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PHARMACOLOGIC TREATMENT OF TYPE 2 DIABETES (HE LEBOVITZ AND G BAHTIYAR, SECTION EDITORS)

Pharmacologic Randomized Clinical Trials in Prevention of Type 2 Diabetes

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Abstract

Purpose of Review There have been many randomized clinical trials testing lifestyle and drug interventions to prevent the development of type 2 diabetes in nondiabetic adults at high risk of the disease. We review the major trials using pharmacologic interventions with the primary outcome of preventing diabetes. The trials are grouped according to the main mechanism by which the drugs were thought to have the potential for preventing diabetes.

Recent Findings Drugs in several different classes have been effective in reducing the incidence of diabetes, but evidence for other long-term benefits, such as avoidance of complications and reducing mortality rates, is very limited.

Summary Both drugs and lifestyle interventions are effective in preventing and delaying the onset of type 2 diabetes in high-risk adults. The choices of what drugs to use and when during the development of type 2 diabetes to introduce them are not clear.

Keywords Type 2 diabetes · Pharmacologic prevention · Randomized clinical trials

Introduction

Type 2 diabetes (T2D) is considered at least to some extent preventable, based on many randomized clinical trials (RCTs) that have tested interventions in nondiabetic persons with impaired glucose tolerance (IGT) or other T2D risk factors with the goal of preventing or delaying the onset of diabetes. These trials have tested lifestyle and drug interventions; this paper reviews those using drugs. Both types of intervention studies have been reviewed in more detail elsewhere. Readers are referred to other reviews [1, 2] or to the original publications for more details on the studies summarized here.

This article is part of the Topical Collection on *Pharmacologic Treatment of Type 2 Diabetes*

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Most of the drugs used in these RCTs of T2D prevention were selected because of their known effects on the main physiologic risk factors for T2D: impaired insulin secretion, impaired insulin action, and obesity. The major T2D prevention clinical trials are summarized here, grouped by the main known physiologic effects of the drugs. This classification is inexact because of the connections among these physiologic abnormalities. For example, improved insulin action leads to less demand for insulin secretion. Reducing obesity usually also reduces insulin resistance. Any intervention that improves glycemia also tends to normalize insulin secretion because of glucotoxicity, i.e., hyperglycemia itself impairing beta cell function [3]. Despite these overlaps, we divide the drugs into seven categories: (1) insulin secretagogues, (2) enhancers of insulin action, (3) weight loss drugs, (4) incretin-based therapies (5) alpha glucosidase inhibitors, (6) the renin-angiotensin system blockers, and (7) vitamin D. The first three categories have obvious relationships to the development of T2D. The fourth, incretin-based therapies including GLP-1 agonists, stimulate insulin secretion, slow gastric emptying, suppress glucagon secretion, and induce weight loss. The fifth category, alpha glucosidase inhibitors, decreases post-prandial glucose absorption thereby limiting post-prandial hyperglycemia. The sixth category, renin-angiotensin system blockers, has less obvious connections to the pathophysiology leading to T2D but has been used in two major RCTs of diabetes

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prevention. The seventh, vitamin D, was based on epidemiologic associations of low serum vitamin D concentrations with risk of T2D.

Most RCTs for prevention included only persons with IGT, with or without obesity or elevated fasting plasma glucose. Therefore, the effectiveness of drug interventions in persons who do not have IGT has not been well studied.

The major RCTs are described below according to drug category and summarized in Table 1 [4–23, 24•, 25, 26]. Within drug category, studies are listed in chronological order. Incident diabetes was the primary outcome of most of the RCTs reviewed here. Several RCTs with other primary outcomes, such as cardiovascular disease (CVD), included diabetes as a secondary outcome, often in only a subset of participants. Not all such studies are included in this review.

Drugs Affecting Primarily Insulin Secretion

T2D is caused by a combination of inadequate insulin secretion and insulin resistance. Therefore stimulating insulin secretion might prevent progression of subdiabetic hyperglycemia to overt T2D. Drug-stimulating insulin secretion was limited to sulfonylureas until recently. The first was tolbutamide, a rapidly acting sulfonylurea approved for treatment of diabetes in Germany in 1956. Two RCTs of tolbutamide were started in the 1960s. They preceded current definitions of IGT and diabetes, so the terms used to describe these trials have slightly different definitions than those used today. Meglitinides, rapidly-acting insulin secretagogues, were approved in the USA in 1997.

The Bedford (UK) trial of tolbutamide In the Bedford study 241 adults with IGT were randomized to tolbutamide or placebo and to two dietary groups in a 2-by-2 factorial design [4]. During 10 years, 15% of subjects developed diabetes, but there were no significant effects of either the drug or diet interventions.

The Malmöhus (Sweden) trial of tolbutamide Tolbutamide was also tested in 147 men with IGT (defined by local criteria at the time) in Malmöhus County, Sweden. All study participants were given dietary advice and randomly assigned to tolbutamide, matching placebo, or neither. Tolbutamide was reported to prevent diabetes when the trial was analyzed by estimated drug adherence [5] but not when analyzed by intention-to-treat [6].

The availability of national vital statistics in Sweden enabled calculation of long-term mortality rates after the trial ended. The all-cause mortality rate ratio (drug compared with placebo or no drug) was 0.66 (95% confidence interval, (CI) = 0.39 to 1.10) and the ischemic heart disease mortality rate ratio was 0.42 (95% CI = 0.16 to1.12) [6]. While these effect estimates were imprecise in this small RCT, they were among the first to suggest health benefits of drug treatment of IGT beyond progression to diabetes.

The results of these early studies were inconclusive, largely owing to their small sample sizes. Further evidence for pharmacologic prevention of T2D was not produced until the 2000s.

The NAVIGATOR trial of nateglinide Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) was a 2-by-2 factorial 5-year RCT of the short-acting insulin secretagogue nateglinide of the meglitinide class [7] and the angiotensin receptor blocker valsartan [26] in 9306 participants with IGT, elevated fasting glucose, and CVD or CVD risk factors. Nateglinide did not affect diabetes incidence (hazard ratio, HR = 1.07, 95% CI = 1.00 to 1.15) and was associated with increased frequency of hypoglycemia and slightly greater weight. The valsartan results are summarized below in the section on renin-angiotensin blockers.

NAVIGATOR also evaluated treatment effects on CVD. Neither drug reduced the incidence of CVD events, thus giving no support to the hypothesis that reducing post-challenge (or postprandial) hyperglycemia with an insulin secretagogue prevents CVD.

Based on these RCTs, we conclude that tolbutamide and nateglinide, aimed primarily at enhancing insulin secretion, have limited promise for preventing or delaying T2D in high-risk adults.

Drugs Affecting Primarily Insulin Action

The biguanides phenformin and metformin have been used in diabetes prevention RCTs. Phenformin was the first drug tested for diabetes prevention, but because of its risk of lactic acidosis, it has been replaced by metformin.

The Whitehall (UK) Trial of Phenformin In the Whitehall study of 204 men with IGT (defined by local criteria used at the time), phenformin had no significant effect, compared with placebo, on the 5-year incidence of diabetes [8].

The Diabetes Prevention Program Trial of Metformin The USA Diabetes Prevention Program (DPP) was a large prevention RCT testing both a lifestyle and a drug intervention [9]. The trial enrolled 3234 nondiabetic adults with IGT, elevated fasting glucose, and overweight or obesity. Three interventions were randomly assigned: an intensive lifestyle modification program, metformin (850 mg twice a day), and placebo. Mean age at baseline was 51 years, mean BMI was 34 kg/m^2, and 45% represented USA minority groups at high risk of T2D. The lifestyle intervention and its effects are described elsewhere [9].

Table 1 Randomized controlled trials of drugs used for preventing type 2 diabetes

Physio-logic Target	Study, place, and primary reference	Year*	Number randomized (sum of all intervention groups)	Drug class	Drug and comparator(s)	Primary follow-up time	Report of outcomes other than diabetes
Insulin secretion	Bedford, UK [4]	1992	241	Sulfonylurea	Tolbutamide, placebo (in 2 × 2 factorial design with diet intervention)	10 years	no
	Malmöhus, Sweden [5, 6]	1980	147	Sulfonylurea	Tolbutamide, placebo, no drug		mortality
	NAVIGATOR‡ [7]	2010	9306	Meglitinide	Nateglinide, placebo (in 2 × 2 factorial design with valsartan)	5 years	CVD#
Insulin action	Whitehall, UK [8]	1979	204	Biguanide	Phenformin, placebo	5 years	no
	Diabetes Prevention Program‡, USA [9]	2002	3234	Biguanide	Metformin, lifestyle, placebo	2.8 years	Further diabetes, microvascular complications
	Diabetes Prevention Program‡, USA [10]	2005	585	Thiazolidinedione	Troglitazone, metformin, lifestyle, placebo	0.9 years	no
	TRIPOD, USA [11]	2002	266	Thiazolidinedione	Troglitazone, placebo	30 months	no
	Indian Diabetes Prevention Program, India [12]	2006	531	Biguanide	Metformin, placebo, lifestyle, placebo	3 years	no
	DREAM‡, International [13]	2006	5269	Thiazolidinedione	Rosiglitazone, placebo (in 2 × 2 factorial design with ramipril)	3 years	CVD and renal
	CANOE, Canada [14]	2010	207	Biguanide + thiazolidinedione	Metformin + rosiglitazone, placebo	4 years	no
	Actos, USA [15]	2011	602	Thiazolidinedione	Pioglitazone, placebo	2.4 years	CVD
Weight loss§	3 orlistat trials pooled, international [16]	2000	675	Lipase inhibitor	Orlistat, placebo	2 years	no
	Xendos, international [17]	2004	3305	Lipase inhibitor	Orlistat, placebo	4 years	no
	SEQUEL, international [18]	2012	475	Appetite suppressants	Phentermine + topiramide, placebo	2 years	no
GLP-1 agonists	SCALE, international [19, 20]	2017	2254	GLP-1 agonist	Liraglutide, placebo	3 years	no
Alpha gluco-sidease inhibitors	STOP NIDDM, international [21, 22]	2002	1429	Alpha glucosidase inhibitor	Acarbose, placebo	3.3 years	CVD
	Voglibose trial in Japan [23]	2009	1780	Alpha glucosidase inhibitor	Voglibose, placebo	48 weeks	no
	Acarbose Cardiovascular Evaluation, China [24•]	2017	6522	Alpha glucosidase inhibitor	Acarbose, placebo	5 years	CVD
Renin-angiotensin system blockers	DREAM‡, international [25]	2006	5269	Angiotensin converting enzyme inhibitor	Ramipril, placebo (in 2 × 2 factorial design with rosiglitazone)	3 years	CVD and renal
	NAVIGATOR [26]	2010	9306	Angiotensin receptor blocker	Valsartan, placebo (in 2 × 2 factorial design with nateglinide)	5 years	CVD

The table gives only brief descriptions of the trials. Because results are presented with different measures and different time frames among the trials, they are not always directly comparable and are therefore not included in the table, but they are summarized in the text description of each trial

*Year of first publication of primary results

‡This trial appears in two places in the table because two different drugs were used

CVD is cardiovascular disease

§Some drugs are listed in other categories but may also cause weight loss (e.g., metformin, liraglutide)

The initial phase of the trial was stopped in prematurely in 2001 because of the clear benefits of both interventions on development of diabetes. The metformin group had a 31% lower diabetes incidence, compared with placebo, during the mean follow-up of 2.8 years (HR = 0.69, 95% CI = 0.57 to 0.83) and a weight loss of 1.7 kg, compared with a 0.3 kg gain in the placebo group. Metformin treatment was associated with weight loss and improved estimated insulin sensitivity, which contributed to much of its diabetes prevention effect [27, 28], and was more effective among women reporting a history of gestational diabetes [29].

When the primary results were announced in 2001, study participants were unmasked to their treatments and the study findings, and they were invited to enroll in the long-term follow-up study—the Diabetes Prevention Program Outcomes Study (DPPOS) [30]. Because of the beneficial effects of both the lifestyle and metformin interventions, all participants were offered a group-implemented lifestyle intervention, metformin was continued in the group originally randomized to it, and placebo was discontinued. At an average of 15 years after randomization, DPPOS participants were assessed for retinopathy, nephropathy, and neuropathy, which did not differ significantly among the original metformin and placebo groups [31]. The estimated costs of medical care outside of the study were lower in the metformin than in the placebo group, a saving that exceeded the estimated cost of delivering the metformin intervention [32]. Because health care costs reflect a broader range of health problems than an assessment of complications at a single time point, this cost-effectiveness analysis provides evidence for long-term health and economic benefits of the metformin intervention.

The Diabetes Prevention Program Trial of Troglitazone Initially, the DPP had a fourth intervention arm, in addition to the placebo, metformin, or lifestyle intervention arms. The thiazolidenedione drug troglitazone was randomly assigned to 585 participants [10]. This study arm was terminated prematurely because of the potential for hepatic toxicity. Troglitazone was used for an average of 0.9 years in DPP, during which time it reduced the incidence of diabetes by 75% compared with placebo. This was a greater incidence rate reduction than achieved by the metformin or lifestyle interventions among the subset of participants randomized during the same time. This follow-up time was too short, however, to suggest whether this dramatic effect would have persisted long-term.

The TRIPOD trial of troglitazone Troglitazone in Prevention of Diabetes (TRIPOD) enrolled 266 nondiabetic Hispanic women with previous gestational diabetes, about 70% of whom had IGT. They were randomized to troglitazone or placebo. As in the DPP, the drug was discontinued before planned study-end because of the potential for liver toxicity. Troglitazone reduced the development of diabetes by 55% over 2.5 years [11].

The Indian Diabetes Prevention Program Trial of Metformin The design of the Indian Diabetes Prevention Program was similar to that of the USA DPP except for inclusion of a combined lifestyle and metformin intervention group in addition to lifestyle only, metformin only, and placebo groups [12]. It enrolled 531 Asian Indians with IGT. The metformin dose (250 to 500 mg twice per day) was substantially lower than the dose of 850 mg twice per day used in the DPP. During an average follow-up of 30 months, the 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). Thus, both the lifestyle and metformin interventions reduced diabetes incidence, but their combination produced no additional risk reduction. The risk reductions were lower than in the DPP, perhaps because the interventions were less intense.

The DREAM Trial of Rosiglitazone Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) tested ramipril and rosiglitazone in a 2-by-2 factorial design in 5269 participants with elevated fasting glucose, IGT, or both [13, 25]. Rosiglitazone is in the same thiazolidinedione class as troglitazone which, in previous RCTs, led to substantial reductions in diabetes incidence rates, as described above. The incidence of diabetes was reduced by 62% by rosiglitazone 8 mg/day (HR = 0.38, 95% CI = 0.33 to 0.44), and 50% of rosiglitazone-treated patients reverted to normoglycemia, compared with 30% of placebo-treated patients. The ramipril treatment arm is described below in the section on renin-angiotensin system inhibitors. 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. Side effects of rosiglitazone included weight gain, edema, and higher incidence of the rare outcome of congestive heart failure [13].

The CANOE Trial of the Combination of Rosiglitazone and Metformin The Canadian Normoglycemia Outcomes Evaluation (CANOE) tested a combination of two drugs affecting insulin action. Submaximal doses of metformin (500 mg twice daily) and rosiglitazone (2 mg twice daily) were compared with placebo in 207 persons with IGT [14]. During 3.9 years, the 2-drug treatment resulted in a relative risk reduction for diabetes of 66% (95% CI = 41 to 80). This combination therapy was effective and well tolerated, showing the value of drug combinations in preventing T2D.

The ACT NOW Trial of Pioglitazone Another thiazolidinedione drug, pioglitazone, was tested in ACT NOW, an RCT in 602 with IGT [15]. Participants were randomized to pioglitazone 30 mg per day or placebo and followed for 2.4 years. The study was completed by only 70% of the pioglitazone group

and 76% of the placebo group. Pioglitazone led to a 72% reduction in diabetes incidence compared with placebo (HR = 0.28, 95% CI = 0.16 to 0.49). This study replicated the large effects of the thiazolidinedione drugs troglitazone and rosiglitazone on reducing diabetes incidence but having adverse effects on weight gain and edema.

Drugs Affecting Primarily Body Weight

Overweight and obesity are major risk factors for T2D, suggesting that drugs that reduce weight, but do not have known direct effects on insulin secretion or action, might be effective in preventing T2D.

Orlistat Several RCTs have been performed in obese adults using the weight-loss drug orlistat, an intestinal lipase inhibitor. Three such trials were presented in a pooled analysis [16]. Orlistat was reported to reduce 2-year cumulative diabetes incidence by 61% compared with placebo among those with IGT at randomization. Only 69% of the subjects, however, completed the 2-year study. The high drop-out rate, presumably due to side effects, complicates interpretation of these results.

In a 4-year RCT of orlistat, diabetes incidence was reduced by 37% [17]. Similarly to the other orlistat trials, interpretation and generalizability of this trial was limited by the low percentages (52% of orlistat and 24% of placebo participants) completing the trial.

The SEQUEL Secondary Analysis of a Study of Phentermine-Topiramate for Weight Loss SEQUEL was a follow-up study of CONQUER, a weight loss RCT of phentermine and topiramate combinations compared with placebo for weight loss [18]. SEQUEL included a subset of centers and participants in CONQUER with additional follow-up for diabetes incidence. Diabetes incidence was lower in the active treatment groups compared with placebo, and the diabetes risk reduction was associated with the amount of weight loss. It is not clear how the SEQUEL subset represents all those randomized in the original RCT, and loss to follow-up was not well described, complicating interpretation of the results.

Incretin-Based Therapies

Liraglutide, a GLP-1 agonist, was evaluated in a 56-week RCT of 3731 nondiabetic adults with obesity [19]. The study was extended for 2 additional years in those participants with "prediabetes" by American Diabetes Association criteria [33]. The diabetes incidence rate was reduced by liraglutide 3 mg/day by 79% (HR = 0.21, 95% CI = 0.13 to 0.34) in this subgroup, but 50% of the participants were lost to follow-up [20]. After imputation of missing data, the diabetes incidence rate was estimated to be reduced by 66% (HR = 0.34, 95% CI = 0.22 to 0.53). The liraglutide group had substantially greater weight loss (− 6.1 kg vs. − 1.9 kg in liraglutide and placebo respectively) at study completion.

Liraglutide, in the setting of a weight loss RCT, appeared to be much more effective than the insulin secretagogues tolbutamide or nateglinide, but its interpretation is limited by the high rate of loss to follow-up. It is not known how much of this effect was due to its many physiologic effects, including stimulating insulin secretion, slowing gastric emptying, suppressing glucagon secretion, and inducing weight loss.

Short-term studies of the GLP-1 agonist exenatide [34] and the DPP-4 inhibitor vildagliptin [35] in individuals with "prediabetes" reported improvements in glucose tolerance but were too brief and small to assess prevention of diabetes. The authors of a Cochrane systematic review concluded that the clinical trials of DPP-4 inhibitors were not sufficiently large or long enough to provide firm evidence on their effects on risk of T2D [36].

Alpha Glucosidase Inhibitors

Alpha glucosidase inhibitors have no known direct effects on insulin secretion or action, but lower post-prandial hyperglycemia by slowing glucose absorption from the gut. They have been tested for diabetes prevention under the hypothesis that dampening post-prandial glucose excursions in persons with IGT may help preserve insulin secretion or action, thus preventing incident T2D.

The STOP-NIDDM Trial of Acarbose This RCT tested acarbose, an alpha glucosidase inhibitor, in high risk adults. It included 1429 subjects with IGT and elevated fasting glucose who were randomized to acarbose or placebo [21]. Over a 3.3-year follow-up period, acarbose led to a 25% reduction in the incidence of diabetes. Weight loss contributed to this effect. Thirty-one percent of the acarbose group did not complete the study; the drop-out rate was attributed to gastrointestinal side effects (flatulence, diarrhea, and abdominal cramps) that may limit its applicability for diabetes prevention in general practice.

STOP-NIDDM also studied treatment effects beyond the development of diabetes. Compared with placebo, the acarbose arm had a lower incidence of CVD events (although based on few cases) [22], slower progression of carotid intimal thickness [37], and more favorable levels of several CVD risk factors [22], suggesting that acarbose may be effective not only for preventing T2D but also CVD.

The Japanese Trial of Voglibose Voglibose, another alpha glucosidase inhibitor, was studied in an RCT in Japanese adults with IGT [23]. The diabetes outcome was defined by a combination of HbA_{1c} and plasma glucose concentrations. The study was terminated after approximately 1 year because of

efficacy, with voglibose reducing diabetes incidence by 40% (HR = 0.60, 95% CI = 0.43 to 0.82). Drug acceptance in this trial was greater than with acarbose in STOP-NIDDM, with 86% of the voglibose group and 83% of the placebo group completing the trial. Because of the trial's short duration, long-term acceptance and efficacy of voglibose for diabetes prevention remain uncertain.

The Chinese Acarbose Cardiovascular Evaluation (ACE) Trial This trial enrolled 6522 Chinese adults with IGT and coronary heart disease in a trial of acarbose versus placebo [24•]. The incidence of diabetes was reduced by 18% (HR 0.82, 95% CI 0.71 to 0.94) over 5 years, but, similar to other studies of acarbose, approximately half of the participants in each treatment group permanently discontinued study medication. There were no significant treatment effects on the primary outcome of CVD. Therefore, the hypothesis from the much smaller STOP-NIDDM trial that acarbose would prevent CVD was not supported.

Renin-Angiotensin System Blockers

Blockage of the renin-angiotensin system was tested in two RCTs—one testing angiotensin-converting-enzyme inhibitor ramipril and the other one testing the angiotensin receptor blocker valsartan.

The DREAM trial and its rosiglitazone arm are described above in the section on drugs primarily affecting insulin action. Ramipril was chosen as the second active treatment in this 2-by-2 factorial trial based on a secondary analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial of ramipril. In HOPE, ramipril reduced the incidence of self-reported diabetes, leading the investigators to plan another RCT of ramipril with diabetes incidence as a primary outcome [38]. By contrast with HOPE, ramipril had no significant effect on diabetes incidence in DREAM (HR = 0.91, 95% CI = 0.80 to 1.03) [25].

NAVIGATOR, a 2 × 2 factorial trial of nateglinide and valsartan, is described above in the section on drugs increasing insulin secretion. Valsartan was associated with a small reduction in diabetes incidence compared with placebo (HR = 0.86, 95% CI = 0.80 to 0.92). There was no significant interaction between the effects of the two drugs. About 80% of the participants completed the trial [26].

Vitamin D

Low serum concentrations of 25-hydroxyvitamin D are associated with incidence of T2D in epidemiologic studies, leading to the hypothesis that treatment with oral vitamin D_3 would reduce the incidence of T2D in nondiabetic persons at high risk of T2D. This was tested in an RCT of 2423 adults meeting American Diabetes Association criteria for "prediabetes" who were randomized to treatment with 4000 IU vitamin D_3 or placebo [39•]. Participants were not selected based on serum 25-hydroxyvitamin D concentration, although this concentration was measured. There was no significant effect of the treatment on overall diabetes incidence (HR = 0.88, 95% CI = 0.75 to 1.04). In a post-hoc analysis of the 103 participants who were vitamin D deficient at baseline (< 12 mg/ml), the treatment was effective (HR = 0.38, 95% CI = 0.18 to 0.80). Thus, this vitamin supplementation had no significant effect on diabetes incidence in the larger population but was effective in those who were deficient who also warrant supplementation for other reasons.

Conclusions

Comparison of drug classes

Despite the dual defects in insulin secretion and action that cause T2D, drugs affecting insulin action have been much more effective in RCTs. Does this suggest that insulin resistance is more important than impaired insulin secretion or just that we have more effective drugs for insulin action? Use of insulin secretagogues is limited in that excessive doses can cause hypoglycemia. This may explain why higher, potentially more effective, doses have not been used in prevention studies. Other classes of drugs, except for the GLP-1 agonist liraglutide, have shown no effect or less effect than drugs affecting insulin action. One might hypothesize that combinations of drugs improving both insulin secretion and action might be synergistic while having tolerable side effects, but as far as we are aware, this has not been tested.

Several newer drugs (SGLT2i and GLP-1 agonists) have recently been shown to improve glycemic control and reduce the incidence of vascular complications or death in adults with established T2D [40–44]. With the exception of liraglutide, these drugs have not, to our knowledge, been evaluated for T2D prevention. They may not be, given the time and expense required for RCTs of diabetes prevention, especially since new drugs should be compared with those already shown to reduce T2D incidence.

This review does not discuss lifestyle modification that is generally recommended as the primary intervention for T2D prevention and is discussed in detail elsewhere [1, 2]. We are aware of only two RCTs that compared a drug (metformin) and lifestyle intervention with each other. In one, they were equally effective [12], and in the other, the lifestyle intervention was more effective over 3 years [9]. For individuals initially prescribed lifestyle change for diabetes prevention, the appropriate indication to add a drug (i.e., failure to lose weight or progression of sub-diabetic hyperglycemia) has not been studied.

Limited Evidence for Long-Term Benefits

A major limitation of all the RCTs reviewed here is the limited evidence of long-term benefits on microvascular complications [31] or heart disease [7, 13, 24•, 25, 26]. Hints from earlier, smaller RCTs that treating IGT could prevent CVD [6, 22] have not been confirmed. This lack of evidence for benefit beyond preventing hyperglycemia from progressing to diabetes diagnostic levels must also be taken into consideration along with drug safety, a special concern for thiazolidinediones that have been reported to be associated with CVD, cancer, edema, and weight gain (reviewed in [1]). Pioglitazone, however, was reported to prevent CVD, cerebrovascular disease, and diabetes in insulin resistant persons with a recent stroke or transient ischemic attack [45, 46]. Whether the reported CVD and renal benefits of GLP-1 agonists and SGLT2 inhibitors in established diabetes would also apply to people with "prediabetes", (who presumably have lower CVD risk), is not known. In a recent review, we concluded that there was some evidence that lifestyle interventions to prevent T2D also reduced the incidence of vascular complications, but such evidence was lacking for pharmacologic interventions for diabetes prevention [47].

To Whom Should Drug Prevention Be Offered?

If drugs are considered in addition to or instead of lifestyle intervention, what characteristics would identify people most likely to benefit? The different RCTs differed in eligibility criteria, but all included some definition of IGT and most required overweight or obesity. In the USA DPP, effects on T2D prevention varied with entry characteristics. In general, those with highest levels of T2D risk factors had the greatest reductions in T2D incidence, especially when expressed on an absolute, rather than risk ratio, scale [48••]. The relatively new field of pharmacogenetic research in T2D prevention may also lead to selection of treatment candidates or drugs according to genotype.

The therapeutic dilemma

Despite the evidence that several drugs can prevent or delay the onset of T2D in high risk adults, none is approved for this purpose in the USA. We suggest there are two major reasons for this lack of approved indication: (1) metformin and several of the other drugs discussed lack patent protection that would provide a financial incentive for the manufacturer to seek approval, and (2) there is limited evidence that use of these drugs for diabetes prevention prevents vascular complications or mortality or has other long-term benefits. Of 17,352 adults in a health insurance plan in 2010–2012 who might be candidates for diabetes prevention, only an estimated 3.7% were prescribed metformin [49]. In the USA National Health Interview Survey of 2016–2017, an estimated 14.5% of adults with elevated body mass index and diagnosed "prediabetes" reported taking oral medication to lower glucose concentrations [50]. The American Diabetes Association, however, recommends that "metformin therapy for prevention of T2D should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior gestational diabetes mellitus" [51]. Even if a drug is prescribed for T2D prevention, the prescriber must choose between a tried-and-true old drug such as metformin or a newer, possibly more effective, drug that has not been tested for diabetes prevention or for which the long-term balance of benefits and harms is unknown.

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Compliance with Ethical Standards

Conflict of Interest William C. Knowler reports that he is a collaborator and co-author for some of the studies described in this review.

Jill P. Crandall reports that she is a collaborator and co-author on one of the studies included in this review.

Human and Animal Rights and Informed Consent This article reviews human studies, some of which were performed by the authors. However, there was no interaction with human subjects in writing this article, which is based entirely on previously published material.

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- • Of importance
- •• Of major importance

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