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, antihypertensive agents, antihypoglycemic 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, hydroxymethyl-glutaryl (HMG)-CoA reductase inhibitors.
and performed data extraction. Cohen’s remaining studies for potential inclusion and this review was updated by including diabetes incidence (current through Au-
abstract form. A detailed systematic re-
and if the study was published only in
citation was a review or duplicate article,
diabetes incidence rates and were likely
treated with metformin (relative risk [RR]
bo-treated patients versus 4.8% in those
tested in patients with preexisting diabe-
tics were excluded if the intervention was
test in patients with preexisting diabet-
ses were excluded if the intervention was
treatment rate during follow-up is a major

Two reviewers (R.P. and S.R.M.) inde-
ceptively examined abstracts of the re-
ferences of all included reports.

RESULTS — Of the 5,511 initial cita-
ions, 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 cita-
tions, 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, exam-
ined the effect of oral hypoglycemic agents on diabetes incidence (Table 1).

Biguanides. The largest and most meth-
odologically rigorous trial was the Diabe-
tes Prevention Program (DPP), which randomized 2,155 individuals with IGT to
treatment or placebo (4). After a mean follow-up period of 2.8 years, the inci-
dence of diabetes was 7.8% in the place-
bo-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 anal-
yses, the benefits of metformin were pri-
marily observed in patients <60 years of age (RR 0.66, 95% CI 0.40–0.79 for pa-
patients 25–44 years old) and patients with
a BMI ≥35 kg/m² (0.47, 0.35–0.63).

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
(10 R R 0.75, 95% CI 0.63–0.90) dur-
ing 39 months of observation (17). Nearly
25% of individuals discontinued therapy
early, predominantly due to acarbose-
induced gastrointestinal toxicity. At study
des, 60% of eligible patients were ob-
served for a 3-month washout period,
during which 15% of acarbose-treated
patients developed diabetes compared
with 10.5% of placebo-treated patients.

Sulfonylureas. Two studies examined
the effect of tolbutamide therapy on dia-
betes incidence in patients with IGT or

to normal/elevated fasting glucose lev-
(19,20). Neither study reported a sta-
tistically significant decrease in the type 2
diabetes incidence compared with con-
tral or placebo, although both studies
were small and potentially underpowered
(Table 1).

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

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

Antihypertensive drugs
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 Diabe-
tes in Obese Subjects (XENDOS) study,
the attrition rate was 57% (Table 2) (23).

A pooled analysis of three RCTs en-
rolling 642 obese patients reported a non-
significant reduction in the incidence of
type 2 diabetes from 2 to 0.6% with or-
listat 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 un-
changed or increased by thiazide diuretics
and B-blockers and unchanged or de-
creased by ACE inhibitors, calcium channel
blockers, and angiotensin receptor
blockers (11). Six placebo-controlled tri-
als were included in this review. Thiazide
diuretic–based treatment regimens were
associated with non–statistically signifi-
cant 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 to 7% in the European
## Drug therapy and type 2 diabetes

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

<table>
<thead>
<tr>
<th>Study (locale)</th>
<th>Population* (mean age or age range)</th>
<th>Definition of type 2 diabetes</th>
<th>Comparison and daily dose (sample size; incidence of type 2 diabetes)</th>
<th>RR (95% CI)</th>
<th>Follow-up (years/rate†)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCTs</strong></td>
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<tr>
<td>Diabetes Prevention Program (U.S.) (4)</td>
<td>2,153 patients with IGT and a FPG level of 5.3–6.9 mmol/l (&gt;25 years)</td>
<td>FPG ≥ 7 mmol/l or 2-h OGTT glucose level ≥ 11.1 mmol/l. Positive result confirmed with repeat testing</td>
<td>Metformin 1,700 mg (1,073; 22%) vs. placebo (1,082; 29%)</td>
<td>0.69 (0.57–0.83)</td>
<td>2.8/93%</td>
</tr>
<tr>
<td>Li et al. (China) (14)</td>
<td>90 patients with IGT (30–60 years)</td>
<td>Postmeal or post-OGTT glucose level ≥ 11.1 mmol/l</td>
<td>Metformin 750 mg (42; 7%) vs. placebo: (43; 14%)</td>
<td>0.51 (0.14–1.9)‡</td>
<td>1.0/94%</td>
</tr>
<tr>
<td>BIGPRO (France) (15)</td>
<td>457 patients with a high waist-to-hip ratio (50 years)</td>
<td>Self-reported or FPG ≥ 7.8 mmol/l</td>
<td>Metformin 1,700 mg (227; 0%) vs. placebo (230; 2%). Only five cases of type 2 diabetes in the placebo group.</td>
<td>Unable to calculate</td>
<td>1.0/71%</td>
</tr>
<tr>
<td>Jarrett et al. (England) (16)</td>
<td>204 men with IGT from the Whitehall Survey (56 years)</td>
<td>2 successive or 3 nonsuccesive 2-h postglucose levels &gt; 11.1 mmol/l or a 2-h post-OGTT level of &gt; 11.1 mmol/l at year 5 or symptoms/signs</td>
<td>Phenformin 50 mg (92; 14%) vs. placebo (89; 16%)</td>
<td>0.90 (0.45–1.80)‡</td>
<td>5.0/89%</td>
</tr>
<tr>
<td>STOP-NIDDM (Canada and Europe) (17)</td>
<td>1,429 patients with IGT and a FPG level of 5.6–7.7 mmol/l (40–70 years)</td>
<td>2-h OGTT glucose level ≥ 11.1 mmol/l</td>
<td>Acarbose 300 mg (682; 32%) vs. placebo (686; 42%)</td>
<td>0.75 (0.63–0.90)</td>
<td>3.3/96%</td>
</tr>
<tr>
<td>TRIPOD (U.S.) (21)</td>
<td>266 Hispanic women with gestational diabetes (35 years)</td>
<td>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</td>
<td>Troglitazone 400 mg (114; 20%) vs. placebo (122; 45%)</td>
<td>0.45 (0.25–0.83)</td>
<td>2.5/67%</td>
</tr>
<tr>
<td>Santor et al. (Sweden) (19)</td>
<td>97 men with glucose intolerance (43 years)</td>
<td>3-h OGTT test with 10 capillary glucose readings. All readings had to be 3 SDs above the mean to diagnose diabetes.</td>
<td>Tolbutamide 1,500 mg (49; 10%) vs. placebo (48; 12.5%)</td>
<td>0.82 (0.27–2.5)‡</td>
<td>9–10/100%</td>
</tr>
<tr>
<td>Keen et al. (U.K.) (20)</td>
<td>248 patients with IGT from the Bedford Diabetes Survey (57 years)</td>
<td>2 successive or 3 nonsuccessive 2-h postglucose levels &gt; 11.1 mmol/l or a 2-h post-OGTT level of &gt; 11.1 mmol/l plus symptoms/signs</td>
<td>Tolbutamide 1,000 mg (123; 11%) vs. placebo (125; 9%)</td>
<td>1.20 (0.56–2.6)‡</td>
<td>7.0/not specified</td>
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<tr>
<td><strong>Cohort studies</strong></td>
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<tr>
<td>Yang et al. (China) (13)</td>
<td>261 patients with IGT (&gt; 25 years)</td>
<td>Not specified</td>
<td>Metformin 750 mg (81; 4.1%) vs. control (83; 11.6%) Acarbose 150 mg (83; 2%) vs. control (85; 11.6%)</td>
<td>0.31 (0.09–1.1)‡</td>
<td>3.0/95%</td>
</tr>
<tr>
<td>Durbin (22)</td>
<td>172 patients with IGT (29–86 years) with a FPG level of 5.6–7.0 mmol/l and a 2-h post-prandial glucose level between 7.8 mmol/l and 11.1 mmol/l</td>
<td>Not stated</td>
<td>Tolbutamide 400 mg daily then rosiglitazone 4 mg daily or pioglitazone 30 mg daily (101; 3.0%) vs. untreated comparison group (71; 26%)</td>
<td>0.11 (0.03–0.36)</td>
<td>3.0/100%</td>
</tr>
</tbody>
</table>

*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 Candesantin in Heart Failure Assessment of Reduction in Mortality and Mor-
### Table 2—Studies of other agents and type 2 diabetes incidence

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

Continued on following page
Drug therapy and type 2 diabetes

Table 2—Continued

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

*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; RGP, random plasma glucose; ERT, estrogen replacement therapy; HTN, hypertension.

Drug therapy and type 2 diabetes

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, B-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 B-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-
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Table 3—Ongoing and future RCTs of drug therapy to prevent type 2 diabetes

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

*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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