Glucose intolerance, 1 of the 5 metabolic syndrome components, is an established cardiovascular disease (CVD) risk factor. The presence of other metabolic syndrome components enhances the CVD risk associated with glucose intolerance, and there is evidence that CVD risk may not be substantially increased in the small subgroup of subjects with type 2 diabetes who do not have the metabolic syndrome. Subjects with prediabetes may, therefore, be a high-risk subgroup among the population with metabolic syndrome. Approaches to preventing or delaying the progression of glucose intolerance provide an important opportunity to slow the epidemic of type 2 diabetes around the world. Furthermore, the prevention paradigm affords the opportunity to test whether these approaches improve cardiovascular risk and thereby reduce CVD complications. The results of the Diabetes Prevention Program (DPP), which studied the effects of lifestyle change or metformin therapy on type 2 diabetes development in overweight or obese subjects with impaired glucose tolerance (IGT), are presented here as a model of long-term interventions in otherwise healthy subjects with increased cardiometabolic risk. This approach evaluates the epidemiological value of characterizing metabolic syndrome risks in the context of dysglycemia and the type 2 diabetes prevention treatments studied.

Abstract—This review describes the effect of lifestyle change or metformin compared with standard care on incident type 2 diabetes and cardiometabolic risk factors in the Diabetes Prevention Program and its Outcome Study. The Diabetes Prevention Program was a randomized controlled clinical trial of intensive lifestyle and metformin treatments versus standard care in 3234 subjects at high risk for type 2 diabetes. At baseline, hypertension was present in 28% of subjects, and 53% had metabolic syndrome with considerable variation in risk factors by age, sex, and race. Over 2.8 years, type 2 diabetes incidence fell by 58% and 31% in the lifestyle and metformin groups, respectively, and metabolic syndrome prevalence fell by one-third with lifestyle change but was not reduced by metformin. In placebo- and metformin-treated subjects, the prevalence of hypertension and dyslipidemia increased during the Diabetes Prevention Program, whereas lifestyle intervention slowed these increases significantly. During long-term follow-up using modified interventions, type 2 diabetes incidence and metabolic syndrome prevalence in subjects at high risk for type 2 diabetes. Metformin had more modest effects. (Arterioscler Thromb Vasc Biol. 2012;32:2077-2090.)

Key Words: lifestyle ■ metabolic syndrome ■ metformin ■ prediabetes

The DPP and its Outcome Study
The DPP Population
The DPP recruited 3234 subjects at 27 centers across the United States using a variety of screening approaches that identified individuals at high risk for type 2 diabetes. Criteria for entry included a fasting glucose ≥5.3 mmol/L, IGT on an oral glucose tolerance test according to American Diabetes Association criteria (2-hour glucose value, 7.8–11.1 mmol/L), and a body mass index (BMI) ≥24 (≥22 in Asians). Recent onset myocardial infarction was an exclusion criterion, and <5% had clinically evident CVD. Eligible subjects were randomized originally into 4 treatment groups: an intensive lifestyle program, with the aim of achieving and maintaining at least 7% weight reduction through a low-calorie, low-fat diet and engaging in at least 150
minutes of physical activity per week, metformin 850 mg twice daily, troglitazone 400 mg daily, and standard lifestyle plus metformin+troglitazone placebo. The troglitazone group was discontinued after 2 years because of the drug’s potential for liver toxicity. From a CVD risk standpoint, the DPP cohort was relatively young; the average age at baseline was 50.6 (±10.7 [SEM]) years, with 67.7% being women and 69.4% having a family history of type 2 diabetes. One of the strengths of the DPP was its multiethnic study population; 54.7% were white, 19.9% black, 15.7% Hispanic, 5.3% American Indian, and 4.4% Asian American. The population was obese (mean BMI, 34.0±6.7 kg/m²; waist-to-hip ratio, 0.92±0.09), with mean fasting and 2-hour glucose values of 5.9 and 9.1 mmol/L, respectively, and glycated hemoglobin of 5.9±0.5%.

After the initial phase of DPP was completed, participants were offered the opportunity to enroll in an additional follow-up study (the DPP Outcome Study or DPPOS). Eighty-eight percent enrolled and after an approximate 1-year bridge period, all 3 DPP intervention groups were offered group-implemented lifestyle support. Thus, the design and interventions in the original lifestyle intervention group was offered additional group lifestyle support. Therefore, the design and interventions in this phase of the study changed, with conversion of the standard care placebo group in DPP to group lifestyle in DPPOS, an additional median duration of 5.7 years. Metformin treatment continued in the original metformin-treated subjects, and the original lifestyle intervention group was offered additional group lifestyle support. Thus, the design and interventions in this phase of the study changed, with conversion of the standard care placebo group in DPP to group lifestyle in DPPOS, the former metformin-only group to metformin plus group lifestyle, and a reduction in the intensity of the lifestyle program in those who had been in the DPP intensive lifestyle group.

Baseline Prevalence of Cardiovascular Risk Factors and Metabolic Syndrome Components

Hypertension and Dyslipidemia

Although this was a population defined by glucose intolerance, due to the eligibility criteria only 33% had fasting glucose levels ≥6.1 mmol/L. Hypertension was present in ~30% of participants based on the finding of a blood pressure (BP) ≥140/90 mm Hg (13%) or the use of antihypertensive medication (17%), which is just over half the prevalence of hypertension typical for type 2 diabetes. Hypertension was more common in black (36%) than white (27%) or Hispanic (22%) participants and was associated with higher fasting insulin (a surrogate of insulin resistance) and greater adiposity.4 Forty-nine percent of men and 41% of women had triglyceride levels ≥1.69 mmol/L, and 52% of men and 60% of women had high-density lipoprotein cholesterol (HDL-C) levels ≤<1.03 and ≤1.29 mmol/L, respectively, whereas 45% of men and 41% of women had low-density lipoprotein cholesterol (LDL-C) values ≥3.36 mmol/L; only 5.2% of subjects were receiving lipid-lowering medications at study entry.3 This prevalence of abnormal lipid levels are similar to what is typically found in subjects with type 2 diabetes.6 Using an ultracentrifugal cut point of Rf ≤0.263 to define LDL phenotype B, 41% of men and 25% of women had predominantly small, dense LDL, respectively. Women had significantly lower triglyceride and LDL-C than men (1.70 versus 1.95 mmol/L and 3.20 versus 3.38 mmol/L) and significantly higher HDL-C levels (1.24 versus 1.04 mmol/L) and LDL peak particle density of Rf (0.270 versus 0.257) values; among women, estrogen users had higher triglyceride and HDL-C levels than nonusers. Triglyceride concentrations and LDL peak particle density were lower, and HDL-C was higher in blacks compared with other ethnic groups as has been previously noted. Although insulin resistance and BMI were independent determinants of both triglyceride and HDL-C concentrations, insulin resistance contributed to more of their baseline variance than BMI did.5

Metabolic Syndrome

Using the original National Cholesterol Education Program criteria for metabolic syndrome,7 53% of the DPP cohort had the metabolic syndrome at study entry, and the prevalence did not differ by age, sex, or major population race/ethnicity group.8 The lack of an age effect may be attributed to the fact that the increasing prevalence of the metabolic syndrome with age in the general population is strongly associated with type 2 diabetes development, which we excluded in our participants. It was somewhat surprising, however, not to identify differences by sex or race/ethnicity as has been described in the general population. This may reflect the impact of a similar degree of glucose intolerance being present throughout our population. In this obese population, an enlarged waist circumference (78%) was the most common abnormality, followed next in frequency by low HDL-C (57%), increased triglyceride (46%), elevated BP (45%), and elevated fasting glucose (33%) in that order. The study entry criteria ensured fairly uniform type 2 diabetes risk throughout our population, but despite this the metabolic syndrome phenotype varied considerably by age, sex, and race. The prevalence of enlarged waist and low HDL-C diminished with age (82% and 70%, respectively, in those 25–44 years decreasing to 73% and 40%, respectively, in those >60 years) as the proportion with elevated BP increased (31% in those 25–44 years to 63% in those >60 years). Women more frequently had increased waist circumference and low HDL-C levels, whereas men more frequently had high triglyceride levels, high fasting blood glucose levels (>6.1 mmol/L), and elevated BP. Blacks were more likely to have an elevated BP and less likely to have an elevated triglyceride or low HDL-C. The prevalence of metabolic syndrome at baseline in the DPP increased to 69% if the updated criteria using a lower fasting glucose cut point of ≥5.6 mmol/L are applied.9 Those with fasting glucose ≥6.2 mmol/L had essentially the same distribution of metabolic syndrome components as those with glucose values below this cut point.

Markers of Inflammation and Coagulation

High-sensitivity C-reactive protein (CRP) levels were higher in women than men (4.64 versus 1.92 mg/L), and 31% of men versus 69% of women had values ≥3 mg/L, a cut point proposed to identify increased risk for CVD.9 In DPP, CRP levels correlated more strongly with BMI than with homeostasis model assessment-insulin resistance (HOMA-IR), differing from some other reports suggesting the opposite.10 This may reflect the limitations of the use of an insulin resistance surrogate or the fact that the population was, on average, obese. Fibrinogen levels were higher in women than men and highest in blacks and correlated with both HOMA-IR and BMI, whereas the tissue plasminogen activator value, used as a surrogate of plasminogen activator inhibitor-1, was higher in men.5 Median adiponectin values were higher in women than men (7.8 versus 6.3 μg/mL) as is typical, varied significantly between major race/ethnic groups (white 7.7, Hispanic 7.3, black 6.0 μg/mL), and correlated most strongly with age, fasting insulin/HOMA-IR, and
HDL-C and less strongly with triglyceride and BMI. The baseline adiponectin level was a robust inverse predictor of type 2 diabetes development after adjustment for BMI and indices of insulin secretion and sensitivity, and this was not affected by sex and race/ethnicity or type of intervention. Having the metabolic syndrome at baseline increased the risk of developing type 2 diabetes by 1.7- to 2.0-fold (differing by intervention group), and this was attributed to independent effects of elevated fasting glucose and in the placebo and lifestyle treatment groups but not metformin group, also increased waist circumference (unpublished data).

The picture that emerges is of an obese cohort with a 1.5- to 2-fold greater prevalence of the metabolic syndrome than what has been reported for the general population and where the presence of the metabolic syndrome identifies a subgroup at further increased risk for type 2 diabetes development. Over two-thirds of women and one-third of men have what has been proposed to be high-risk levels of CRP. However, the prevalence of metabolic syndrome was lower among our subjects with IGT than has been described in type 2 diabetes, where the prevalence is ≈90%. Furthermore, although it seems that subjects with IGT in the DPP have a similar prevalence of the metabolic syndrome irrespective of their age, sex, or ethnicity, the composition of the risk factor cluster varied considerably in both type and severity among subgroups. These findings suggest a state at intermediary cardiometabolic risk between what has been reported for the general population versus type 2 diabetes.

**Effect of Interventions on Type 2 Diabetes Outcomes**

The blinded treatment phase of the DPP was terminated 1 year early, after a mean follow-up of 2.8 years, because efficacy had been obtained on the basis of 65% of the planned person-years of observation. Final close-out occurred after an average of 3.2 years. Half of the participants receiving the lifestyle intervention had achieved the weight loss goal and 74% met the physical activity goal by the end of the training curriculum at 24 weeks, with 38% maintaining the weight loss goal and 58% maintaining the activity goal through their last visit. Both energy and fat intake were significantly reduced in the intensive lifestyle program compared with the other 2 groups. The incidence of type 2 diabetes was 58% lower in the lifestyle (4.8 cases per 100 person-years) than the placebo group (11.0 cases per 100 person-years) and in the metformin group (7.8 cases per 100 person-years) was reduced by 31% versus placebo treatment. This meant that 6.9 lifestyle and 13.9 metformin participants needed to be treated to prevent 1 case of type 2 diabetes. Although this is a highly significant reduction in type 2 diabetes incidence, its full significance on health and healthcare costs must await the results of long-term follow-up (see DPPOS below). Treatment effects did not differ according to sex or race/ethnicity, although the benefit of metformin was less in those with a lower BMI or fasting glucose, and the advantage of lifestyle over metformin was greater in older people and in those with a higher BMI. In the lifestyle group, weight loss was the dominant predictor of reduced type 2 diabetes incidence (16% risk reduction per kg weight loss), which in turn was predicted by the reduction in fat calories and the increase in physical activity. Of note, change in waist circumference was not a better predictor of type 2 diabetes development than weight change, probably because at this level of obesity the 2 measurements correlate with each other very strongly (r=0.90). Furthermore, subcutaneous abdominal fat measured by computed tomography was not predictive of type 2 diabetes development, whereas visceral fat content was no better than waist circumference in this prediction.

Overall physical activity did not have an independent effect on the hazard rate, although as noted it played a critical role in achieving weight reduction. Beyond this, those who did not meet the weight loss goal but did meet the physical activity goal had a 44% reduction in type 2 diabetes incidence independent of the smaller weight loss (−2.9 kg) that occurred in this subgroup. This suggested that the effects of weight reduction and increased activity on type 2 diabetes development operated through pathways that did not have much additive influence. The reduction in type 2 diabetes development in the metformin group was partly explained by a pharmacological effect on fasting glucose levels, consistent with the known effect of metformin to decrease hepatic glucose production, but there were independent effects because of weight loss (−1.7 kg) and reductions in proinsulin concentrations. After a 2-week period of drug washout, there was a 0.25 mmol/L rise in the fasting glucose in metformin-treated subjects (versus a 0.03 mmol/L rise in placebo-treated subjects), but after the washout the metformin group still maintained a 25% lower type 2 diabetes incidence compared with placebo, indicating that the benefit from metformin extended beyond its pharmacological glucose-lowering effect. Overall, higher insulin secretion at baseline and increased insulin sensitivity with treatment were markers of type 2 diabetes prevention. Importantly, weight loss and changes in insulin secretion and sensitivity each independently predicted type 2 diabetes development in the cohort as a whole.

**Effect of Interventions on Cardiometabolic Risk Factors and the Metabolic Syndrome**

CVD events were uncommon in the DPP population, so it was not possible to evaluate the effect of treatment interventions on CVD events after 3 years. There were only 89 CVD events confirmed during the 3-year study period, with 4 CVD deaths in the placebo group, 1 in the metformin group, and 2 in the lifestyle group and no difference in the incidence of nonfatal CVD in the 3 groups (0.53%, 0.47%, and 0.67% per year, respectively). This reflects the relatively low short-term CVD risk of this population and is in line with a recent meta-analysis, suggesting that the increased CVD risk among subjects with IGT compared with those with normal glucose tolerance (NGT) is modest.

**Hypertension and Dyslipidemia**

The lifestyle intervention significantly lowered systolic and diastolic BP (by 3.4 and 3.6 mm Hg, respectively) after 1 year compared with both placebo (−0.9 and −0.9 mm Hg) and metformin (−0.9 and −1.26 mm Hg), and these differences persisted for all 3 years of the study. During the duration of the study, the prevalence of hypertension increased by about one-third from ≈30% of participants at baseline to ≈40% at study end in both the placebo- and metformin-treated groups, whereas the lifestyle intervention completely prevented this increase (Figure 1).
Similarly, the prevalence of dyslipidemia, defined according to the Adult Treatment Panel II criteria existent at the initiation of the study in 1996, namely an LDL-C value ≥3.4 mmol/L or a triglyceride value ≥2.3 mmol/L or the use of lipid-lowering medications, was similarly noted to increase by more than one-half (from 12% at baseline to 20% at 3 years) in the placebo-and metformin-treated groups, and this increase was significantly reduced by the lifestyle intervention. These findings demonstrate that the prevalence of hypertension and dyslipidemia increased quite rapidly in the placebo group in the absence of weight gain, along with the development of type 2 diabetes. As pointed below, these changes seem to parallel deterioration in glucose tolerance. Whereas metformin treatment had no significant effect to blunt these increases, lifestyle intervention prevented the increase in hypertension incidence and significantly reduced the increases in dyslipidemia seen in the other 2 groups. Clinical use of antihypertensive and lipid-lowering medications was unbalanced across the study groups, with less treatment required in the lifestyle group, which, therefore, masked an even greater treatment effect of lifestyle intervention on these parameters.

**Lipids**

Most of the improvement in lipid levels seen with lifestyle intervention was because of the reduction in triglyceride concentrations (−0.296 mmol/L), significantly more than placebo (−0.13 mmol/L) or metformin (−0.08 mmol/L), with a small but significant increase in HDL-C values (+0.026 mmol/L) compared with the placebo (+0.001 mmol/L) or metformin (+0.008 mmol/L) groups. LDL-C levels did not change significantly in any of the 3 groups, although lifestyle intervention did reduce the prevalence of LDL phenotype B compared with the other groups in which it did not change during the study.

**Metabolic Syndrome**

Study of the placebo group over time offers insight into the natural history of the metabolic syndrome in subjects with IGT. Eighteen percent of those with the metabolic syndrome in the placebo group no longer met the criteria at 3 years, whereas 53% of those without the metabolic syndrome at baseline qualified for the diagnosis after 3 years, leading to a net overall
increase in this group from 55% to 61% of the participants (Figure 2). In contrast, in the lifestyle group 38% of those with the metabolic syndrome at baseline no longer met the criteria at 3 years, whereas the incidence of new metabolic syndrome was reduced 41% compared with placebo, yielding an overall reduction in prevalence at 3 years from 51% to 43% (a 16% net decrease). The lifestyle intervention was least effective in those 25 to 44 years of age and more effective in men than women (64% versus 37%); the latter finding may perhaps be because of the modest effect of lifestyle intervention to decrease the incidence of low HDL-C, which was more commonly present among women than men. This was somewhat surprising because weight reduction and physical activity tend to increase HDL-C. It is possible that reduction in saturated fat in the diet, which lowers HDL-C, may have offset HDL-C increases attributable to weight reduction or increased physical activity in the lifestyle group. In contrast, lifestyle intervention reduced the prevalence of elevated triglyceride and BP, which were more common components in men. Similar to the placebo group, 23% of the metformin group with metabolic syndrome at baseline no longer met the criteria at 3 years, but the incidence of new cases was 17% lower than in the placebo group, leading to an overall stability of metabolic syndrome prevalence from 54% at baseline to 55% at the end of the study in this group. Metformin had only a modest effect on triglycerides and HDL-C, and no effect on BP and was not effective compared with placebo subjects after 1 year of interventions. The magnitude of CRP reduction in the lifestyle group is similar to that seen with moderate to high doses of statin drugs. Fibrinogen fell more modestly (~2% and ~0.5%, respectively, in the lifestyle and metformin groups). Mean adiponectin increased 13% in the lifestyle group and by a more modest 3% in the metformin group, and the overall change in adiponectin was predictive of type 2 diabetes development after adjustment for baseline adiponectin. Once again, these data attest to the superiority of the lifestyle intervention over metformin, in this case to reduce markers of inflammation and coagulation. Interestingly, although the nadir for weight loss occurred after 6 months of intervention, CRP levels continued to fall over the subsequent 6 months with no discernible weight change. This indicates that there are ongoing metabolic changes induced by weight reduction that continue to improve even when the weight loss has plateaued. The fall in CRP was associated with improvements in both BMI and HOMA-IR and correlated strongly with the fibrinogen change. Presumably, the change in CRP reflects the reduction in subclinical adipose inflammation associated with weight reduction. It remains to be shown whether reductions in systemic inflammation as a result of weight loss are associated with decreased CVD risk.

**Effect of Changes in Glucose Tolerance on Progression of Cardiometabolic Risk**

Although this cohort with IGT exhibited a cardiometabolic risk profile that was similar to that in type 2 diabetes, as noted above there was a lower prevalence of hypertension and metabolic syndrome than is typically found in type 2 diabetes. Although there was no group with type 2 diabetes available in DPP for direct comparison, others have noted that levels of cardiometabolic risk factors in IGT are generally milder than those typically present in subjects with type 2 diabetes. Thus, it seems likely that the cardiometabolic risk profile becomes more unfavorable as glucose tolerance deteriorates. This was prospectively tested by studying the effect on BP and lipids during transition (or not) from the baseline state of IGT to either normal glucose tolerance (NGT) or type 2 diabetes over the course of the study. Deterioration to type 2 diabetes was accompanied by a significant trend toward increasing systolic and diastolic BP and triglyceride levels, and a significant downward trend in HDL-C and LDL peak particle density, whereas reversion from IGT to NGT showed the opposite trends. LDL-C levels were unaffected by either transition. Importantly, there was no interaction with interventions; in other words, these effects were not different across the 3 intervention arms. Also, there was no unique effect of conversion to type 2 diabetes. Instead, we observed a linear relationship between glycemic measures and risk factor levels. These relationships were stronger for the 2-hour glucose than for the fasting glucose value. In mixed models that included BMI, waist circumference, and HOMA-IR, BMI change best accounted for these glycemia-associated changes in CVD risk factors. Thus, progression of glucose intolerance in DPP was a good marker for deterioration of cardiometabolic risk irrespective of interventions, and conversely reversion to NGT was accompanied by improvements in cardiometabolic risk. These observations provide prospective evidence that worsening of dysglycemia over a 3-year period is accompanied by unfavorable changes in CVD risk and vice versa.

**Effect of Interventions on CRP, Fibrinogen, and Adiponectin**

CRP levels fell 33% in men and 29% in women in the lifestyle group and 14% and 7%, respectively, in the metformin group (significant only for men), with no change in the placebo subjects after 1 year of interventions. The magnitude of CRP reduction in the lifestyle group is similar to that seen with moderate to high doses of statin drugs. Fibrinogen fell more modestly (~2% and ~0.5%, respectively, in the lifestyle and metformin groups). Mean adiponectin increased 13% in the lifestyle group and by a more modest 3% in the metformin group, and the overall change in adiponectin was predictive of type 2 diabetes development after adjustment for baseline adiponectin. Once again, these data attest to the superiority of the lifestyle intervention over metformin, in this case to reduce markers of inflammation and coagulation. Interestingly, although the nadir for weight loss occurred after 6 months of intervention, CRP levels continued to fall over the subsequent 6 months with no discernible weight change. This indicates that there are ongoing metabolic changes induced by weight reduction that continue to improve even when the weight loss has plateaued. The fall in CRP was associated with improvements in both BMI and HOMA-IR and correlated strongly with the fibrinogen change. Presumably, the change in CRP reflects the reduction in subclinical adipose inflammation associated with weight reduction. It remains to be shown whether reductions in systemic inflammation as a result of weight loss are associated with decreased CVD risk.

**Genetic Modifiers of Intervention Effects on Cardiometabolic Risk Factors**

The study of genetic influences on baseline predictors of outcomes and on intervention effects in the DPP has focused principally on the primary outcome, namely type 2 diabetes development. These studies demonstrate that genetic variations that influence risk for type 2 diabetes development may do so in a manner that appears to be independent of interventions in some instances and to influence the effects of either or both of the active interventions in others. These findings have relevance for cardiometabolic risk as well. Such effects are pathophysiologically instructive, although at this point they do not significantly add to the prediction of type 2 diabetes beyond what is provided by standard type 2 diabetes risk factors.

For example, a genetic risk score based on 34 type 2 diabetes–associated loci was shown to be associated with increased risk of development of type 2 diabetes and a lower probability of returning to NGT in DPP. At baseline, the
genetic risk score was associated with a lower insulinogenic index, illustrating that most of the type 2 diabetes loci identified so far are related to β-cell function. The interactions of this risk score with CVD risk factors are somewhat paradoxical, in part because the IGT eligibility requirement in DPP meant that those with more significant β-cell deficits had relatively less insulin resistance than those with lower genetic risk. Using median splits for markers of insulin resistance and secretion at baseline, triglyceride, CRP, fibrinogen, and tissue plasminogen activator were all higher, and HDL-C and LDL peak particle density were lower in those with greater insulin resistance; there was no effect of insulin secretion on these cardiometabolic risk factors. It was, therefore, not surprising to discover that participants in the highest type 2 diabetes genetic risk score quartile in this population had a lower waist circumference and triglyceride levels and higher HDL-C values. Whether this subgroup will continue to demonstrate a more benign cardiometabolic risk profile, particularly in those who progress to type 2 diabetes, remains to be determined. Although there was no interaction between interventions and the effects of the genetic risk score, those in the highest quartile of risk did not benefit from metformin treatment, possibly because metformin does not preserve β-cell function significantly.

Lowered effectiveness of metformin in reducing type 2 diabetes development was also observed in a study of a common polymorphism in the metformin transporter gene SLC47A1 and possibly several other genes related to metformin pharmacokinetics and action. An increased risk of type 2 diabetes was noted in homozygous carriers of the risk allele at the Pro12Ala polymorphism of the pivotal adipogenesis gene, PPARG, regardless of intervention; the same genotype was interestingly found to be associated with less central obesity and visceral adipose tissue in this obese population at baseline and was associated with less weight reduction with both metformin and lifestyle interventions.

On the other hand, a missense polymorphism in ENPP1, a gene that has been reported to influence insulin signaling, was associated with an increased risk for type 2 diabetes that was eliminated by lifestyle intervention and reduced by metformin, suggesting that carriers may benefit disproportionately from these interventions. Two polymorphisms in the obesity-related genes FTO and INSIG23 were associated with baseline adiposity. In the case of FTO, a collaborative study showed that the increased weight was attenuated 30% by physical activity, suggesting that these individuals were particularly susceptible to lifestyle intervention. The INSIG23 polymorphism was associated with greater reduction of subcutaneous adiposity at 1 year of intervention and was found to have nominally significant gene–lifestyle interactions with weight change.

The effect of a genetic determinant of type 2 diabetes risk or of factors associated with CVD risk is not always simply related to the purported end point. As an example, although polymorphisms of the adiponectin gene ADIPOQ are significantly associated with adiponectin concentrations, they did not relate to type 2 diabetes risk, despite the clear association of adiponectin concentrations with type 2 diabetes risk. This raises questions about a direct causative relationship between circulating adiponectin and type 2 diabetes development. Furthermore, the finding that variants in the adiponectin receptor 1 gene (ADIPOR1) were associated with type 2 diabetes development independent of adiponectin concentrations supports the notion that changes in receptor concentration or activity may have relevance for adiponectin signaling in insulin-resistant states. Another instance is the finding that the well-studied missense polymorphism in the glucokinase regulatory protein gene (GCKR) was associated with higher triglyceride and CRP levels but also with lower glucose and HOMA-IR at baseline and without any effect on type 2 diabetes development. This is of interest because the phenotype contrasts with the typical clinical associations between these risk factors. Furthermore, lifestyle intervention partially mitigated the effect of the polymorphism on higher triglyceride, whereas the minor allele appeared to enhance the effect of metformin on HOMA-IR. These unexpected observations may provide insight into important previously unrecognized biological effects on type 2 diabetes and CVD risk.

Longer-Term Effects of Interventions on Type 2 Diabetes Development and CVD Risk Factors

As described earlier, after the initial phase of DPP was completed, 88% of participants enrolled in the DPPOS follow-up study (median duration of 5.7 years), with all 3 DPP intervention groups being offered group-implemented lifestyle intervention after an approximate 1-year bridge period. Metformin treatment continued in the original metformin-treated subjects, and the original lifestyle intervention group was offered additional lifestyle support. The lifestyle group continued to gain weight, which plateaued after a further 2 to 3 years at ≈2 kg below baseline weight, overlapping with the metformin group that maintained a fairly stable 2 kg weight reduction (Figure 3). The placebo group lost little weight during the entire study. Type 2 diabetes incidence fell quite dramatically in the placebo group during the DPPOS to 5.6%/year (from 11.0%/year in DPP) and was significantly lower in the metformin group (4.9% compared with 7.8% in DPP), with both groups approximating the lower incidence achieved in the lifestyle intervention group in DPP (5.9% compared with 4.8% in DPP). The basis for these findings is difficult to explain because there was little weight change with the addition of group lifestyle to the placebo and metformin groups during the DPPOS phase. It is possible that the intensive lifestyle and metformin interventions in DPP had their greatest initial impact on those IGT participants who were most susceptible to develop type 2 diabetes, following which type 2 diabetes development stabilized at a reduced rate of ≈5% per year in all groups. Certainly, the addition of group lifestyle intervention did not yield any additional noticeable benefit to the metformin intervention compared with the placebo group, which was surprising. Overall after 10 years in the study, type 2 diabetes had occurred in 42% of the lifestyle, 47% of the metformin, and 52% of the placebo groups, representing a long-term 34% reduction in type 2 diabetes incidence in the lifestyle group and an 18% reduction in the metformin/group lifestyle arm. Although not as dramatic as the original DPP findings, persistent reductions in type 2 diabetes incidence of...
this magnitude would be expected to have a major impact on health and healthcare costs. A recent economic analysis found that during the 10-year period, from a payer perspective, lifestyle was cost-effective and metformin was marginally cost-saving compared with placebo.\textsuperscript{33} Longer-term follow-up will reveal whether development of type 2 diabetes complications can be reduced, in which case these economic benefits will be substantially enhanced.

During the DPPOS, HDL-C levels increased equally in all 3 groups by 12%, and triglyceride levels in the placebo and metformin groups gradually fell until they were similar in value to those in the lifestyle group, producing a net $0.25$ mmol/L decrease from the baseline values in DPP\textsuperscript{34} (Figure 3). There is no obvious explanation for the significant rise in HDL-C; in particular, we have ruled out technical problems in the laboratory measurements, and it is not attributable to reported changes in medications or other measured factors in the study. LDL-C levels fell similarly in all 3 groups by $0.5$ mmol/L, mostly as a result of the increased use of statins with time; the use of lipid-lowering medications increased from $5\%$ at baseline to $32\%$ to $37\%$ at the end of DPPOS, with significantly less use in the lifestyle group.\textsuperscript{34} Although the magnitude of change in triglyceride and LDL-C was smaller in the nonstatin users, the same trends as were seen overall were noted. Interestingly, there were no significant differences in lipid measurements between the 3 groups after 10 years. Antihypertensive medication use increased from $15\%$ of participants at DPP baseline to $50\%$ at the end of DPPOS, with slightly less use in the lifestyle group. Both systolic and diastolic BP fell in DPPOS to reach the values achieved in the intensive lifestyle program group at DPP end. In the case of the diastolic BP, values decreased further in all 3 groups (the decrease in DPPOS was $-3$ mm Hg for systolic and $-6$ mm Hg for diastolic BP) such that as for lipids, there were no differences in BP between the 3 groups at 10 years. The average triglyceride value at study end was $1.4$ mmol/L, LDL-C $2.7$ mmol/L, HDL-C $1.32$ mmol/L, and BP $121/73$ mm Hg.\textsuperscript{34}
Comparisons With Other Type 2 Diabetes Prevention Trials

There have been 4 other type 2 diabetes prevention trials that tested lifestyle intervention in subjects with IGT, one of which also tested low-dose metformin. These were the China Da Qing Diabetes Prevention Study (CDQDPS), the Finnish Diabetes Prevention Study (FDPS), the Indian Diabetes Prevention Program (IDPP) that included metformin intervention arms, and a Japanese study. All were considerably smaller than DPP, had differences in design, and except for the FDPS, were conducted in Asian subjects who were considerably less overweight than in DPP. Thus, a much smaller amount of weight reduction was achieved in these studies, even though each of the studies demonstrated significant reduction in type 2 diabetes incidence with lifestyle change (26%–58% reduction). The best comparison with DPP is the FDPS, which is the only 1 of the 4 studies to publish data on the metabolic syndrome. The design of the FDPS was similar to the lifestyle intervention arm of DPP and produced the same benefit for type 2 diabetes prevention; the participants were slightly older and less overweight and had lower triglyceride and higher HDL-C levels at baseline than those in DPP. In the FDPS, 74% had the metabolic syndrome (using the definition of ≥2.6.1 mmol/L for fasting glucose) at baseline, with elevated BP (80%), fasting glucose (77%), and abdominal obesity (72%) being the most common components. By the end of the 3.9-year study, the prevalence of the metabolic syndrome fell in the lifestyle arm as for DPP to 63%. This was found to be because of reductions in prevalence of all metabolic syndrome components, except fasting glucose. The intervention did not change HDL-C or LDL-C significantly but did lower triglyceride and systolic BP and diastolic BP as was found in DPP. These findings parallel some of our key findings in DPP. However, unlike in DPP the prevalence of the metabolic syndrome did not increase in the placebo group. It is possible that DPP participants were less advanced in the trajectory toward the metabolic syndrome than those in FDPS.

The IDPP, which incorporated both lifestyle advice and low-dose metformin (500 g/day) arms, as well as a combined lifestyle and metformin interventions, had a median follow-up of 30 months. Although there was no significant weight change in any of the groups, type 2 diabetes incidence was reduced 26% to 28% in the 3 intervention groups compared with the standard care group. Participants had a high baseline prevalence of elevated triglycerides, apolipoprotein B, or LDL-C, and low HDL-C was common. The only change in cardiometabolic risk factors was seen in the combined lifestyle plus metformin group, in which BP, LDL-C, and apolipoprotein B values decreased slightly at the follow-up visit. As in DPP, the prevalence of hypertension increased in all groups over time, from 30% at baseline to 55% at study end.

The CDQDPS recently published its 20-year follow-up data. In this study, individuals were assigned, according to which clinic they attended, to a program of dietary modification, exercise, or both versus standard care for a period of 6 years. Despite ending all formal interventions after this point, type 2 diabetes incidence in the combined intervention groups was reduced 43% compared with the standard care group at 20 years, but there was no significant reduction of CVD events in the intervention groups. No follow-up cardiovascular risk data are available, although 65% of events were cerebrovascular as is typical in China, so comparisons with Western studies are difficult to make.

Summary and Future Directions

A central aim of the DPP was to determine whether a lifestyle change intervention and a widely available pharmacointervention, with a track record of safety and possible cardioprotective properties, might simultaneously reduce type 2 diabetes incidence and improve CVD risk in prediabetic subjects. By tracking the long-term trajectories to type 2 diabetes and CVD development within the design of a clinical trial, the DPP constitutes a unique model to test these questions in people with IGT, 33% of whom also had impaired fasting glucose. It is clear from the data that these subjects are heterogeneous from a cardiometabolic risk standpoint so that an important clinically practical objective is to identify subgroups with greater CVD risk from those with less risk at this early point in disease development. The presence of the metabolic syndrome is likely one such determinant, and it is evident that increasing body weight is a key common denominator driving development of both cardiometabolic risk and type 2 diabetes. It remains unproven, but it is likely that continuous measures of individual metabolic syndrome components will provide better discrimination for CVD in this population than the categorical metabolic syndrome approach. In addition, it is also possible that newer biomarkers such as CRP, adiponectin, tissue plasminogen activator (PAI-1), and endothelial function markers, as well as genetic polymorphisms linked to either type 2 diabetes or CVD development, will at the very least advance our understanding of these biological processes, if not add to the ability to differentiate the level of risk earlier on in the course of these diseases.

The DPP clearly demonstrated that this population had a high risk for metabolic deterioration. Not only was the risk for type 2 diabetes development high in this population (11% per year), but so too was the risk for developing the metabolic syndrome among the half of the population who did not have the syndrome at baseline (=8% new cases per year in this subgroup). In parallel to this, the prevalence of both hypertension and dyslipidemia progressed in the standard care group at about the same pace (3% yearly). The trajectory of deterioration in cardiometabolic risk was closely aligned to worsening of glucose tolerance, both of which were strongly associated with weight gain. It was not surprising, therefore, that during the DPP phase of the study, intensive lifestyle intervention and the ensuing weight reduction not only reduced type 2 diabetes incidence in half but also decreased the frequency of those with established metabolic syndrome by almost the same proportion in the standard care group (38%), while preventing 41% of new cases. These effects were particularly beneficial in younger adults and in men. At the same time, progression in the prevalence of hypertension was completely prevented by lifestyle change, whereas that of dyslipidemia was significantly ameliorated—mainly because of the reduction in triglyceride and LDL phenotype B. Metformin treatment was
about half as potent as lifestyle change for type 2 diabetes prevention and even less effective for metabolic syndrome prevention. These findings are probably largely explained by the more modest weight reduction engendered by metformin, together with its pharmacological antihyperglycemic effect, and point to the superiority of lifestyle change compared with metformin on overall metabolic risk in the DPP.

The alterations in design in the DPP follow-up study (DPPOS) were associated with several changes in the trajectories of metabolic risk. First, type 2 diabetes development fell to ~5% per year in all 3 modified intervention groups. This suggests that the characteristics of the population as far as their type 2 diabetes risk is concerned was significantly altered after the first 3 years of the study, because type 2 diabetes incidence fell significantly or remained stable for the follow-up period, despite any weight change. Second, although studies of the long-term prevalence of the metabolic syndrome in DPPOS remain to be completed, tracking of metabolic syndrome components demonstrated substantial ongoing cardiometabolic risk improvement. More detailed studies will elucidate whether an alteration in the cardiometabolic status of the post-DPP population might parallel that seen for type 2 diabetes risk, as well as document the longer-term trajectories of cardiometabolic risk factors in relation to further deterioration of glucose tolerance and weight gain.

Undoubtedly, the increasing use of statin drugs and antihypertensive agents contributed significantly to these trends, although they were used less in the lifestyle group. In addition, similar, if less, robust improvements in lipids were noted in those who did not use lipid-lowering drugs, and some of the findings, such as the rather impressive increases in HDL-C, are unexplained. Ultimately, these findings will need to be evaluated in relation to CVD surrogates and finally clinical events. Meanwhile, the increased tendency to bring these individuals into the healthcare system and the medical vigilance they experience both within and outside the study protocol undoubtedly will influence the long-term results, and thus these findings may not be directly generalizable to the community. They nevertheless attest to what is possible in the field of type 2 diabetes prevention and the amelioration of associated cardiometabolic risk.

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Disclosures

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