.

§ Follow-up after the main study or major outcomes other than diabetes in the main study. See text for details and references.

SOURCE: References are listed within the table.

If these criteria were not met, but at least one of the following values was found—1-hour glucose ≥8.9 mmol/L (*160 mg/dL*), 2-hour glucose ≥6.7 mmol/L (*120 mg/dL*), or 3-hour glucose ≥4.7 mmol/L (*85 mg/dL*)—subjects met the glycemic eligibility criteria, which here for simplicity are termed "IGT" (10). This complex definition of IGT is also difficult to compare with definitions used subsequently. Study participants received dietary advice to limit their carbohydrate and lipid intake and, if overweight, their total energy intake. They were also randomly assigned to tolbutamide (0.5 mg three times per day), matching placebo, or neither drug nor placebo.

Although the original report from this RCT was widely interpreted as showing prevention by tolbutamide, that conclusion was not based on the currently adopted "intention-to-treat" principle, i.e., analysis by assigned treatment group regardless of adherence. The study was originally reported based on an analysis of a very small number, 23, of those thought to have continued taking tolbutamide throughout, among whom none developed diabetes. When analyzed by intention-to-treat, the 10-year cumulative incidence of diabetes was 10% in men assigned tolbutamide treatment and 13% in the two groups assigned placebo or no drug (incidence rate ratio 0.8, 95% CI 0.3–2.0) (10).

None of these pioneering studies established whether diabetes could be prevented or delayed, and their findings were inconclusive, owing to their small sample sizes, limited measures of adherence, and small number of drugs available for testing diabetes prevention. Whether pharmacologic prevention of type 2 diabetes was possible remained unknown until the 2000s.

DA QING RCT OF LIFESTYLE MODIFICATION (1997)

Several subsequent RCTs formally tested the hypothesis that amelioration of recognized risk factors for type 2 diabetes, namely lifestyle modification directed at weight loss and/or increased physical activity or exercise, could prevent or delay type 2 diabetes. The Da Qing study was a cluster-randomized clinical trial evaluating four combinations of diet and exercise interventions given for 6 years (11). Interventions were randomly assigned according to which of 33 clinics the participants attended and included a program of dietary modification, exercise, or both. The 577 participants had IGT by 1985 World Health Organization (WHO) criteria (12) and were followed for 6 years in the initial phase. The dietary intervention focused on increased consumption of vegetables and reduced consumption of alcohol and simple carbohydrates. Overweight individuals (body mass index [BMI] ≥25 kg/m^2) were also advised to limit energy intake. Participants in the exercise-only group were instructed to increase their daily activity by the equivalent of at least 20 minutes of brisk walking. The diet plus exercise group received both interventions, and patients who attended usual-care clinics served as a control group.

The 6-year cumulative incidence of diabetes was high in all groups: 44% in the diet-only group, 41% in the exercise-only group, 46% in the diet plus exercise group, and 68% in the control group. The relationship between the amount of weight lost and diabetes incidence was inconsistent, and all three interventions were similarly effective in preventing diabetes.

After the 6-year intervention period, active treatment and formal follow-up were discontinued. Follow-up data were obtained by examination and record review 23 years after randomization. The four randomized groups were collapsed into a comparison of the one group with neither intervention (8 clusters) with the pooled three groups with diet, exercise, or both interventions (25 clusters). Annual incidence rates were lower during long-term follow-up than during the treatment period, likely due to less frequent glucose tolerance testing or earlier development of diabetes in the persons at highest risk. Over the entire 23-year period, diabetes incidence rates in the combined intervention groups (diet, exercise, or both) were 0.55 (95% CI 0.40–0.76) times the incidence rate in the control group (13).

RCTS WITH ORLISTAT (2000; 2004)

Because overweight and obesity are major risk factors for type 2 diabetes, drugs that affect weight, but do not have a known direct effect on plasma glucose concentration, were hypothesized to prevent diabetes development. Several RCTs have been performed in obese adults using orlistat, an intestinal lipase inhibitor used for weight loss. Three such trials were discussed in a pooled analysis (14). Compared with placebo, orlistat was reported to reduce 2-year cumulative diabetes incidence by 61% (7.6% in the placebo group vs. 3.0% in the orlistat group) among those with IGT at randomization. Owing to orlistat's gastrointestinal side effects, however, only 69% of the subjects completed the 2-year follow-up and outcome assessment. Thus, an intention-to-treat analysis, in which outcome data are analyzed on nearly all study subjects regardless of adherence, was not possible.

A subsequent 4-year RCT of orlistat, the Xendos study, reported a 37% reduction in diabetes incidence (15). As with earlier orlistat studies, a low percentage of participants completed the trial (52% of the orlistat group and 34% of the placebo group), making it difficult to interpret the results or reliably estimate the effects of the drug. Although orlistat may be beneficial in those who can tolerate it, the high discontinuation rate owing to side effects limits its widespread use for diabetes prevention.

FINNISH DIABETES PREVENTION STUDY (2001)

The Finnish Diabetes Prevention Study (DPS) (4) was a randomized study of 522 overweight or obese, middle-aged adults with IGT according to the 1985 WHO criteria (12). Mean age was 55 years, and mean BMI was 31 kg/m^2. The lifestyle intervention included dietary and exercise components. The weight-loss goal was ≥5% of baseline weight. To achieve this target, participants were instructed to reduce fat intake and

increase consumption of fiber, whole grains, vegetables and low-fat dairy products. The exercise component involved moderate-intensity exercise for at least 30 minutes per day. Seven treatment goals were decreased fat consumption, changed quality of dietary fat, increased vegetable consumption, decreased sugar consumption, decreased salt consumption, decreased alcohol consumption, and increased exercise.

Results were reported following the intention-to-treat principle, with end-of-study data available for 92% of the study cohort. The intervention and control groups lost an average of 4.2 kg and 0.8 kg in the first year of the study. Compared with the control group, the intervention group had a 58% reduction in diabetes incidence, from 78 to 32 cases per 1,000 person-years, during the whole study (which averaged 4 years per person). Although this study was not designed to assess the individual contributions of the diet and exercise components, participants who achieved more of the lifestyle goals had greater reductions in diabetes incidence.

After cessation of the intervention, the reduction in the incidence of diabetes persisted during 9 additional years of follow-up (for 13 years after randomization). During the total follow-up, the adjusted hazard ratio (HR) for diabetes (intervention group vs. control group) was 0.61 (95% CI 0.48–0.79) (16). The corresponding hazard ratio during the post-intervention follow-up was 0.67 (95% CI 0.48–0.95). Adherence to the lifestyle intervention during the intervention phase was associated with risk reduction during follow-up. That some risk reduction in the former intervention group persisted when no further intervention was provided suggests that active provision of the intervention may not be necessary for some long-term benefit to occur. It is not known whether the original 58% risk reduction would have persisted had the intensive intervention been maintained.

U.S. DIABETES PREVENTION PROGRAM (2002)

The U.S. Diabetes Prevention Program (DPP) was a large and comprehensive prevention RCT (3). The DPP enrolled 3,234 nondiabetic, overweight or obese, mostly middle-aged adults with IGT and FPG values of 95–<126 mg/dL (*5.3–<7.0 mmol/L*). Eligibility in the American Indian centers was based on IGT and FPG <126 mg/dL. Participants were randomized with equal probability to an intensive lifestyle intervention, metformin (850 mg twice per day), or placebo. The metformin and placebo groups received printed material containing standard lifestyle recommendations. The DPP preferentially enrolled individuals from racial/ethnic and age groups at particularly high risk of developing type 2 diabetes: overall, 45% of participants were from high-risk ethnic groups (African Americans, Hispanic Americans, American Indians, and Asian Americans), and 20% were age 60–85 years at baseline. Mean BMI at baseline was 34 kg/m^2.

The DPP intensive lifestyle intervention was intended to achieve a 7% loss in body weight over 24 weeks. Participants were instructed in individual behavioral modification counseling sessions to perform 150 minutes moderate-intensity physical activity (such as brisk walking) per week and to eat a low-fat, reduced-calorie diet. After the initial 24-week period of counseling, monthly individual or group sessions were conducted to help maintain weight loss and activity levels. The lifestyle-intervention group achieved a mean weight loss of 7% (an average of 7.0 kg) within the first year and had an overall mean weight loss of 5.6% (an average of 5.6 kg) during follow-up (mean duration 2.8 years); the physical activity goals were met by 74% of lifestyle intervention participants in the first 24 weeks of the study.

The double-masked phase of the trial was stopped in 2001, approximately 1 year before the planned end-date, on the advice of the independent data and safety monitoring board because of the clear benefits of metformin and lifestyle intervention on development of diabetes.

The lifestyle intervention was associated with a 58% reduction (95% CI 48%–66%) in the incidence of diabetes, based on annual OGTTs and mid-year FPG levels, compared with placebo plus standard lifestyle recommendations (3). The diagnosis of diabetes had to be confirmed with repeat testing. Of note, 93% of the surviving three-arm study cohort attended a scheduled visit within 5 months of the early stopping date. Early stopping of the trial for efficacy, as was done in several other RCTs described below, may complicate estimation of treatment effects, as described later in this chapter.

Changes in physical activity and diet (primarily, a reduced calorie intake from fat) predicted weight loss, and weight loss, in turn, was associated with a reduced risk of developing type 2 diabetes. Weight loss was the predominant predictor of reduced diabetes incidence, with a 16% reduction in risk per kilogram of weight lost (17). These findings suggest that interventions to reduce diabetes risk in overweight or obese individuals should primarily aim to induce weight loss. However, among 495 lifestyle participants not meeting the weight loss goal, diabetes risk was 44% lower in the 329 who met the physical activity goal than among the 166 who did not (17). The effectiveness of the DPP lifestyle intervention was similar in all ethnic groups and both sexes and was greatest in older participants (age 60–85 years) (3).

In the metformin arm, adherence to study drug was high, with 70%–80% of participants taking at least 80% of their twice per day metformin, based on pill counts, during the trial (3). Assignment to metformin reduced the risk of developing diabetes by 31% compared with placebo during the mean follow-up of 2.8 years. An average 1.7 kg weight loss was reported in the metformin group compared with a 0.3 kg weight gain in the placebo group. In secondary analyses, 64% of the beneficial effect of metformin on diabetes risk was attributed to weight loss (18). Favorable changes in insulin sensitivity and in secretion of proinsulin also contributed to the decreased diabetes risk seen in metformin-treated patients (19).

The large size of the DPP allowed examination of heterogeneity of subgroups in terms of diabetes incidence and treatment effects. Despite the racial/ethnic diversity of participants, there were no significant differences by race/ethnicity either in diabetes risk or in the preventive effects of metformin or lifestyle modification. Other well-known diabetes risk factors, including BMI and fasting and postload plasma glucose in the OGTT, predicted diabetes in the DPP. There were generally no significant subgroup interactions, on a hazard rate ratio scale, based on these and other predictors with the effects of lifestyle intervention compared with placebo, i.e., the lifestyle intervention was uniformly effective in terms of reducing diabetes hazard ratios across all subgroups, with one exception. That exception was a statistically significant interaction ($p<0.05$) of baseline 2-hour glucose in the OGTT with the effect of the lifestyle intervention compared with placebo. The diabetes risk reduction was greatest in those with lower 2-hour glucose concentrations.

Because the lifestyle intervention effect was uniform across most subgroups on a hazard ratio scale, the absolute risk reduction by lifestyle intervention was greater in those with higher levels of risk factors. This is illustrated by FPG, a diabetes risk factor that did not have a significant interaction with the lifestyle intervention on the hazard ratio scale. Compared with placebo, the lifestyle intervention reduced diabetes incidence rates by 55% in those with baseline FPG 95–109 mg/dL (*5.3–6.1 mmol/L*) and by 63% in those with baseline FPG 110–125 mg/dL (*6.1–6.9 mmol/L*), i.e., there was no significant FPG-by-treatment interaction on the hazard ratio scale. Yet the incidence rate *difference* (absolute effect) was much greater in the higher (22.3 - 8.8 = 13.5 cases/100 person-years) than in the lower FPG group (6.4 - 2.9 = 3.5 cases/100 person-years). Thus, the lifestyle intervention led to a much greater *absolute* reduction in diabetes incidence in those entering the trial with higher FPG. In general, the interventions prevented more cases of diabetes per person in those with greater levels of risk factors at baseline, arguing for the value of the high-risk approach to diabetes prevention.

There were two statistically significant interactions with the preventive effect of metformin compared with placebo; metformin was significantly more effective in those with greater baseline BMI and greater FPG concentrations (3). These interactions of baseline variables with intervention effects came from secondary analyses of many baseline variables. Therefore, they should not be considered definitive, and implications for who should be offered different preventative interventions should be made cautiously.

Following the initial DPP report, a secondary analysis of history of gestational diabetes was reported. Women reporting a history of gestational diabetes were compared with women who had given birth at least once but had no history of gestational diabetes. The women with prior gestational diabetes had an especially high risk of developing diabetes in the DPP, with a strong benefit with metformin (50% reduction in incidence compared with placebo) compared with an insignificant 14% reduction in parous women without a history of gestational diabetes. The lifestyle intervention was similarly effective in those with a history of gestational diabetes (53% reduction compared with placebo) or without such a history (49% reduction) (20).

In addition to the 3,234 participants randomly assigned to the placebo, metformin, or lifestyle interventions, 585 were randomly assigned troglitazone, a drug in the thiazolidenedione class. Recruitment to this group and participants' ongoing treatment were terminated before DPP recruitment was completed owing to concern over possible hepatotoxic effects (21). During the average of 0.9 years before it was discontinued in the DPP, troglitazone reduced the incidence of diabetes by 75% compared with placebo—the largest risk reduction of all the DPP interventions among the subset of participants randomized during the period when troglitazone was being used in the DPP. Whether the reduction in incidence would have persisted, had troglitazone therapy been continued, is unknown. Other RCTs of thiazolidinediones have shown preventive effects (see below).

DPP results were unmasked and published (3). Following a drug washout period (22), all participants were offered a group-implemented lifestyle intervention, because it had been the most effective treatment. Placebo was discontinued, and unmasked metformin was continued as a study intervention in the original metformin group during long-term follow-up, known as the Diabetes Prevention Program Outcomes Study (DPPOS) (23). Eighty-eight percent of the surviving DPP cohort enrolled in DPPOS.

During the DPPOS, annual diabetes incidence rates in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the former lifestyle group. During a mean follow-up of 15 years since DPP randomization, diabetes incidence was reduced by 27% in the lifestyle intervention group (HR 0.73, 95% CI 0.65–0.83, $p<0.0001$) and by 18% in the metformin group (HR 0.82, 95% CI 0.72–0.93, $p=0.001$) compared with the placebo group, with declining between-group differences over time. At year 15, the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group, and 62% in the placebo group (24).

Some of the strong diabetes risk factors persisted during the DPPOS. For example, over 10 years since randomization, women with a history of gestational diabetes assigned to placebo had a 48% higher risk of developing diabetes compared with women without a history of gestational diabetes who reported at least one delivery. In women with a history of gestational diabetes, the lifestyle and metformin interventions reduced progression to diabetes compared with placebo by 35% and 40%, respectively. Among the women without a history of gestational diabetes, the lifestyle intervention reduced the progression to diabetes by

30%, and metformin did not significantly reduce the progression to diabetes (25).

Glycemic eligibility criteria for the DPP were based on fasting and 2-hour post-load plasma glucose. A1c was measured but not used in determining eligibility. Even among these high-risk individuals, baseline A1c was an additional strong predictor of diabetes. After excluding the few participants with A1c ≥6.5% (*48 mmol/mol*) at study entry, treatment effects were evaluated in a *post hoc* secondary analysis with an alternate diabetes definition of A1c ≥6.5%. Metformin and lifestyle interventions were both effective, compared with placebo, in preventing this outcome, and their effects did not differ significantly from each other (26).

TROGLITAZONE IN PREVENTION OF DIABETES STUDY OF WOMEN WITH PREVIOUS GESTATIONAL DIABETES (2002)

The Troglitazone in Prevention of Diabetes (TRIPOD) study was an RCT of troglitazone compared with placebo in 266 nondiabetic Hispanic women with previous gestational diabetes, about 70% of whom had IGT at entry into the trial. Troglitazone reduced the development of diabetes by 55% over 2.5 years (27). As in the DPP, the drug was discontinued before planned study-end because of safety concerns. The preventive effect of troglitazone was suggested to be mediated by improved insulin sensitivity reducing demand for insulin secretion, thus protecting the beta cells. During an 8-month follow-up after troglitazone was discontinued, seven new cases of diabetes developed: six in the former placebo group and one in the former troglitazone group. This large difference, albeit in a small number of cases, was interpreted as showing a persistent beneficial effect of the drug following its discontinuation.

ACARBOSE IN THE STUDY TO PREVENT NON-INSULIN-DEPENDENT DIABETES MELLITUS (2002)

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) RCT examined the effect of the alpha-glucosidase inhibitor acarbose to prevent diabetes in a high-risk cohort (28). The rationale for use of acarbose in diabetes prevention was based on its effect to lower postprandial hyperglycemia, which is characteristic of IGT. Mild postprandial hyperglycemia was hypothesized to be sufficient to induce glucose toxicity, further impair insulin secretion and action, and thus contribute to the progression of IGT to overt diabetes (29). A total of 1,429 subjects with IGT and IFG (5.6–7.7 mmol/L or *101–139 mg/dL*) were enrolled in the trial and randomized in a double-blind fashion to acarbose gradually titrated to 100 mg three times per day with meal or identical placebo (28). Incident diabetes was defined by plasma glucose ≥11.1 mmol/L (*200 mg/dL*) at 2 hours in a 75 g OGTT.

Over a 3.3-year follow-up period, acarbose was associated with a 25% reduction in the incidence of diabetes. Although weight loss contributed to the decreased risk of diabetes, acarbose treatment remained effective after adjustment for age, sex, and BMI. Furthermore, acarbose was associated with reversion of IGT to normal glucose tolerance (HR 1.42, 95% CI 1.24–1.62).

Approximately one-quarter of the cohort (including 31% of the acarbose group) did not complete the study, leading to some uncertainty in the estimate of the acarbose effect. The high drop-out rate in acarbose-treated patients was attributed to its known gastrointestinal side effects (flatulence, diarrhea, and abdominal cramps) that may limit its applicability for diabetes prevention in general practice. The STOP-NIDDM trial was also notable for studying treatment effects beyond the development of diabetes, as discussed in the section *Extended Follow-Up for Outcomes Beyond Hyperglycemia*.

LIFESTYLE INTERVENTION IN JAPANESE MEN WITH IGT (2005)

Japanese men with IGT (by criteria approximating the WHO criteria) were recruited at health screening examinations. The mean BMI was 24 kg/m^2. They were randomly assigned in an approximate 4:1 ratio to a standard intervention group (n=356) or to an intensive lifestyle intervention group (n=102) aimed at achieving and maintaining weight loss. The cumulative incidence of diabetes over 4 years of follow-up, determined by at least two consecutive FPG concentrations of ≥140 mg/dL (*7.8 mmol/L*), was 67% lower in the intensive lifestyle intervention group (p=0.04) (30). Though the observation is in line with the other lifestyle intervention trials, it is difficult to compare with other studies because it used different criteria: FPG <140 mg/dL instead of <126 mg/dL as an inclusion criterion and FPG ≥140 mg/dL on two consecutive occasions to confirm the diagnosis of diabetes.

INDIAN DIABETES PREVENTION PROGRAMME (2006)

The Indian Diabetes Prevention Programme (IDPP) extended the previous studies by (a) enrolling 531 Asian Indians who were younger and had lower BMI, on average, then volunteers in the previous studies and (b) testing a lifestyle intervention and metformin as in the U.S. DPP, but adding a group in which the lifestyle and metformin interventions were combined (31). At study entry, participants (420 men and 111 women) had a mean age of 46 years, and mean BMI was 26 kg/m^2. The metformin dose (250 to 500 mg twice per day, with most study time on the lower dose) was substantially lower than that in the DPP (850 mg twice per day).

Participants were followed an average of 30 months, during which time cumulative incidence rates of diabetes were 55.0% (control group), 39.3% (lifestyle modification group), 40.5% (metformin group), and 39.5% (lifestyle modification plus metformin group). The cumulative incidence reductions were 28.5% (95% CI 20.5%–37.3%, p=0.018) in the lifestyle modification group, 26.4% (95% CI 19.1%–35.1%, p=0.029) in the metformin group, and 28.2% (95% CI 20.3%–37.0%, p=0.022) in the lifestyle modification plus metformin group compared with the control group. Thus, both the lifestyle modification and metformin interventions reduced diabetes incidence, but their effects were not additive.

DIABETES REDUCTION ASSESSMENT WITH RAMIPRIL AND ROSIGLITAZONE MEDICATION (2006)

Following *post hoc* analyses that suggested angiotensin-converting enzyme inhibitors might reduce diabetes risk (32), ramipril, a drug in this class, and the thiazolidinedione rosiglitazone, were studied for diabetes prevention in the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study (33,34). In two earlier RCTs, the thiazolidinedione drug troglitazone had large effects in reducing the incidence rate of diabetes, but troglitazone was subsequently withdrawn from the market owing to rare but serious liver toxicity. DREAM tested ramipril and rosiglitazone in a 2-by-2 factorial design in 5,269 participants with IFG, IGT, or both. IFG was defined by FPG 110–<126 mg/dL (6.1–<7.0 mg/dL) and IGT by 2-hour plasma glucose 140–<200 mg/dL (7.8–<11.1 mmol/L) in an OGTT.

For ramipril, the hazard ratio for developing diabetes was 0.91 (95% CI 0.80–1.03). The incidence of diabetes was reduced by 62% by rosiglitazone (HR 0.38, 95% CI 0.33–0.44), and 50% of rosiglitazone-treated patients reverted to normoglycemia compared with 30% of placebo-treated patients. There was no synergistic effect of the drugs in participants who were randomly allocated to both ramipril and rosiglitazone, i.e., the effect of each drug was the same in the presence or absence of the other drug.

Like metformin, rosiglitazone seems to be most effective in individuals with a high BMI (rosiglitazone conferred risk reductions of 40% for those with BMI <28 kg/m^2 and 68% for BMI >33 kg/m^2). Notable side effects, including weight gain (rosiglitazone-treated patients gained 2.2 kg more than placebo-treated patients) and edema, were observed. The frequency of congestive heart failure was also increased in the rosiglitazone group (HR 7.03, 95% CI 1.60–30.9), but there were few cases (0.5% in the rosiglitazone group and 0.1% in the rosiglitazone-placebo group) in this generally healthy population (34).

VOGLIBOSE RCT (2009)

Japanese adults with IGT and at least one other diabetes risk factor were enrolled in an RCT of voglibose, an alpha-glucosidase inhibitor, for reducing the incidence of diabetes (35). The diabetes outcome was defined by A1c ≥6.5% and, on two occasions, either FPG ≥7.0 mmol/L, 2-hour plasma glucose ≥11.1 mmol/L, or random plasma glucose ≥11.1 mmol/L.

The study was terminated before its planned end because of efficacy. At termination after approximately 1-year of follow-up, the diabetes hazard rate ratio (voglibose vs. placebo) was 0.60 (95% CI 0.43–0.82). Participant acceptance was greater than with acarbose in the STOP-NIDDM trial, with 86% of participants assigned to voglibose and 83% of those assigned to placebo completing the trial. Reasons for withdrawal included adverse events and poor compliance, which compromised the intention-to-treat principle. Voglibose appeared to be moderately well tolerated and reduced the incidence of diabetes. Because follow-up was terminated after about 1 year, long-term acceptance and efficacy of this medicine for diabetes prevention remain uncertain.

NATEGLINIDE AND VALSARTAN IN IMPAIRED GLUCOSE TOLERANCE OUTCOME RESEARCH TRIAL (2010)

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) RCT employed a 2-by-2 factorial design using the angiotensin receptor blocker valsartan (36) and the short-acting insulin secretagogue nateglinide (37) in 9,306 participants with IGT, FPG 95–<126 mg/dL (5.3–<7.0 mmol/L), and CVD or CVD risk factors. The mean age was 64 years, and mean BMI was 30.5 kg/m^2. All participants received standard lifestyle intervention and were followed for a mean of 5 years.

Nateglinide (60 mg three times daily) did not reduce the cumulative incidence of diabetes compared with placebo (HR 1.07, 95% CI 1.00–1.15) and was associated with increased frequency of hypoglycemic events (19.6% with nateglinide vs. 11.3% with placebo, p<0.001) and slightly greater weight (+0.35 kg, p=0.001) over the course of the study. Treatment with valsartan (160 mg once daily) was associated with a modest, albeit significant, reduction in incident diabetes compared with placebo (HR 0.86, 95% CI 0.80–0.92). Combination therapy of nateglinide with valsartan provided no advantage over valsartan alone. This study was also limited by a fairly high rate of study drug discontinuation for adverse effects (ranging from 10.4% to 12.0% in the four randomized groups), and only approximately 80% completed the trial.

CANADIAN NORMOGLYCEMIA OUTCOMES EVALUATION TRIAL OF THE COMBINATION OF ROSIGLITAZONE AND METFORMIN (2010)

In the Canadian Normoglycemia Outcomes Evaluation (CANOE) RCT, investigators tested the efficacy of a combination of submaximal doses of two drugs, metformin (500 mg twice daily) and rosiglitazone (2 mg twice daily) vs. placebo on prevention of incident diabetes in a small cohort (n=207) with IGT (38). In the placebo group, mean age was 55 years and mean BMI was 32 kg/m^2. In the rosiglitazone plus metformin group, mean age was 50 years and mean BMI was 31 kg/m^2.

After a median follow-up of 3.9 years, the two-drug treatment resulted in a relative risk reduction for diabetes of 66%, 95% CI 41%–80% (HR 0.34), and 80% regressed to normoglycemia compared with 52% in the placebo group (p=0.0002). The low-dose combination therapy was reportedly well tolerated, with similar rates of weight gain as in the placebo arm. There were no differences in reported congestive heart failure, myocardial infarction, or fractures between treatment groups, although the study had little power to detect these.

The similar efficacy and tolerability of the low-dose combination, compared with larger doses of the individual agents, suggest an advantage of low-dose combination therapy over full dose

thiazolidinedione; however, continued concern over cardiovascular and skeletal adverse effects of the thiazolidinedione drugs has dampened enthusiasm for their use in prevention or treatment of diabetes.

ACTOS NOW FOR THE PREVENTION OF DIABETES TRIAL OF PIOGLITAZONE (2011)

The Actos Now for the Prevention of Diabetes (ACT NOW) trial was an RCT of the thiazolidinedione pioglitazone for the prevention of diabetes (39). Six hundred two adults with IGT were enrolled. Mean age was 52 years, and mean BMI was 34 kg/m^2. Participants were randomized to treatment with pioglitazone 30 mg per day or placebo, with median follow-up of 2.4 years.

The study was completed by only 70% of the pioglitazone group and 76% of the placebo group, thus limiting interpretability. The hazard rate ratio for development of diabetes was 0.28 (95% CI 0.16–0.49), i.e., there was a 72% reduction in incidence with pioglitazone. This study replicated the large effects of the thiazolidinedione drugs troglitazone and rosiglitazone on reducing diabetes incidence. As with other drugs in this class, pioglitazone was associated with weight gain and edema.

LIFESTYLE INTERVENTION IN OVERWEIGHT JAPANESE ADULTS WITH IMPAIRED FASTING GLUCOSE (2011)

A Japanese RCT, Zensharen, enrolled 641 overweight Japanese subjects, mostly men (72%), in a lifestyle intervention trial (5). Eligibility was based on elevated FPG (100–125 mg/dL or *5.6–6.9 mmol/L*, defined as IFG), similar to the FPG eligibility criteria of the DPP, but IGT was not required. OGTTs were performed to exclude diabetes at entry and to define the diabetes outcome. The median age was 49 years, and the mean BMI was 27 kg/m^2. Subjects were randomized to lifestyle intervention (n=311) or standard treatment serving as controls (n=330).

The intensive lifestyle intervention reduced diabetes incidence by 44% compared with standard care (i.e., HR 0.56, 95% CI 0.36–0.87), results similar to the other lifestyle intervention trials. The hazard rate reduction was greater among subgroups at higher baseline risk as determined either by IGT, FPG ≥110 mg/dL (*6.1 mmol/L*), or A1c ≥5.6% (*38 mmol/mol*) by the Japan Diabetes Society method (approximately 6.0% [*42 mmol/mol*] by the National Glycohemoglobin Standardization Program [NGSP] method). These high-risk subgroups contained fewer than half the participants, but the majority of the outcome events (baseline NGSP-equivalent A1c was ≥6.0% in 29% of the participants who experienced 57% of the outcomes). In those with NGSP-equivalent A1c ≥6.0%, the hazard rate was reduced by 76% (HR 0.24, 95% CI 0.12–0.48), the greatest relative risk reduction of any subgroup presented. There was no risk reduction among the subjects with isolated IFG (i.e., IFG with normal 2-hour glucose), although the effect estimate was very imprecise in this lower-risk group that experienced only 22 outcome events.

This trial, therefore, showed that other glycemic measures, such as elevated A1c or IGT, refine the high-risk characteristics of people initially identified through FPG. These results support suggestions that A1c could be used to identify persons for prevention interventions (40) or to further stratify risk among persons selected by other criteria (26). This RCT also confirms that intervention effects are hard to establish or nonexistent in persons without multiple risk factors. Data are still lacking on type 2 diabetes prevention in persons with elevated A1c but without elevated fasting or postload glucose concentrations.

SEQUEL SECONDARY ANALYSIS OF A STUDY OF PHENTERMINE-TOPIRAMATE FOR WEIGHT LOSS (2012)

SEQUEL was an extension of a subset of centers and participants in the CONQUER RCT of combinations of phentermine and topiramate (at two dose levels compared with placebo) for weight loss (41). The incidence of diabetes was evaluated in a subgroup of 475 subjects with prediabetes and/or the metabolic syndrome at baseline. After 108 weeks of follow-up since randomization, the lower and higher combination doses were associated with 70% and 79% reductions in diabetes incidence (HR 0.30 and 0.21, confidence intervals not given), respectively. The risk reduction was associated with the amount of weight loss achieved. This study showed that drugs for diabetes prevention may not need to be restricted to those directly influencing hyperglycemia, insulin secretion, or insulin sensitivity, but may be effective through weight loss.

Some limitations make interpretation difficult. SEQUEL was a secondary analysis of a subset of participants in the CONQUER weight loss study, and it is not clear how this subset represents all those randomized in the original RCT. The problem common to pharmacologic weight loss studies, loss to follow-up, was not well described. A strategy of carrying forward the last observation was used to impute a substantial fraction of values, but there was not a clear description of the frequency of missing data or the characteristics of participants with missing outcome data. Loss to follow-up in such studies is not likely to be random but rather due to frustration with lack of weight loss, weight regain, or drug side effects.

AN RCT OF LIRAGLUTIDE IN WEIGHT MANAGEMENT (2015)

Liraglutide, a glucagon-like peptide-1 analogue, was evaluated in a 56-week RCT (SCALE) of 2,254 nondiabetic adults with BMI ≥30 kg/m^2 or ≥27 kg/m^2 if they also had dyslipidemia or hypertension (42). The dose of liraglutide used in this study was 3 mg per day, higher than that approved for treatment of diabetes. Baseline mean age was 45 years, mean weight was 106 kg, and mean BMI was 38 kg/m^2.

During the 3 years of follow-up since randomization, the diabetes incidence rate was reduced by 79% (HR 0.21, 95% CI 0.13–0.34). Half the participants were lost to follow-up, complicating interpretation of this result. In a sensitivity analysis making various assumptions to impute

missing data, the diabetes incidence rate was estimated to be reduced by 66% (HR 0.34, 95% CI 0.22–0.53) (42).

THE ACARBOSE CARDIOVASCULAR EVALUATION TRIAL (2017)

The Acarbose Cardiovascular Evaluation (ACE) trial, conducted in China, enrolled 6,522 participants with IGT and established coronary heart disease in an RCT of acarbose (50 mg three times per day) versus placebo (43). Incident diabetes was detected by fasting glucose measurements every 4 months and confirmed by an OGTT. The development of diabetes was reduced by 18% (HR 0.82, 95% CI 0.71–0.94, p=0.005) during a median follow-up period of 5 years. There were no significant treatment effects on the primary outcome of CVD. An important limitation of this trial is the fact that approximately half of the participants in each treatment group permanently discontinued study medication before the end of the study.

THE CONTRIBUTION OF GENETICS TO DIABETES PREVENTION

In all RCTs described in the previous section, eligibility was based on clinical and demographic variables, but not on estimates of genetic susceptibility to type 2 diabetes. Some of the trials, however, saved DNA samples for later genetic analyses.

The most extensive genetic analyses of a diabetes prevention trial have been conducted in the DPP. The main hypothesis was that genetic variants shown to be associated with type 2 diabetes in case-control studies would also predict diabetes incidence in the nondiabetic, but high-risk, participants in the DPP. The study also tested for genotype-by-treatment interactions in effects on diabetes hazard rates. Such an interaction indicates that the effect of a treatment, for example in comparison with the placebo group, differs according to genotype. Equivalently, it indicates that the effect of the genotype differs by treatment group. Lack of significant interaction is consistent with the hypothesis that the effect of a treatment is independent of genotype.

Shortly after variants in the *TCF7L2* gene were found to associate with type 2 diabetes (44), the finding was replicated in the DPP (45). The high-risk variants in this gene predicted the development of diabetes in the DPP placebo group, an effect diminished by metformin and abolished by lifestyle intervention. Although the genotype-by-treatment interactions were not statistically significant, both interventions appeared to be more effective in the participants carrying the high-risk genotypes. Subsequently, many other diabetes-susceptibility genes have been typed in the DPP. In general, their ability to predict diabetes has been confirmed, and the treatment effects are at least as great in the participants carrying more susceptibility variants (46). Therefore, far from indicating inevitability of developing diabetes, high-risk genotypes may identify persons most likely to benefit from diabetes prevention interventions, in that interventions may lower their risk to approximate that of those with low-risk genotypes.

In the DPP, several single nucleotide polymorphisms (SNPs) had significant interactions with metformin treatment on incidence rates of diabetes (47). One of the findings replicated a report from the Rotterdam Study, a population-based cohort study in the Netherlands, that a variant in the *SLC47A1* gene that encodes the multidrug and toxin extrusion 1 transporter protein (MATE1) is associated with response to metformin (48). In the DPP, a genetic risk score was created from 17 genetic variants previously reported to associate with insulin sensitivity. This score was associated with estimated insulin sensitivity at baseline in the DPP, but the lifestyle and metformin interventions improved insulin sensitivity regardless of the degree of genetic susceptibility estimated from this risk score (49).

In the STOP-NIDDM trial, a number of candidate gene polymorphisms were evaluated in a subgroup of 770 subjects. Women carrying the combination of the G-allele of SNP +45 and the T-allele of SNP +276 of the adiponectin gene had an especially high risk of developing diabetes (odds ratio 22.2, 95% CI 2.7–183.3) (50). This high risk was neutralized by acarbose. Three other genotypes were associated with an increased effect of acarbose on the prevention of diabetes: SNPs of the peroxisome proliferator-activated receptor (PPAR)-delta gene, Gly482Ser of the PPAR-gamma coactivator (PGC-1)-alpha gene, and Pro12Ala of the PPAR-gamma gene (51). The 3' UTR (untranslated region) of the leptin receptor gene and the combination of the G-allele of SNP +45 and the T-allele of SNP +276 of the adiponectin gene were associated with increased weight loss (50,52). Finally, the Gly250Ala SNP of the hepatic lipase gene was associated with an increased risk of diabetes and a reduction in the conversion of IGT to normal glucose tolerance (53).

None of 19 SNPs associated with diabetes in other populations predicted development of diabetes in the Finnish DPS, nor did a genetic risk score composed of these SNPs predict diabetes or modify the preventive effect of the lifestyle intervention (54). It is unclear whether the lack of diabetes prediction by the genetic risk score in this study was owing to the smaller sample size of 522 compared with many other genetics studies or to other factors distinguishing these Finnish study participants.

In summary, in prevention of type 2 diabetes, the beneficial effects of lifestyle interventions and of some medicines overcome genetic risk. More discussion of genetic susceptibility for type 2 diabetes is provided in Chapter 14 *Genetics of Type 2 Diabetes*.

EXTENDED FOLLOW-UP FOR OUTCOMES BEYOND HYPERGLYCEMIA

Diabetes is defined by measures of hyperglycemia, but it is also associated with many adverse health conditions, including microvascular and macrovascular disease, neuropathy, depression, and some forms of cancer. The RCTs discussed in the preceding sections were highly successful in showing that type 2 diabetes, defined solely and conventionally on the basis of glycemia, can be prevented or delayed, but most were not designed to evaluate these other health outcomes. Thus, the overall impact of the interventions on health is less clear. For example, if the effect of an intervention is to prevent or delay progression from just below a diagnostic threshold to barely crossing it, has the intervention improved long-term health? This is difficult to evaluate because (a) the measures of health that should be evaluated are many and (b) the time and resources required to measure them in RCTs may be prohibitive. Therefore, evidence of benefits of preventive interventions beyond glycemia is limited.

One of the first hints came from one of the early trials, that in Malmöhus, Sweden (9,10) described in the section *Early U.K. and Swedish Prevention Studies Using Drugs (1979–1982)*. Although there was no significant effect of tolbutamide on diabetes incidence, by intention-to-treat analysis, long-term mortality rates were ascertained after the end of the trial. The all-cause mortality rate ratio (drug compared with placebo or no drug) was 0.66 (95% CI 0.39–1.10) and the ischemic heart disease mortality rate ratio was 0.42 (95% CI 0.16–1.12) (10). While these effects were not statistically significant in this small RCT, they were among the first to suggest that drug treatment of IGT might have health benefits beyond reducing hyperglycemia from progressing to diabetes. The results also do not support the widely held notion that the first generation sulfonylureas might be cardiotoxic in patients with diabetes.

More evidence came from the STOP-NIDDM trial. In this study, treatment with acarbose was associated with a 49% reduction in cardiovascular events (15 vs. 32 subjects; HR 0.51, 95% CI 0.01–0.95, p=0.03) (55). Although statistically significant, these results should be interpreted with caution due to the small number of events. Additional evidence of potential CVD benefits of acarbose includes its effect to slow progression of carotid intimal medial thickness, a measure of subclinical atherosclerosis, which was measured in a subset of the cohort (n=132) (56). Beneficial effects on several CVD risk factors (waist circumference, blood pressure, and plasma triglycerides) were also reported (55). However, the ACE trial, conducted in 6,255 individuals with IGT and coronary heart disease, failed to demonstrate any reduction of CVD events (for the primary five-point major adverse cardiovascular events outcome, HR 0.98, 95% CI 0.86–1.11, p=0.73) during an average of 5 years of follow-up (43). This more recent evidence does not support a substantive role for acarbose in secondary prevention of cardiovascular events in the current era of CVD risk reduction with statins (used by 93% of participants), renin-angiotensin-aldosterone system (RAAS) blockers (used by 59%), and antiplatelet therapy (used by 98%).

The NAVIGATOR trial was designed not only to test diabetes prevention by valsartan and nateglinide, but also to extend follow-up long enough to evaluate treatment effects on CVD outcomes. Neither drug, alone or in combination, had any effect on a composite primary outcome of CVD death, nonfatal myocardial infarction or stroke, revascularization, or hospitalization for angina or congestive heart failure, nor on a "core" composite that excluded revascularization and angina (36,37). This lack of effect occurred despite greater reductions in systolic (6.3 vs. 3.8 mmHg, p<0.001) and diastolic blood pressure (4.4 vs. 3.0 mmHg, p<0.001) with valsartan than with placebo (36). In contrast to the STOP-NIDDM results with acarbose, the null results of the nateglinide versus placebo comparison do not support the contention that reducing post-challenge (or postprandial) hyperglycemia with an insulin secretagogue has a specific role in preventing CVD in the setting of prediabetes.

The Finnish DPS reported 10-year follow-up for mortality and cardiovascular morbidity. Compared with the control group, the lifestyle intervention group had a nonsignificantly lower mortality rate (HR 0.57, 95% CI 0.21–1.58), but similar cardiovascular morbidity (HR 1.04, 95% CI 0.72–1.51) (57). These results suggested a mortality benefit, but owing to the limited sample size of 522, the confidence intervals were too wide to allow for definitive conclusions.

The Da Qing study reported treatment effects on microvascular complications and mortality after ≥20 years of follow-up. At 20 years after randomization, the pooled intervention groups had a 47% reduction in severe retinopathy (HR 0.53, 95% CI 0.29–0.99) (58). The study was inconclusive with respect to severe nephropathy (HR 1.05, 95% CI 0.16–7.05). By 23 years after randomization, the all-cause mortality rates were reduced by 54% in women, with no effect in men (13). Limitations of this study included the small number of 33 clusters randomized, some important differences in risk factors among the groups at baseline, and incomplete follow-up.

The DPP reported extended follow-up for diabetes incidence and plans to assess even longer-term outcomes of diabetes and its complications (23,24). Many CVD risk factors were more favorable in the lifestyle intervention group than in the metformin and placebo groups (24), although cardiovascular event rates have not been reported as of December 2017. After an average of 15 years since randomization, DPP participants were evaluated for a composite microvascular/neuropathy outcome defined by the average prevalence of diabetic retinopathy assessed by central grading of retinal photographs, nephropathy assessed by albuminuria or estimated glomerular filtration rate, and neuropathy assessed by light touch sensation (24). There were no significant

treatment effects overall, but significant sex-by-treatment interactions, such that in women, but not men, the composite prevalence of complications was approximately 22% lower in the lifestyle intervention group than in the placebo or metformin treatment groups. Those who had not developed diabetes had a 28% lower prevalence of complications than those who had developed diabetes.

To what extent any long-term benefits of diabetes prevention interventions on outcomes are related purely to their glycemic effects as opposed to glycemia-independent effects, such as on blood pressure, lipids, inflammation, and coagulation, is unknown.

DISCUSSION

The RCTs of type 2 diabetes prevention conducted in Bedford and Whitehall (U.K.) and Malmöhus County (Sweden) set the stage for subsequent, more definitive RCTs. None of these three early RCTs showed a significant prevention effect when analyzed by intention to treat. While this could have been owing to lack of effect of the drugs used, other possible explanations for the findings are small sample sizes, lack of reinforcement and monitoring of drug-taking behavior, and the inclusion of many individuals at relatively low risk for diabetes. For example, it was estimated that only 18% of participants in the Malmöhus trial would have met current definitions of IGT, with most of the rest having normal glucose regulation (10). Therefore, they would have lower estimated diabetes risk than participants in most of the other RCTs.

The first major RCTs of lifestyle weight loss interventions were the Da Qing (11), Finnish DPS (4), and the DPP (3). While there were modest benefits in the Da Qing, the lifestyle intervention in both the DPS and DPP reduced diabetes incidence by 58%. Subsequent studies of diabetes prevention in Japan (5) and India (31) confirmed the benefit of lifestyle-modification programs. Even with quite modest weight losses (0–2 kg), risk reductions of 67% and 28% were achieved in the Japanese and Indian studies, respectively. The differences in study design and participant characteristics make direct comparisons difficult, but these findings support the effectiveness of lifestyle modification across a broad range of ethnic groups and cultures. Further, although conducted in only one country, the U.S. DPP participants represented a broad range of race/ethnicity, with all groups having similar absolute incidence rates of diabetes and preventive effects of lifestyle intervention.

Many drugs to prevent or delay type 2 diabetes have been tested in RCTs. The greatest risk reductions (approximately 60%–75%) were achieved with the thiazolidinedione drugs troglitazone (21,27), rosiglitazone (34), and pioglitazone (39). Troglitazone is no longer available because of its liver toxicity. All thiazolidinediones have worrisome side effects, including edema, bone loss, and sustained weight gain. Further, concerns about bladder cancer, fractures, and CVD (59) have dampened enthusiasm for this class of drug, for either prevention or treatment of diabetes. However, some initial reports of safety problems with thiazolidinedione have not been replicated. On August 1, 2017, based on review of RCTs, the U.S. Food and Drug Administration (FDA) reported an updated review of rosiglitazone safety concluding that risk of death, heart attack, and stroke were not clearly different between rosiglitazone and metformin plus placebo (60). On December 11, 2017, however, the FDA reported an updated review of pioglitazone safety, reaffirming earlier warnings that pioglitazone may be linked to an increased risk of bladder cancer (61).

The alpha-glucosidase inhibitors, both acarbose and voglibose, reduced the risk of progression of prediabetes to diabetes, but in contrast to thiazolidinediones, have excellent safety profiles. Their gastrointestinal side effects can be minimized by starting with a low dose and gradually increasing it. Metformin, although less effective than the thiazolidinediones in reducing diabetes incidence, causes modest weight loss that is sustained for at least 10 years (23,24) and reduced diabetes incidence by 31% compared with placebo during 3 years in the DPP (3) with lesser risk reductions in long-term follow-up (23,24). The IDPP also reported reductions in diabetes risk with 250 mg of metformin administered two times daily (lower than the 850 mg twice per day used in the DPP) (31). The CANOE trial showed preventive effects of metformin and rosiglitazone given together in low doses used to minimize adverse effects (38). The excellent safety record, long experience with metformin in the treatment of diabetes, and its low cost make metformin an attractive option for diabetes prevention, although it is contraindicated in persons with advanced kidney disease.

Direct comparison of the effects of different drugs with each other or with weight loss is difficult, however, because most trials tested only one intervention, and the trials differed in eligibility criteria, outcome assessment, drug dosage, lifestyle intervention intensity, and treatment of the comparison group. In the DPP, a direct comparison of lifestyle and metformin, lifestyle was more effective, but in the IDPP, metformin, weight loss intervention, and both in combination had similar effects (31). During long-term follow-up of the DPP, during which time metformin was continued in the originally randomized group and lifestyle intervention was offered to the entire cohort, metformin and lifestyle resulted in similar cumulative incidence rates of diabetes after 15 years (56% in the metformin group and 55% in the original lifestyle group), compared with 62% in the placebo group (24). It is unknown whether this waning of the superior results of lifestyle would have been avoided had the

difference in intensity of the lifestyle intervention between the treatment groups been maintained.

Weight-loss agents have been studied in small numbers of individuals at increased risk of diabetes. Orlistat, an intestinal lipase inhibitor, reduced the development of diabetes in obese people with IGT (14,15). The effect of this drug on diabetes might be attributable to weight loss, which was greater than that achieved with lifestyle change alone. Low completion rates, however, suggest that this therapy has limited acceptability and make the estimates of the size of treatment effects unreliable. Several methods have been used to impute missing weight data for subjects who drop out of weight loss studies. None is satisfactory, however (62,63). The major problem is that dropping out of a weight loss trial is likely to be related to lack of success with weight loss or maintenance; hence, data are not missing at random, and commonly used methods, such as analysis of "completers only" or "last observation carried forward," may be seriously biased.

Several RCTs reporting large treatment effects were terminated earlier than planned for efficacy. This practice, often justified on ethical grounds, potentially leads to overestimation of treatment effects (64,65). This fact, along with heterogeneity among trials in the nature of the interventions and the participants, makes meta-analysis and summarizing these trials difficult.

Clearly, there is a need for more effective interventions, because even the best interventions studied in RCTs were considerably less than 100% effective. Better interventions could include more effective drugs with acceptable side effects or more effective approaches to weight loss and improving physical activity and fitness. It might be more effective to start prevention much earlier than has been done in RCTs so far, i.e., when abnormalities leading to diabetes may be more reversible than they are in persons with IGT. Starting earlier in the disease process has similar logistic obstacles as population-based prevention, i.e., providing interventions to populations at large regardless of level of diabetes risk. RCTs for either situation (early intervention in high-risk persons or population interventions) would be prohibitively long and expensive. Population approaches to diabetes prevention will usually require evaluation methods other than RCTs. Further, whether implementing treatment to prevent diabetes is more efficacious in preventing important health outcomes (e.g., microvascular complications) than a strategy of active case finding and aggressive treatment of established diabetes has not been established.

It remains unclear who should be offered diabetes prevention interventions, because evidence for prevention comes from trials conducted only in adults at high risk of diabetes to enhance power to detect meaningful treatment effects. Most type 2 diabetes prevention trials have enrolled only persons with IGT. Other predictors of type 2 diabetes, such as BMI, FPG, A1c, genotype, or diabetes risk scores based on questionnaires and medical history, might also be used instead of IGT to identify persons for RCTs or prevention services (26,66). Despite abundant evidence that these and other factors predict type 2 diabetes, evidence is lacking that intervention will reduce diabetes incidence in persons selected solely by such criteria or among populations without identified risk factors. Such evidence is critical for widespread implementation, however, because the OGTT required for identification of IGT is cumbersome, poorly reproducible, and not routinely performed in most settings.

Offering prevention interventions to high-risk persons first requires identification of such persons. Using current definitions of prediabetes based, in part, on IGT, implies that most people with prediabetes remain unknown, unless widespread testing with OGTTs is implemented. In the absence of such routine testing, only 11% of adults in the United States with prediabetes (defined by American Diabetes Association criteria for FPG or A1c) are estimated to be aware of their condition (67). Widespread implementation of diabetes prevention activities, therefore, depends on efforts to identify persons with prediabetes by current definitions, using simpler predictive tests, or population-based interventions. Widespread screening for prediabetes by current definitions using FPG or A1c is advocated by many but is not widely practiced and controversial owing to cost, inconvenience, and scarcity of direct evidence for long-term health benefit. As discussed above, most of the RCTs of diabetes prevention have enrolled adults with IGT, with or without other risk factors such as IFG, overweight or obesity, CVD risk factors, or CVD. Two RCTs enrolled sufficient numbers of persons with isolated IFG (i.e., persons who did not have IGT) to evaluate prevention in such persons, who would be much easier to detect. In DREAM, 14% of participants at entry had isolated IFG, 57.5% had isolated IGT, and 28.5% had both IFG and IGT (34). Rosiglitazone reduced diabetes incidence in all three subgroups, and there was no significant difference in its effect among these groups. In fact, the point estimate for the incidence ratio was lowest (i.e., greatest effect) among those with isolated IFG (HR 0.30, 95% CI 0.19–0.49), but with the widest confidence interval because this was the smallest subgroup. In a Japanese study, by contrast, participants with IFG were enrolled without regard to 2-hour plasma glucose or A1c, except that diabetes was excluded by an OGTT (5). Lifestyle intervention was successful overall (44% incidence rate reduction, HR 0.56), but it was even more effective in subsets at higher baseline risk, for example incidence rates were reduced by 76% (HR 0.24) in those with A1c ≥6.0%.

Although a number of genetic variants affect type 2 diabetes susceptibility, they add little to readily obtained clinical measures in short-term disease prediction, and persons at greatest genetic risk benefit at least as much from preventive interventions as those at lower genetic risk (45,46,47). Current knowledge does not indicate a need to test genetic susceptibility in selecting individuals for prevention or prescribing the optimal interventions,

although evidence suggests that some interventions may be more effective in those with greater estimated genetic susceptibility to type 2 diabetes (45,46) or that some genotypes predict response to metformin (47,48). The role for genotyping is likely to increase with results of further research, especially pharmacogenetic research, i.e., in which the choice of drugs may be optimized with knowledge of gene variants that affect drug action or tolerability.

Good methods are available for preventing type 2 diabetes in high-risk persons, but in addition to improving these interventions, it is important to determine which individuals can benefit the most from them. Currently, the best strategy for selecting individuals for diabetes prevention interventions is unclear. A major factor limiting the evidence from RCTs is that baseline risk of type 2 diabetes determines study power, which depends on numbers of events occurring in the trial. Providing evidence for effective interventions in low-risk persons is likely not feasible because of the size and duration of RCTs needed to attain adequate power. On the other hand, if interventions were beneficial in persons of low or average risk and could be delivered economically, more cases of diabetes might be prevented or delayed by targeting large numbers of lower-risk persons. This leads to the consideration of preventive measures applied to populations rather than targeted to high-risk individuals.

Following publication of results from the DPP and the other lifestyle intervention RCTs, many "implementation" activities have been described. Many of these studies were small, short-duration (1 year or less) RCTs, so they reported outcomes of weight loss or other diabetes risk factors, but not of the incidence of diabetes itself. These RCTs consistently produced weight loss, the magnitude of which was associated with measures of adherence to the programs, such as session attendance, as reported (68) or reviewed elsewhere (69,70,71). The YMCA program has been especially influential. Its curriculum based on the DPP was evaluated in an individual-based RCT from 2008 to 2010. The intervention arm resulted in mean weight loss during 1 year of 2.3 kg more than in the standard care group; mean weight loss was 5.3 kg more in participants attending at least nine lessons in the intervention (72). This chapter does not review the extensive literature on behavioral, drug, or surgical weight loss interventions that were not focused on diabetes or its risk factors. It is likely, however, that any successful weight-loss intervention will also reduce risk of type 2 diabetes, albeit balanced by side effects, risks, and costs specific to the intervention. A review of 44 trials testing DPP-based lifestyle interventions concluded that the interventions achieved not only weight loss but also improved cardiometabolic risk factors (73).

Widespread implementation of the findings of the major RCTs, however, does not require further RCTs. RCTs are suitable (and ideal) for evaluating the efficacy of an intervention when the efficacy is not already known. By contrast, implementation of RCT findings is in the realm of providing services that may be difficult to evaluate (74), but they may not need formal evaluation because they are presumed to be safe and effective.

When treatment or preventive methods are integrated into routine practice, they are not routinely evaluated formally. There are, however, a variety of methods other than individual-based RCTs that can be used to evaluate implemented programs, as discussed by Ackermann *et al.* (75,76). They can range from cluster randomized trials to "natural experiments" in which the health effects of environmental or political changes are evaluated—either by pre-post comparisons or comparisons with other locations where such changes were not made. While such methods lack the rigor and internal validity of RCTs, they are necessary for evaluation of large-scale changes.

Because of the widespread acceptance that lifestyle interventions can prevent or delay the onset of type 2 diabetes, although to varying degrees depending on intervention intensity and characteristics of the persons receiving them (66), a challenge is how to provide interventions to the large numbers of people who might benefit. An early example of such a program is the Montana Cardiovascular Disease and Diabetes Prevention Program. This was a service program, rather than an RCT, that produced weight loss in adults at high risk of diabetes (77). Another such program was the Special Diabetes Program for Indians conducted by the U.S. Indian Health Service (78). The program provided preventive service without a comparison group, so quantifying its effectiveness was difficult (74). As discussed, however, rigorous evaluation is not always necessary or possible when established findings are implemented in practice.

U.S. government programs that encourage diabetes prevention interventions have been established. The National Diabetes Prevention Program—or National DPP—is a partnership of public and private organizations working to reduce the growing problem of prediabetes and type 2 diabetes. The partners work to make it easier for people with prediabetes to participate in evidence-based, affordable, and high-quality lifestyle change programs to reduce their risk of type 2 diabetes and improve their overall health. The program provides information about diabetes and diabetes prevention and sources of programs available by location (79). The U.S. Centers for Medicare and Medicaid Services (CMS) recognized the value and potential cost savings of lifestyle interventions for diabetes prevention. This was based on a determination by the Chief Actuary of the CMS that the program developed by the YMCA of the USA Diabetes Prevention Program (Y-USA DPP) would either reduce spending without reducing quality of care or improve quality of care without increasing spending. Medicare will pay for individual-based lifestyle interventions patterned after the DPP to its beneficiaries who are overweight or obese and do not have diabetes, but meet criteria for "prediabetes" based on A1c, FPG, or 2-hour plasma glucose in an OGTT (80).

This has the potential to extend individual-based interventions on a much larger scale than done previously.

Widespread implementation may require changes at a community or societal level rather than interventions directed at individuals. This area is beyond the scope of this chapter, but it is discussed elsewhere (81,82). An example is changing tax policy to discourage consumption of nonessential energy-dense food and sugar-sweetened beverages. An evaluation of household food purchase before and after implementation of a tax on these food items indicated an average 5.1% reduction of purchases of taxed items (83). Because the tax was implemented nationally, there was no comparison group. No data were presented on effects on weight or other health measures. While it is widely hypothesized that changes in food policy and the built environment (e.g., encouraging personal energy expenditure rather than motor vehicles for transportation) will reduce obesity and type 2 diabetes (84), there is limited direct evidence that they will do so.

By contrast with implementation of lifestyle interventions, little has been published on implementation of pharmacological preventive interventions, largely owing to the lack of approval of medicines for diabetes prevention by regulatory agencies, such as the FDA. A pharmacoepidemiologic analysis of more than 1 million persons covered by insurance revealed that of those identified as being at high risk for diabetes, less than 4% were prescribed metformin over a 3-year period (85).

The cost of identifying potentially large fractions of the population as being at moderate to high risk of developing diabetes and then providing effective interventions must be taken into account. Considering these potentially large costs, the ultimate benefit of prevention on human health and the cost-benefit need to be established. The DPPOS has demonstrated potential cost savings of prevention to date (with metformin) (86).

Other critical questions about diabetes prevention—some answered and some not—are listed in Table 38.2.

TABLE 38.2. What Can Diabetes Prevention Activities Accomplish?

OUTCOME	CAN THIS OUTCOME BE ACCOMPLISHED?	SUMMARY OF EVIDENCE
Prevent or delay diabetes defined by glucose criteria in high-risk persons	Yes	Many trials
Reduce diabetes incidence to near zero for many years (ideal "prevention")	No	All trials had substantially high diabetes incidence even with the most effective interventions
Prevent or delay diabetes in children or adults at average risk	Unknown	No clinical trial evidence
Prevent or delay diabetes by population-level intervention	Unknown	No clinical trial evidence
Prevent complications of diabetes	Mixed results	Limited, but inconsistent, evidence of prevention of retinopathy
Prevent other diabetes-associated illnesses, such as cancer	Unknown	No clinical trial evidence
Reduce mortality rates	Unknown	Limited, but inconsistent, evidence of reduction of mortality rates
Reduce costs	Unknown	One study suggests cost-savings with metformin and cost-effectiveness with lifestyle intervention.

SOURCE: Original table constructed by W. C. Knowler, J. P. Crandall, J. L. Chiasson, and D. M. Nathan

CONCLUSIONS

Many different interventions are partially successful in preventing or delaying the onset of diabetes in nondiabetic adults who are at higher-than-average risk of diabetes by virtue of having impaired glucose regulation (IFG or IGT) and being overweight or obese. The largest preventive effects have been seen with weight loss through lifestyle interventions and by treatment with thiazolidinedione drugs, such as troglitazone, rosiglitazone, or pioglitazone. These drugs, however, are not in widespread use, either for prevention or treatment of type 2 diabetes, because of adverse effects and cost.

Although costs for the drugs have fallen, there still may be substantial costs to prescribing the drugs and monitoring their safety. Metformin, a less effective but safer drug that has had the longest experience in an RCT (DPP/DPPOS), is generally recommended for prevention and treatment of type 2 diabetes. The most commonly recommended preventive therapy, and perhaps the safest and with the most additional benefits, is weight loss through lifestyle intervention. As beneficial as some of the preventive interventions are, none are completely effective in that diabetes still develops in most participants, all selected because of their high risk, in RCTs when follow-up is extended. More effective interventions are still needed. Evidence for prevention of type 2 diabetes in persons of average risk, i.e., representing the general population of nondiabetic adults, or in children, is lacking.

The long-term benefits on nonglycemic outcomes are less certain. Most of the prevention RCTs have been too small and too short to evaluate long-term diabetes complications. Early studies suggested a reduction in CVD. More recently, the

Da Qing and DPP RCTs suggested benefits of lifestyle intervention on microvascular complications or mortality, but only in women. Of note, although the Look AHEAD (Action for Health in Diabetes) RCT of lifestyle intervention in adults with type 2 diabetes showed no benefit on cardiovascular events, it led to a reduction in incidence of advanced nephropathy, but also only in women (87). Reasons for the apparent sex differences in prevention of long-term complications, despite lack of sex differences in diabetes prevention, are not known.

There is still a serious shortage of data on long-term effects of these preventive interventions: do they simply affect the biochemical diagnosis of diabetes or do they also have long-term benefits in terms of diabetes microvascular and macrovascular complications, other conditions associated with diabetes, such as cancer, and longevity?

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
ACE . . . . . .Acarbose Cardiovascular Evaluation trial
BMI . . . . . .body mass index
CANOE . . . . . .Canadian Normoglycemia Outcomes Evaluation
CI. . . . . .confidence interval
CMS. . . . . .Centers for Medicare and Medicaid Services
CVD . . . . . .cardiovascular disease
DPP . . . . . .Diabetes Prevention Program
DPPOS. . . . . .Diabetes Prevention Program Outcome Study
DPS . . . . . .Diabetes Prevention Study
DREAM . . . . . .Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication study
FDA . . . . . .U.S. Food and Drug Administration
FPG . . . . . .fasting plasma glucose
HR . . . . . .hazard ratio
IDPP . . . . . .Indian Diabetes Prevention Programme
IFG. . . . . .impaired fasting glucose
IGT. . . . . .impaired glucose tolerance
NAVIGATOR. . .Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research trial
NGSP. . . . . .National Glycohemoglobin Standardization Program
OGTT . . . . . .oral glucose tolerance test
PPAR . . . . . .peroxisome proliferator-activated receptor
RCT . . . . . .randomized controlled trial
SNP . . . . . .single nucleotide polymorphism
STOP-NIDDM. .Study to Prevent Non-Insulin-Dependent Diabetes
WHO . . . . . .World Health Organization

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

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DUALITY OF INTEREST

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