A Systematic Review of Drug Therapy to Delay or Prevent Type 2 Diabetes

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OBJECTIVE — To systematically review the evidence for the prevention of type 2 diabetes by pharmacological therapies.

RESEARCH DESIGN AND METHODS — Randomized controlled trials and cohort studies examining the effect of oral hypoglycemic agents, antiobesity agents, antihypertensive agents, statins, fibrates, and estrogen on the incidence of type 2 diabetes were identified from MEDLINE, EMBASE, the Cochrane Controlled Trials Registry, and searches of reference lists. Two reviewers independently assessed studies for inclusion and performed data extraction.

RESULTS — Ten studies of oral hypoglycemic agents and 15 studies of nonoral hypoglycemic agents were found. Oral hypoglycemic agents and orlistat are the only drugs that have been studied in randomized controlled trials with diabetes incidence as the primary end point. In the largest studies of 2.5–4.0 years' duration, metformin (relative risk [RR] 0.69, 95% CI 0.57–0.83), acarbose (0.75, 0.63–0.90), troglitazone (0.45, 0.25–0.83), and orlistat (hazard ratio [HR] 0.63, 95% CI 0.46–0.86) have all been shown to decrease diabetes incidence compared with placebo; however, follow-up rates varied from 43 to 96%. Current evidence for statins, fibrates, antihypertensive agents, and estrogen is inconclusive. In addition, the critical question of whether drugs are preventing, or simply delaying, onset of diabetes remains unresolved.

CONCLUSIONS — Currently, no single agent can be definitively recommended for diabetes prevention. Future studies should be designed with diabetes incidence as the primary outcome and should be of sufficient duration to differentiate between genuine diabetes prevention as opposed to simple delay or masking of this condition.

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Diabetes currently affects an estimated 171 million individuals worldwide (1). In the U.S. alone, diabetes is the fifth leading cause of death and was responsible for an estimated $132 billion in direct and indirect costs in 2002 (2). With a projected doubling of the number of global cases of diabetes by 2030 (1), the development of effective diabetes prevention strategies is of paramount importance.

Recent studies have shown that intensive lifestyle interventions, primarily in patients with impaired glucose tolerance (IGT), may decrease the incidence of type 2 diabetes by up to 58% (3,4). Lifestyle modification may be considered an ideal method of diabetes prevention because of beneficial effects on the entire cardiovascular risk profile as well as noncardiovascular benefits related to weight loss and an improved diet (5–7). However, long-term adherence to such interventions (8) and feasibility in a nontrial setting remain potentially limiting factors to widespread implementation.

Pharmacological therapy to prevent type 2 diabetes may be an important therapeutic modality in those patients in whom lifestyle interventions fail, are not sufficiently potent, or are not feasible. A number of different drug classes have been previously studied (9,10). An important distinction is whether such agents prevent or simply delay the diagnosis of diabetes. It is unclear whether a short-term delay in the biochemical diagnosis of diabetes is a useful surrogate end point and whether the effects of drug therapy are sustained, cost-effective, and free of serious adverse effects. We conducted this systematic review to evaluate the current evidence for the prevention of type 2 diabetes by pharmacological therapies.

RESEARCH DESIGN AND METHODS

— Detailed search strategies were designed to detect randomized controlled trials (RCTs) and cohort studies examining the effects of drug therapy on the subsequent incidence of type 2 diabetes. We searched the Cochrane Controlled Trials Registry (first quarter, 2004), MEDLINE (1966 to June, week 3, 2004), and EMBASE (1980 to week 26, 2004). Reference lists of original studies and narrative reviews were also searched manually. The search was not limited by language and is considered up-to-date as of 1 June 2004.

Studies were included if they reported, or provided sufficient data to calculate, type 2 diabetes incidence using an intention-to-treat analysis. In studies with multiple interventions, only the results of drug intervention arms compared with a placebo or control group were included.

A medical librarian (J.V.) performed the initial search with input from the other authors. The search was limited to adult patients (aged >18 years) with a minimum study sample size of 50 patients. In addition to a general drug search, a specific search for the following agents was performed: sulfonylureas, metformin, phenformin, acarbose, thiazolidinediones, insulin, hydroxymethylglutaryl (HMG)-CoA reductase inhibitors

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Abbreviations: DPP, Diabetes Prevention Program; IGT, impaired glucose tolerance; RCT, randomized controlled trial; STOP-NIDDM, Study To Prevent Noninsulin-Dependent Diabetes Mellitus.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

(hereafter, referred to as "statins"), estrogen, phentermine, orlistat, sibutramine, ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, and α-blockers. Articles were excluded if the intervention was tested in patients with preexisting diabetes, the sample size was <50 patients, the citation was a review or duplicate article, and if the study was published only in abstract form. A detailed systematic review of antihypertensive drugs and type 2 diabetes incidence (current through August 2003) has recently been published, and this review was updated by including studies published after August 2003 (11).

Two reviewers (R.P. and S.R.M.) independently examined abstracts of the remaining studies for potential inclusion and performed data extraction. Cohen's κ coefficients were calculated to assess interobserver agreement for study inclusion and data extraction. Disagreements were resolved by consensus.

A priori, we decided that quantitative meta-analyses of data would not be possible due to substantial between-study differences in end point definitions, patient populations, and interventions.

RESULTS — Of the 5,511 initial citations, 5,222 were potentially relevant upon initial screening (online appendix [available at http://care.diabetesjournals.org]). Of these, 4,247 citations involved prevalent cases of type 2 diabetes and were excluded. After screening the titles and abstracts of the remaining 975 citations, 36 full-text articles were reviewed and 10 articles met inclusion criteria. An additional 15 articles were identified through manual searches and review of the reference lists of all included reports.

Interobserver agreement was 1.0 for study inclusion and 0.91 for data extraction.

Oral hypoglycemic agents

Ten studies, including eight RCTs, examined the effect of oral hypoglycemic agents on diabetes incidence (Table 1).

Biguanides. The largest and most methodologically rigorous trial was the Diabetes Prevention Program (DPP), which randomized 2,155 individuals with IGT to metformin or placebo (4). After a mean follow-up period of 2.8 years, the incidence of diabetes was 7.8% in the placebo-treated patients versus 4.8% in those treated with metformin (relative risk [RR] 0.69, 95% CI 0.57–0.83); metformin was also associated with a 2.0-kg (95% CI 0.8–3.2) weight reduction compared with placebo. In post hoc subgroup analyses, the benefits of metformin were primarily observed in patients <60 years of age (RR 0.66, 95% CI 0.40–0.79 for patients 25–44 years old) and patients with a BMI ≥35 kg/m^2 (0.47, 0.35–0.63).

After metformin was discontinued at the end of the DPP study, patients were observed for a 1- to 2-week washout period, and the number of new cases of diabetes was ascertained (12). In the 79% of eligible patients who completed a washout visit, the incidence of diabetes increased from 25.2 to 30.6% in the metformin group and from 33.4 to 36.7% in the placebo group. When results of the washout period were included in the overall analysis, metformin still significantly decreased diabetes incidence (RR 0.75, 95% CI 0.62–0.92).

The remaining biguanide studies found no significant reduction in the incidence of diabetes compared with placebo using intention-to-treat analyses (13–17). All of these studies had very low diabetes incidence rates and were likely underpowered.

Acarbose. Acarbose was studied in one RCT and one cohort study (13,17). In the Study To Prevent Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, the incidence of diabetes was 32% in the acarbose group and 42% in the placebo group (RR 0.75, 95% CI 0.63–0.90) during 39 months of observation (17). Nearly 25% of individuals discontinued therapy early, predominantly due to acarbose-induced gastrointestinal toxicity. At study end, 60% of eligible patients were observed for a 3-month washout period, during which 15% of acarbose-treated patients developed diabetes compared with 10.5% of placebo-treated patients. In a secondary analysis, acarbose reduced cardiovascular events from 4.7 to 2.1% (hazard ratio [HR] 0.51, 95% CI 0.28–0.95) (18).

Sulfonylureas. Two studies examined the effect of tolbutamide therapy on diabetes incidence in patients with IGT or high-normal/elevated fasting glucose levels (19,20). Neither study reported a statistically significant decrease in the type 2 diabetes incidence compared with control or placebo, although both studies were small and potentially underpowered (Table 1).

Thiazolidinediones. While the Troglitazone Prevention of Diabetes (TRIPOD) study reported a reduction in the incidence of type 2 diabetes from 45 to 20% (RR 0.45, 95% CI 0.25–0.83) with troglitazone (associated with a nonsignificant weight gain compared with placebo of 0.3 kg [95% CI 0.8–1.4]), the nearly 33% attrition rate during follow-up is a major limitation (21). Eight months postdrug discontinuation, type 2 diabetes incidence was assessed in approximately one-half of eligible patients, with one patient (2%) in the troglitazone arm and six patients (15%) in the placebo group developing diabetes.

One additional small cohort study found a significant reduction in diabetes incidence with thiazolidinedione therapy (Table 1) (22).

Antiobesity agents

While orlistat reduced the incidence of type 2 diabetes from 9 to 6% (RR 0.63, 95% CI 0.46–0.86) and weight by 2.8 kg (95% CI 1.1–4.5) compared with placebo in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study, the attrition rate was 57% (Table 2) (23). Ninety-one percent of orlistat-treated patients experienced gastrointestinal side effects in the first year of therapy compared with 65% of the placebo arm.

A pooled analysis of three RCTs enrolling 642 obese patients reported a nonsignificant reduction in the incidence of type 2 diabetes from 2 to 0.6% with orlistat therapy (RR 0.25, 95% CI 0.05–1.2) (24). The CIs were wide, reflecting the low absolute incidence of diabetes within these trials, and attrition rates averaged >30%.

Antihypertensive drugs

A recently published systematic review of 24 studies involving antihypertensive drugs found that diabetes incidence is unchanged or increased by thiazide diuretics and β-blockers and unchanged or decreased by ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers (11). Six placebo-controlled trials were included in this review. Thiazide diuretic–based treatment regimens were associated with non–statistically significant increases in the incidence of type 2 diabetes from 7.5 to 8.6% in the Systolic Hypertension in the Elderly Program (SHEP) trial (RR 1.2, 95% CI 0.9–1.5) and from 4.7 to7% in the European

Table 1—*Studies of oral hypoglycemic agents to reduce type 2 diabetes incidence*

Study (locale)	Population* (mean age or age range)	Definition of type 2 diabetes	Comparison and daily dose (sample size; incidence of type 2 diabetes)	RR (95% CI)	Follow-up (years/rate†)
RCTs					
Diabetes Prevention Program (U.S.) (4)	2,155 patients with IGT and a FPG level of 5.3–6.9 mmol/l (>25 years)	FPG ≥7 mmol/l or 2-h OGTT glucose level ≥11.1 mmol/l. Positive result confirmed with repeat testing	Metformin 1,700 mg (1,073; 22%) vs. placebo (1,082; 29%)	0.69 (0.57–0.83)	2.8/93%
Li et al. (China) (14)	90 patients with IGT (30–60 years)	Postmeal or post-OGTT glucose level ≥11.1 mmol/L	Metformin 750 mg (42; 7%) vs. placebo: (43; 14%)	0.51 (0.14–1.9)‡	1.0/94%
BIGPRO (France) (15)	457 patients with a high waist-to-hip ratio (50 years)	Self-reported or FPG ≥7.8 mmol/l	Metformin 1,700 mg (227; 0%) vs. placebo (230; 2%). Only five cases of type 2 diabetes in the placebo group.	Unable to calculate	1.0/71%
Jarrett et al. (England) (16)	204 men with IGT from the Whitehall Survey (56 years)	2 successive or 3 nonsuccessive 2-h postglucose levels >11.1 mmol/l or a 2-h post-OGTT level of >11.1 mmol/l at year 5 or symptoms/signs	Phenformin 50 mg (92; 14%) vs. placebo (89; 16%)	0.90 (0.45–1.80)‡	5.0/89%
STOP-NIDDM (Canada and Europe) (17)	1,429 patients with IGT and a FPG level of 5.6–7.7 mmol/l (40–70 years)	2-h OGTT glucose level ≥11.1 mmol/l	Acarbose 300 mg (682; 32%) vs. placebo (686; 42%)	0.75 (0.63–0.90)	3.3/96%
TRIPOD (U.S.) (21)	266 Hispanic women with gestational diabetes (35 years)	Symptoms plus a random glucose level ≥11.1 mmol/l or FPG ≥7.0 mmol/l or a 2-h OGTT level of ≥11.1 mmol/l	Troglitazone 400 mg (114; 20%) vs. placebo (122; 45%)	0.45 (0.25–0.83)	2.5/67%
Sartor et al. (Sweden) (19)	97 men with glucose intolerance (43 years)	3-h OGTT test with 10 capillary glucose readings. All readings had to be 3 SDs above the mean to diagnose diabetes.	Tolbutamide 1,500 mg (49; 10%) vs. placebo (48; 12.5%)	0.82 (0.27–2.5)‡	9–10/100%
Keen et al. (U.K.) (20)	248 patients with IGT from the Bedford Diabetes Survey (57 years)	2 successive or 3 nonsuccessive 2-h postglucose levels >11.1 mmol/l or a 2-h post-OGTT level of >11.1 mmol/l plus symptoms/signs	Tolbutamide 1,000 mg (123; 11%) vs. placebo (125; 9%)	1.20 (0.56–2.6)‡	7.0/not specified
Cohort studies					
Yang et al. (China) (13)	261 patients with IGT (> 25 years)	Not specified	Metformin 750 mg (81; 4.1%) vs. control (83; 11.6%) Acarbose 150 mg (83; 2%) vs. control (83; 11.6%)	0.31 (0.09–1.1)‡ 0.20 (0.05–0.89)‡	3.0/95%
Durbin (22)	172 patients with IGT (29–86 years) with a FPG level of 5.6–7.0 mmol/l and a 2-h postprandial glucose level between 7.8 mmol/l and 11.1 mmol/l	Not stated	Troglitazone 400 mg daily then rosiglitazone 4 mg daily or pioglitazone 30 mg daily (101; 3.0%) vs. untreated comparison group (71; 26%)	0.11 (0.03–0.36)	3.0/100%

*Excluding patients with type 2 diabetes at baseline. †Refers to the percentage of patients with complete follow-up. ‡RR and CI, calculated from the data presented using intention-to-treat analysis. FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

Working Party on High Blood Pressure in the Elderly (EWHPE) trial (1.5, 0.85–1.6) (25,26). ACE inhibitor therapy lowered diabetes incidence in the Heart Outcomes Prevention Evaluation (HOPE) trial from 5.4 to 3.6% (0.66, 0.51–0.85) and from 22 to 6% in a small group of patients with heart failure (0.26, 0.13–0.53) (27,28). Angiotensin receptor blocker therapy significantly decreased diabetes incidence in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Mor-

Table 2—*Studies of other agents and type 2 diabetes incidence*

Study (locale)	Population* (mean age or age range)	Definition of type 2 diabetes	Comparison and daily dose (sample size; incidence of type 2 diabetes)	RR (95% CI)	Follow-up (years/rate†)
Antiobesity Agent—RCTs					
XENDOS (Sweden) (23)	3,305 obese patients (30–60 years)	2-h OGTT whole-blood glucose level of ≥10 mmol/L. Repeated or confirmed by a whole-blood FPG ≥6.7 mmol/l	Orlistat 360 mg (1,640; 6%) vs. placebo (1,637; 9%)	HR 0.63 (0.46–0.86)	4.0/43%
Heymsfield et al. (U.S. and Europe) (24)	642 obese patients (mean age 44 years). Pooled analysis of three RCTs.	2-h OGTT level >11.1 mmol/l	Orlistat 360 mg (340; 0.6%) vs. placebo (302; 2%)	0.25 (0.05–1.2)‡	2.0/69%
Antihypertensive agents—RCTs					
INVEST (North America, Europe, and Central America) (31)	6,176 patients with hypertension and CAD (≥50 years)	Not specified	Verapamil-based therapy (8,098; 7.0%) vs. Atenolol-based therapy (8,078; 8.2%) Trandolapril and hydrocholorthiazide were second-line agents.	0.85 (0.77–0.95)	2.7/97.5%
VALUE (U.S. and 31 other countries) (32)	10,419 hypertensive patients at high cardiovascular risk (≥50 years)	FPG ≥7.8 mmol/l	Valsartan-based therapy (5,267; 13%) vs. Amlodipine-based therapy (5,152; 16%)	OR 0.77 (0.69–0.86)	4.2/99%
Statins—post hoc analysis of RCTs					
WOSCOPS (Scotland) (33)	6,447 men with dyslipidemia and no prior CAD (45–64 years)	Two FPG ≥7.8 mmol/l and level at least 2.0 mmol/l or more above baseline	Pravastatin 40 mg (2,999) vs. placebo (2,975)	0.70 (0.50–0.99)	4.9/93%
Heart Protection Study (U.K.) (34)	14,573 patients at high cardiovascular risk (40–80 years)	Physician reported or new prescription for antidiabetes medication	Simvastatin 40 mg (7,283; 4.6%) vs. placebo (7,325; 4.0%)	1.15 (0.99–1.34)‡	5.0/100%
LIPID (Australia and New Zealand) (35)	6,997 patients with dyslipidemia (31–75 years)	FPG level 7.0 mmol/l or prescription of antidiabetes medication	Pravastatin 40 mg (3,150; 4.0%) vs. placebo (3,067; 4.5%)	0.89 (0.70–1.13)‡	6.0/100%
ASCOT-LLA (U.K. and Scandinavia) (36)	7,773 hypertensive patients at high cardiovascular risk (40–79 years)	FPG ≥7.0 mmol/l or 2-h OGTT glucose level ≥11.1 mmol/l or two RPG levels ≥11.1 mmol/l with clinical evidence of diabetes	Atorvastatin 10 mg (3,910; 3.0%) vs. placebo (3,863; 2.6%)	1.15 (0.91–1.44)	3.3/99%
Fibrates—post hoc analysis of RCT					
BIP (Israel) (37)	303 patients with IGT from the Bezafibrate Infarction Prevention Trial	FPG level ≥7.0 mmol/l	Bezafibrate 400 mg (156; 42%) vs. placebo (147; 54%)	HR 0.70 (0.49–0.99)	6.2/100%
Estrogen replacement therapy—post hoc analysis of RCT					
HERS (U.S) (38)	2,029 postmenopausal Caucasian women with CAD (<80 years)	FPG ≥6.9 mmol/l or self-reported or used of antidiabetic agent or development of diabetes complications	Estrogen 0.625 mg/medroxyprogesterone. 2.5 mg (999; 6.2%) vs. placebo (1,030; 9.5%)	0.65 (0.48–0.89)	4.1/98%
Estrogen replacement therapy—cohort studies					
Rossi et al. (Italy) (40)	673 healthy, nonobese postmenopausal women (mean age 54 years)	Use of diabetes medication or FPG >7.0 mmol/l or random glucose >11.1 mmol/l or physician reported	Transdermal ERT 50 μg (144; 4%) vs. no ERT (529; 10%). All patients received progesterone.	0.5 (0.3–0.6)	3.7/100%

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Table 2—*Continued*

Study (locale)	Population* (mean age or age range)	Definition of type 2 diabetes	Comparison and daily dose (sample size; incidence of type 2 diabetes)	RR (95% CI)	Follow-up (years/rate†)
Strong Heart Study (U.S.) (41)	857 postmenopausal American-Indian women (45–74 years)	FPG ≥7.0 mmol/l or 2-h postmeal glucose/OGTT level of ≥11.1 mmol/l	Current ERT users (132) vs. never/past ERT users (723)	OR 1.1 (0.6–2.0)	4.0/96%
Nurses Health Study (U.S.) (39)	21,028 postmenopausal women (mean age 50 years)	Self-reported	Current use (7,314; 2.3% vs. never used (9,761; 7.6%)	0.82 (0.7—0.96)	12/93%
			Former use (3,953; 8.7%) vs. never used	1.07 (0.95–1.2)	
Hammond et al. (U.S.) (42)	582 estrogen-deficient women (mean age 47 years; U.S.)	Not specified	Estrogen users (287; 3.5%) vs. nonusers (295; 11.9%)	0.29 (0.15–0.58)	1.3 y/not available (only patients with at least 5 years follow-up were included)
Rancho Bernardo Study (U.S.) (43)	1,006 postmenopausal women (age 50–70 years)	FPG ≥7.8 mmol/l or 2-h OGTT level of ≥11.1 mmol/l or physician reported or use of diabetes medication	Current users (226; 11%) vs. never users of ERT (225; 14%)	1.10 (0.48–2.48)	11.5/84%
			Past users (374; 13%) vs. never users	1.11 (0.66–1.84)	

*Excluding patients with DM2 at baseline; †refers to the percentage of patients with complete follow-up; ‡RR and CIs calculated from the data presented using intention-to-treat analysis. OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; CAD, coronary artery disease; SES, socioeconomic status; FH, family history; RPG, random plasma glucose; ERT, estrogen replacement therapy; HTN, hypertension.

bidity (CHARM) study from 7 to 6% (0.78, 0.64–0.96) and resulted in a nonsignificant decrease in diabetes incidence from 5.3 to 4.3% in the Study of Cognition and Prognosis in the elderly (SCOPE) trial (0.81, 0.62–1.06) (29,30).

Overall, diabetes incidence was not a prespecified, primary end point in any study, and there was insufficient evidence to definitively recommend any given antihypertensive drug class in patients at risk of developing type 2 diabetes (11).

We found two additional studies published after the aforementioned systematic review (Table 2). In 16,176 hypertensive patients with coronary artery disease enrolled in the International Verapamil-Trandolapril Study (INVEST), a verapamil-based treatment regimen was associated with a decrease in the incidence of type 2 diabetes from 8.2 to 7% compared with an atenolol-based regimen (RR 0.85, 95% CI 0.77–0.95) (Table 2) (31). Diabetes incidence was not a predefined end point in this study and no adjustment was made for concomitant therapies, which could potentially affect diabetes incidence. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of 10,419 hypertensive patients at high cardiovascular risk, a valsartan-based treatment regimen was associated with a decrease in the incidence of type 2 diabetes from 16 to 13% compared with an amlodipine-based regimen (odds ratio [OR] 0.77, 95% CI 0.69–0.86) (32).

Statins

Four post hoc analyses of placebo-controlled statin trials reported conflicting results regarding the effect of statin therapy on diabetes incidence (Table 2). In the West of Scotland Coronary Prevention Study (WOSCOPS), diabetes incidence was significantly lower with pravastatin treatment (RR 0.70, 95% CI 0.50–0.99) (33). In the Heart Protection Study, 4.6% of simvastatin-treated patients developed diabetes versus 4.0% in the placebo arm (1.15, 0.99–1.34) and in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, 4.0% of pravastatin-treated patients developed new diabetes versus 4.5% in the placebo group (0.89, 0.70–1.13) (34,35). In the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA), the incidence of diabetes was 3.0% in the atorvastatin arm and 2.6% in the placebo group (1.15, 0.91–1.44) (36).

Fibrates

In a post hoc analysis of 303 patients with IGT from the Bezafibrate Infarction Prevention (BIP) trial, bezafibrate therapy was associated with a reduction in diabetes incidence from 54 to 42% compared with placebo (HR 0.70, 95% CI 0.49–0.99) (Table 2) (37).

Estrogen

One RCT and five cohort studies have examined the association between estrogen use and diabetes incidence (Table 2). Post hoc analysis of the Heart Estrogen/Progestin Replacement Study (HERS) study reported that combination estrogen and progesterone therapy was associated with a significant reduction in the incidence of diabetes from 9.5 to 6.2% compared with placebo (RR 0.65, 95% CI 0.48–0.89) (Table 2) (38).

The Nurses Health Study, which was the largest of the cohort studies, found that over 12 years, current estrogen use was associated with a significant reduction in diabetes incidence compared with never users (RR 0.82, 95% CI 0.70–0.96) (39). Diabetes incidence in former estrogen users was not significantly different from never users (1.07, 0.95–1.2). Of the remaining four cohort studies (40–43), only one reported a significant covariate-

adjusted reduction in diabetes incidence in users of estrogen replacement compared with nonusers. Several trials failed to adjust for potentially important covariates such as family history, weight, or baseline glucose measurements.

CONCLUSIONS — In summary, a number of studies have examined the impact of different drugs on diabetes incidence, including oral hypoglycemic agents, antiobesity drugs, statins, fibrates, estrogen, and antihypertensive drugs. Oral hypoglycemic medications and orlistat are the only drugs that have been studied in RCTs with diabetes incidence as the primary end point. The adequately powered studies have shown significant decreases in diabetes incidence with metformin, acarbose, troglitazone, and orlistat; however, high attrition rates were found in trials of the latter two agents. Evidence for statins, estrogen, and antihypertensive agents is conflicting and is limited to cohort studies and secondary post hoc analyses of RCTs.

A potential limitation of any systematic review (including ours) is the possibility of publication bias. In addition, studies reporting diabetes incidence as a secondary or post hoc end point were difficult to identify using standard search strategies because this information was contained within the text of studies and identifiable only by performing manual searches. Indeed, our use of manual searching and examination of bibliographies yielded more valid studies for inclusion than our original search strategy. Regardless, while the possibility of missing trials reporting secondary or post hoc analyses exists, we feel that it is unlikely that any definitive studies were missed.

Besides the reduction in glucose levels achieved by oral hypoglycemic agents, it is likely that drug-induced weight loss is contributing to the observed reduction in diabetes incidence. All but one (thiazolidinediones) of the agents reported to lower type 2 diabetes incidence directly or to indirectly promote weight loss. Weight loss has also been the target of lifestyle modification interventions in the diabetes prevention trials (9,10). In contrast to drug therapy, intensive lifestyle interventions have produced reductions in diabetes incidence of 42–58% in the three largest studies to date, despite modest degrees of weight loss of ~5 kg or less compared with control populations (3,4,44). In the DPP, the incidence of type 2 diabetes was 3% lower in the lifestyle arm compared with the metformin arm (RR 0.61, 95% CI 0.49–0.76) and lifestyle modification was efficacious regardless of age, sex, BMI, or ethnic background (4). Assuming that such intensive lifestyle interventions can be successfully implemented in a more practical and equally effective form outside of a clinical trial setting, recidivism remains a major problem. Even within the DPP, the number of participants achieving weight loss targets (7% of initial body weight) decreased from 50% at 24 weeks to 34% at the end of follow-up, and the number of individuals who met the target exercise levels (150 min per week) declined from 74 to 58% by the end of the trial.

A critical and unresolved issue is whether drug therapy simply delays or masks the diagnosis of type 2 diabetes, rather than exerting an actual preventative effect. Drugs that acutely lower serum glucose levels may simply lower glucose concentrations to a lower cutoff level than that required for the formal diagnosis of diabetes. In the posttrial washout periods of the STOP-NIDDM and DPP trials, the higher incidence of diabetes in the treatment arms suggests that at least some of the observed benefits were merely due to delay or masking of diabetes. It is unknown if the beneficial effects of the drugs would have persisted if the posttrial follow-up periods were longer. In the TRIPOD study, diabetes incidence, β-cell function, and insulin sensitivity remained stable in the troglitazone arm for at least 8 months after drug discontinuation (21). However, the type 2 diabetes incidence in the posttrial period was very low, and reasons for the high attrition rates in the study were not detailed.

To prove that diabetes is actually prevented, future studies will have to demonstrate arrest of the disease process. Because the average time interval between onset of β-cell dysfunction and development of type 2 diabetes is 10 years (45), follow-up periods will have to be substantially longer. In a recent retrospective cohort analysis of 10,996 patients with diabetes newly treated with oral agents, statin therapy was associated with a 10-month delay in the initiation of insulin therapy (46). However, after 7 years of follow-up, there were no differences between the statin and control groups in their requirements for insulin therapy.

It will also be important to demonstrate a reduction in morbidity and mortality in order to accept that any of these drugs are beneficial in patients who have not yet developed diabetes. The finding that acarbose reduced cardiovascular events in the STOP-NIDDM trial was based on a small number of events and will require confirmation.

There are a number of potential adverse effects associated with drug-related diabetes prevention strategies. For example, hypoglycemia is a potentially limiting side effect of sulfonylurea therapy, occurring at a frequency of 3% in patients with IGT enrolled in the Fasting Hyperglycemia Study (47). Gastrointestinal toxicity contributed to high discontinuation rates in the STOP-NIDDM and XENDOS studies, and troglitazone is no longer available because of the risk of serious hepatotoxicity (48). Given the likelihood of long-term therapy with diabetes prevention agents, additional data regarding adverse events and adherence will be required.

In addition to their clinical effectiveness in diabetes prevention, consideration should also be given to the cost-effectiveness of drug interventions. Two economic analyses of the DPP study have been performed (49,50). In a cost-effectiveness analysis from a societal perspective, the metformin intervention cost $31,300 per case of diabetes delayed or prevented and $99,600 per quality-adjusted life year gained over the 3-year duration of the study (49). Assuming the use of lower-priced generic metformin, cost estimates decreased to $14,300 and $35,000, respectively. In all analyses, the lifestyle intervention was more economically attractive than metformin. A second economic analysis, performed in Europe, also factored in estimates of cost savings for each case of diabetes presumably prevented (50). Metformin was found to be cost-saving in four of the five European countries studied.

A number of currently ongoing studies should provide more definitive evidence (Table 3) (47,51–56). Short-acting insulin secretagogues, renin-angiotensin inhibitors, newer thiazolidinediones, and insulin glargine are among the drug classes being investigated. The majority of these studies are scheduled for completion in the latter half of this decade.

In conclusion, a number of studies have investigated the effects of several different drug classes on type 2 diabetes in-

Table 3—*Ongoing and future RCTs of drug therapy to prevent type 2 diabetes*

Study	Diabetes end point	Population	Comparison	Sample size	Anticipated duration
EDIT (51)	Primary	Patients at risk of type 2 diabetes. 57% have IGT or IFG	Metformin and/or acarbose versus placebo	631	See below*
Fasting hyperglycemia study (47)	Primary	FPG levels between 5.5 and 7.7 mmol/l	Gliclazide versus placebo	227	
NANSY (52)	Primary	Fasting glucose levels of 5.6–6.0 mmol/l	Glimepiride versus placebo	2,000	5–7 years (2005–2007)
DREAM (53)	Coprimary	IGT	Ramipril and/or rosiglitazone versus placebo (2 × 2 factorial design)	4,000	5 years (2006)
NAVIGATOR (54)	Coprimary	IGT and cardiovascular disease or cardiovascular risk factors	Nateglinide and/or valsartan versus placebo (2 × 2 factorial design)	7,500	3 years (2006)
ONTARGET (55)	Secondary	Known cardiovascular disease or diabetes with end-organ damage	Telmisartan versus ramipril versus both	23,400	5 years (2008)
TRANSCEND (55)	Secondary	Patients from ONTARGET who are intolerant of ACE inhibitors	Telmisartan versus placebo	5,000	5 years (2008)
ORIGIN (56)	Secondary	IGT or IFG at high cardiovascular risk	Insulin glargine versus standard care	10,000	5 years (2008)
CANOE (57)	Primary	IGT with at least 40% First Nations Canadians	Rosiglitazone/metformin combination versus placebo	200	5 years (2008)

*Six-year results for both studies have been published only as abstracts. Primary analyses showed no significant difference between groups.

cidence. The available evidence suggests that oral hypoglycemic drugs may reduce diabetes incidence compared with placebo, while the evidence for orlistat, statins, estrogen, and antihypertensive drugs is inconclusive. However, the data are not definitive and no single agent can currently be recommended for diabetes prevention. It is critical that future studies be designed with much longer follow-up periods and with development of new-onset diabetes as the primary outcome, so as to differentiate between genuine diabetes prevention as opposed to simple delay or masking of this condition.

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