# Oral Agents for Type 2 Diabetes: An Update

Bonnie Kimmel, MD, and Silvio E. Inzucchi, MD

Type 2 diabetes is a multifactorial metabolic disease characterized by abnormalities at multiple organ sites. These defects include insulin resistance and insulin deficiency.[1,2] The former is primarily represented by decreased insulin-stimulated glucose uptake in skeletal muscle, augmented endogenous glucose production (predominately in the liver), and enhanced lipolytic activity in fat.[3] The latter is an apparent progressive process with both functional defects in islet cell function and, eventually, apparent loss of β-cell mass.[4,5] These defects are intimately linked, with derangements in one system exacerbating those in the others.[6] Understanding the defects is important, because addressing them forms the cornerstone of current and future therapy for this disease.

Several studies, including the U.K. Prospective Diabetes Study (UKPDS), have now unequivocally shown the benefits of tight glucose control for patients with diabetes.[7–9] In these studies, microvascular complications were significantly and consistently reduced in the more aggressively controlled groups of patients. As a result, various professional organizations have proposed increasingly stringent metabolic targets for their management.[10,11] The extent to which glycemic control affects macrovascular end points, which is the major cause of death in patients with diabetes, remains incompletely understood. Most studies have yet to show definitive benefit. Potential explanations for this discrepancy include study methodology, the potential influence of the degree and timing (postprandial versus fasting) of glucose lowering, or the failure to adequately address insulin resistance in studies published to date. Several investigations are underway to address these issues.

At present, when lifestyle changes fail to reduce glucose levels to the desirable range, the conventional approach is to begin therapy with an oral antihyperglycemic agent. In 2002,[12] we reported a systematic review of oral agents for type 2 diabetes, in which we assessed the efficacy of these drugs, both as monotherapy and in combination, and discussed evidence-based treatment strategies. Now, 3 years later, with a > 50% increase in the number of published trials in this area, we reassess the literature. Have there been any new developments in this field that might alter the therapeutic approach to this increasingly common disease?

## METHODS

A MedLine search was performed to identify all English-language articles of randomized, controlled, clinical trials involving currently and previously available oral agents for type 2 diabetes published after our initial report. As in our earlier analysis, studies were included if they met the following criteria: study period of at least 3 months, minimum of 10 subjects in each group at the conclusion of the study, and hemoglobin $A_{1c}$ (A1C) reported as a major end point. Studies were excluded if they involved insulin, triple oral agent combinations, or investigational drugs, or if the study was limited to a specific subpopulation of type 2 diabetic patients.

### IN BRIEF

The paradigms for oral pharmacological therapy in type 2 diabetes are shifting as we attain new insights into the optimal metabolic control in our patients. Each drug category has unique advantages and disadvantages, and their proper use necessitates a full understanding of their mechanisms of action, glycemic and nonglycemic effects, and prescribing indications. This article reviews published clinical trial data and places them into the context of contemporary, rational therapeutic strategies for this increasingly common condition.

## FINDINGS

There remain five classes of oral antihyperglycemic drugs approved by the U.S. Food and Drug Administration (FDA).

### Sulfonylureas

Sulfonylurea (SU) drugs (e.g., glyburide, glipizide, and glimepiride) improve glucose levels by stimulating insulin secretion by the pancreatic β-cell,[13] with elevated circulating insulin levels partially overcoming peripheral insulin resistance. It is well recognized, however, that with time, patients on SU monotherapy experience a progressive loss of glucose control. Because of this, the question of islet cell "burnout" has been raised. This same phenomenon, however, is noted in patients taking metformin, a drug that does not increase insulin secretion.[14] Therefore, β-cell failure may simply be a fundamental feature of type 2 diabetes itself that is not substantially affected by the type of therapy used.

Treatment with SU agents generally yields a mean absolute A1C reduction of 1–2%.[9,15,16] Several published SU studies

completed since our original report was published confirm these points (Tables 1 and 2).[17–20] SU agents are effective both as monotherapy and in combination with agents that have different mechanisms of antihyperglycemic action (Table 3).

Side effects of SUs include weight gain[9,15,21,22] and hypoglycemia.[9,21,23] Weight gain is of particular concern, given that patients are often obese before therapy initiation. Hypoglycemia risk becomes a more important issue as patients' overall glucose control approaches the normal range. During the past several years, the cardiology community has become disquieted because of the potential effect of SUs on myocardial ischemic preconditioning.[24] The actual importance of this issue in clinical practice remains unclear, but it has likely been exaggerated.

There are no new outcomes data on vascular end points from prospective clinical trials. In some retrospective analyses,[25–27] but not in others,[28–30] worse cardiovascular outcomes have been observed in groups of patients taking SU agents compared to groups taking metformin or thiazolidinediones (TZDs). Without prospective data, it is not possible to make firm conclusions, especially in light of data from previous randomized studies showing no significant increases or decreases in macrovascular risk in SU-treated patients, despite an apparent benefit on microvascular end points.[9]

**Non-SU Secretagogues (Meglitinides)**

Drugs in this class work similarly to SU agents but have a more rapid onset and shorter duration of action. As a result, insulin secretion is stimulated to a greater extent immediately after administration. When drug ingestion is timed with meals, the result is more physiologically appropriate control of postprandial glucose concentrations. The benefit of this effect remains unclear, although epidemiologically, postprandial hyperglycemia is more closely related to cardiovascular morbidity than is fasting glucose.

There are efficacy differences between the two agents within this group, repaglinide and nateglinide. The former has an A1C-lowering effect similar to most other antihyperglycemic agents in both placebo-controlled and head-to-head trials,[31–35] whereas the latter appears to be less efficacious[36–39] (Tables 1 and 2). Both are approved for use as monotherapy and in combination with most other oral agent classes (Table 3).

Side effects are otherwise similar to other secretagogues, including weight gain and hypoglycemia. These likely occur to a lesser degree than with SUs. Meglitinides must also be taken shortly before each meal and therefore have a more frequent dosing schedule than most other agents. Their cost is generally higher than that of SUs.

Long-term outcomes data are still unavailable for this drug class. However, the effect on long-term complication rates is likely to be at least similar to that observed with SUs. It is unlikely that such long-term outcomes studies will ever be conducted.

**Biguanides**

Metformin, a biguanide, acts mainly by decreasing hepatic glucose production[40,41]—primarily gluconeogenesis—probably through effects on AMP-kinase. Circulating glucose levels are thereby reduced. Improved peripheral insulin resistance may also occur, but study results are inconsistent.[40,42–44] Metformin is commonly referred to as an "insulin sensitizer," because glucose levels improve without stimulation of insulin secretion.

Notably, metformin as monotherapy remains the only agent associated with the potential for weight loss.[40,42,45] Other nonglycemic benefits have been reported, including modest lowering of lipid levels,[46,47] and improvements in fibrinolysis,[47] inflammatory markers, and endothelial function.[48]

Numerous studies during the past several years have continued to demonstrate a benefit of metformin on these cardiovascular risk markers.[49] In fact, to date, metformin is the only oral antihyperglycemic agent shown to reduce macrovascular events in patients with type 2 diabetes, in a relatively small substudy of the UKPDS involving overweight subjects.[50] When the drug was added to the regimens of patients no longer responding adequately to SUs, there was a puzzling increase in mortality, an association that remains essentially unexplained.[50] Such a finding appeared to be confirmed in a more recent retrospective analysis.[51] Another group of investigators has suggested a cardiovascular benefit in patients undergoing percutaneous coronary intervention.[52]

In placebo-controlled trials, metformin consistently lowers A1C by 1–2%.[19,46,50,53–58] Trials published since our original report confirm that this drug, while having a unique mechanism of action, reduces A1C to a similar degree as most secretagogues[59,60] (Tables 1 and 2). Metformin is approved for use alone or in combination with all other antidiabetic agents (Table 3). It is also gaining in popularity as a treatment option for women with polycystic ovary syndrome and has been demonstrated by multiple investigators to improve ovulatory capacity and metabolic parameters in this group of insulin-resistant women.[61–63]

Since our original report, the results from the Diabetes Prevention Program[64] have also been published. Metformin was used as one strategy to prevent or delay the development of type 2 diabetes in one arm of this study involving patients with impaired glucose tolerance. The relative risk of progressing to diabetes in metformin-treated patients was reduced by 31%.[64] While less impressive than the 58% risk reduction with lifestyle change, such data have given encouragement to the notion of using pharmacological therapy in patients with prediabetes, at least in the subset who cannot or will not undertake a diet and exercise program.

Gastrointestinal side effects of metformin are common[42] but can be minimized by slow dosage titration. Because of the rare risk of lactic acidosis, several

**Table 1. Antidiabetic Oral Agent Monotherapy: Published, Randomized, Controlled Clinical Trials**

| Authors and Year | Reference | Randomization | *n* | Study Length | A1C Results* |
|---|---|---|---|---|---|
| **SUs** | | | | | |
| Luis Bautista et al. 2003 | 17 | Glimeprimide vs. placebo | 70 | 14 weeks | –1.8% |
| Fischer et al. 2003 | 18 | Glibenclamide vs. placebo | 77 | 16 weeks | –2.0% |
| Garber et al. 2002 | 19 | Glyburide vs. placebo | 800 | 20 weeks | –1.03% |
| UKPDS Group 1998† | 9 | Sulfonylureas vs. diet | 3,867 | 10 years | –0.9% |
| Schade et al. 1998† | 15 | Glimepiride vs. placebo | 249 | 22 weeks | –1.4% |
| Simonson et al. 1984† | 22 | Glipizide GITS vs. placebo | 204 | 12 weeks | –1.8% |
| Rosenstock et al. 1996† | 20 | Glimepiride vs. placebo | 416 | 14 weeks | –2.5% |
| **Metformin** | | | | | |
| Garber et al. 2002 | 19 | Metformin vs. placebo | 800 | 20 weeks | –0.82% |
| Chiasson et al. 2001 | 58 | Metformin vs. placebo | 324 | 36 weeks | –1.25% |
| UKPDS Group 1998† | 50 | Meformin vs. diet | 753 | 10.7 years | –0.8% |
| Hoffmann and Spengler 1997† | 57 | Metformin vs. placebo | 96 | 24 weeks | –1.1 % |
| Garber et al. 1997† | 56 | Metformin vs. placebo | 452 | 11 weeks | –2.0% |
| Grant 1996† | 55 | Metformin vs. placebo | 75 | 6 months | –1.7% |
| DeFronzo and Goodman 1995† | 46 | Metformin vs. placebo | 289 | 29 weeks | –1.5% |
| Nagi and Yudkin 1993† | 54 | Metformin vs. placebo | 27 | 12 weeks | –1.3% |
| Dornan et al. 1991† | 53 | Metformin vs. placebo | 60 | 8 months | –3.0% |
| **AGIs** | | | | | |
| Josse et al. 2003 | 123 | Acarbose vs. placebo | 192 | 12 months | –0.6% |
| Fischer et al. 2003 | 18 | Acarbose vs. placebo | 77 | 16 weeks | –0.7% |
| Drent et al. 2002 | 124 | Miglitol vs. placebo | 384 | 24 weeks | –1.26% |
| Chiasson et al. 2001 | 58 | Miglitol vs. placebo | 324 | 36 weeks | –0.37% |
| Hasche et al. 1999† | 121 | Acarbose vs. placebo | 74 | 24 months | –0.9% |
| Scott et al. 1999† | 120 | Acarbose vs. placebo | 105 | 16 weeks | –0.4% |
| Fischer et al. 1998† | 118 | Acarbose vs. placebo | 495 | 24 weeks | –1.0% |
| Johnston et al. 1998† | 119 | Miglitol vs. placebo | 345 | 12 months | –0.7% |
| Hoffmann and Spengler 1997† | 57 | Acarbose vs. placebo | 96 | 24 weeks | –1.3 % |
| Braun et al. 1996† | 117 | Acarbose vs. placebo | 86 | 24 weeks | –0.9% |
| Coniff et al. 1995† | 116 | Acarbose vs. placebo | 290 | 16 weeks | –0.8% |
| Coniff et al. 1995† | 122 | Acarbose vs. placebo | 212 | 24 weeks | –0.6% |
| Chiasson et al. 1994† | 115 | Acarbose vs. placebo | 354 | 1 year | –0.9% |
| Hotta et al. 1993† | 113 | Acarbose vs. placebo | 40 | 24 weeks | –1.0% |
| Santeusanio et al. 1993† | 114 | Acarbose vs. placebo | 62 | 16 weeks | –0.6% |
| Hanefeld et al. 1991† | 112 | Acarbose vs. placebo | 94 | 24 weeks | –0.6% |
| **TZDs** | | | | | |
| Herz et al. 2003 | 105 | Pioglitazone vs. placebo | 297 | 16 weeks | –0.9% |
| Scherbaum et al. 2002 | 106 | Pioglitazone vs. placebo | 251 | 26 weeks | –1.05% |
| Miyazaki et al. 2002 | 108 | Pioglitazone vs. placebo | 58 | 26 weeks | –2.9% |
| Rosenstock et al. 2002 | 39 | Troglitazone vs. placebo | 599 | 16 weeks | –1.3% |
| Rosenblatt et al. 2001 | 80 | Pioglitazone vs. placebo | 197 | 23 weeks | –1.37% |
| Lebovitz et al. 2001† | 152 | Rosiglitazone vs. placebo | 493 | 26 weeks | –1.5% |
| Phillips et al. 2001† | 151 | Rosiglitazone vs. placebo | 959 | 26 weeks | –1.5% |
| Aronoff et al. 2000† | 153 | Pioglitazone vs. placebo | 408 | 26 weeks | –1.6% |
| Fonseca et al. 1998 † | 150 | Troglitazone vs. placebo | 402 | 6 months | –1.1% |
| **Non-SU Secretagogues** | | | | | |
| Saloranta et al. 2002 | 38 | Nateglinide vs. placebo | 675 | 24 weeks | –0.39% |
| Rosenstock et al. 2002 | 39 | Nateglinide vs. placebo | 599 | 16 weeks | –1.1% |
| Jovanovic et al. 2000† | 31 | Repaglinide vs. placebo | 93 | 6 months | –1.9% |
| Horton et al. 2000† | 37 | Nateglinide vs. placebo | 701 | 24 weeks | –1.0% |
| Hanefeld et al. 2000† | 36 | Nateglinide vs. placebo | 289 | 12 weeks | –0.6% |
| Goldberg et al. 1998† | 32 | Repaglinide vs. placebo | 99 | 18 weeks | –1.7% |

*Values represent the placebo-adjusted absolute percent reduction in A1C of active therapy. Because of different recruitment criteria for individual studies, particularly regarding baseline A1C, direct comparison of one agent to another is difficult from these trials.
†Studies included in our original report.[12] GITS, gastrointestinal therapeutic system.

**Table 2. Antidiabetic Oral Agent Monotherapy: Published, Randomized, Head-to-Head Trials**

| Authors and Year | Reference | Randomization | *n* | Study Length | A1C Results |
|---|---|---|---|---|---|
| **SUs** | | | | | |
| van de Laar et al. 2004 | 126 | Tolbutamide vs. acarbose | 96 | 30 weeks | Tolbutamide more efficacious (A1C –1.8 vs. –1.1% [*P* value not reported]) |
| Kitbachi et al. 2000* | 158 | Glipizide vs. glyburide | 18 | 15 months | Equivalent efficacy |
| Dills and Schneider 1996* | 157 | Glimepiride vs. glyburide | 577 | 1 year | Equivalent efficacy |
| Birkeland et al. 1994* | 156 | Glipizide vs. glyburide | 46 | 15 months | Equivalent efficacy |
| Carlson et al. 1993* | 155 | Glyburide vs. micronized glyburide | 206 | 12 weeks | Equivalent efficacy |
| Rosenstock et al. 1993* | 154 | Glipizide vs. glyburide | 139 | 4 months | Equivalent efficacy |
| Kilo et al. 1992* | 23 | Glipizide vs. glyburide | 34 | 3 months | Equivalent efficacy |
| **Metformin** | | | | | |
| Goldstein et al. 2003 | 59 | Metformin vs. glipizide | 247 | 18 weeks | Equivalent efficacy |
| Marre et al. 2002 | 60 | Metformin vs. glibenclamide | 411 | 16 weeks | Equivalent efficacy |
| Tessier et al. 1999* | 159 | Metformin vs. glicazide | 36 | 24 weeks | Equivalent efficacy |
| UKPDS Group 1998* | 50 | Meformin vs. various sulfonylureas | 753 | 10.7 years | Equivalent efficacy |
| Campbell et al. 1994* | 160 | Metformin vs. glipizide | 48 | 1 year | Metformin more efficacious (A1C –2.6 vs. –1.9% [$P < 0.05$]) |
| Hermann et al. 1994* | 161 | Metformin vs. glyburide | 165 | 6 months | Equivalent efficacy |
| Clarke and Campbell 1977* | 162 | Metformin vs. chlorpropamide | 216 | 1 year | Equivalent efficacy |
| **AGIs** | | | | | |
| Fischer et al. 2003 | 18 | Acarbose vs. glibenclamide | 77 | 16 weeks | Glibenclamide more efficacious (A1C –1.3 vs. 0.0% [$P < 0.0001$]) |
| Salman et al. 2001 | 125 | Acarbose vs. gliclazide | 72 | 24 weeks | Equivalent efficacy |
| Hoffmann and Spengler 1997* | 57 | Acarbose vs. metformin | 96 | 24 weeks | Equivalent efficacy Note: mean metformin dose not maximal (850 mg twice daily) |
| Segal et al. 1997* | 164 | Miglitol vs. glibenclamide | 119 | 24 weeks | Glibenclamide more efficacious (A1C -1.0 vs. -0.8% [*P* value not reported]) Note: mean glibenclamide dose not maximal (3.6 mg daily) |
| Hoffmann and Spengler 1994* | 163 | Acarbose vs. glibenclamide | 96 | 24 weeks | Equivalent efficacy Note: mean glibenclamide dose not maximal (4.3 mg daily) |
| **TZDs** | | | | | |
| Pavo et al. 2003 | 107 | Pioglitazone vs. metformin | 205 | 32 weeks | Equivalent efficacy |
| Khan et al. 2002 | 104 | Pioglitazone vs. rosiglitazone | 127 | 4 months | Equivalent efficacy |
| Rosenstock et al. 2002 | 39 | Troglitazone vs. nateglinide | 599 | 16 weeks | Equivalent efficacy |
| Kirk et al. 1999* | 165 | Troglitazone vs. metformin (in SU-treated patients) | 32 | 14 weeks | Equivalent efficacy |
| Inzucchi et al. 1998* | 40 | Troglitazone vs. metformin | 28 | 3 months | Equivalent efficacy |
| Horton et al. 1998* | 166 | Troglitazone vs. glyburide | 552 | 1 year | Equivalent efficacy |
| **Non-SU Secretagogues** | | | | | |
| Jovanovic et al. 2004 | 33 | Repaglinide vs. pioglitazone | 246 | 24 weeks | Equivalent efficacy |
| Derosa et al. 2003 | 34 | Repaglinide vs. glimeprimide | 124 | 12 months | Equivalent efficacy |
| Madsbad et al. 2001 | 35 | Repaglinide vs. glipizide | 256 | 12 months | Repaglinide more efficacious (A1C +0.2 vs. +0.8% [$P < 0.05$]) |
| Horton et al. 2000* | 37 | Nateglinide vs. metformin | 701 | 24 weeks | Metformin more efficacious (A1C –0.8 vs. –0.5% [$P < 0.01$]) |
| Raskin et al. 2000* | 171 | Repaglinide vs. troglitazone | 256 | 22 weeks | Repaglinide more efficacious (A1C –0.8 vs. –0.4% [$P < 0.05$]) |
| Marbury et al. 1999* | 167 | Repaglinide vs. glyburide | 576 | 12 months | Equivalent efficacy |
| Landgraf et al. 1999* | 168 | Repaglinide vs. glibenclamide | 195 | 14 weeks | Equivalent efficacy |
| Wolffenbuttel and Landgraf 1999* | 169 | Repaglinide vs. glyburide | 424 | 1 year | Equivalent efficacy |
| Moses et al. 1999* | 170 | Repaglinide vs. metformin | 83 | 3 months | Equivalent efficacy |

*Studies included in our original report.[12]

contraindications limit this drug's use, including renal and liver dysfunction, heart failure, dehydration or hemodynamic compromise, and alcohol abuse. Several studies have described a surprising proportion of metformin-treated patients with active contraindications for its use.[65–67] Despite this, complication rates are few, suggesting that current prescribing guidelines may be overly stringent. In fact, a recent retrospective analysis involving heart failure patients demonstrated actual improved outcomes in those treated with this drug.[68]

**TZDs**

TZDs are activators of the nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) and modulate the activity of a host of genes that regulate carbohydrate and lipid metabolism.[69] Currently available TZDs are pioglitazone and rosiglitazone.

Most notably, TZDs improve insulin sensitivity and enhance glucose utilization by adipocytes and skeletal mus-

**Table 3. Antidiabetic Oral Agent Combination Therapy: Published, Randomized, Controlled Trials**

| Authors and Year | Reference | Randomization | *n* | Study Length | A1C Results* |
|---|---|---|---|---|---|
| **SUs + Metformin** | | | | | |
| Marre et al. 2002 | 60 | Metformin + glibenclamide vs. either alone | 411 | 16 weeks | –1.0% vs. metformin<br>–0.9% vs. glibenclamide |
| Garber et al. 2003 | 145 | Glyburide + metformin vs. either alone | 485 | 16 weeks | –0.5% vs. glyburide<br>–0.7% vs. metformin |
| Goldstein et al. 2003 | 59 | Glipizide + metformin vs. either alone | 247 | 18 weeks | –1.1% vs. glipizide<br>–1.0% vs. metformin |
| Garber et al. 2002 | 19 | Glyburide + metformin vs. either alone | 800 | 20 weeks | –0.3% vs. glyburide<br>–0.5% vs. metformin |
| Blonde et al. 2002 | 129 | Glyburide + metformin vs. either alone | 639 | 16 weeks | –1.7% vs. glyburide<br>–1.9% vs. metformin |
| Charpentier et al. 2001 | 130 | Metformin + glimeprimide vs. metformin alone | 372 | 5 months | –0.9% |
| Erle et al. 1999† | 172 | Glyburide + metformin vs. glyburide + placebo | 40 | 6 months | –1.0% |
| UKPDS Group 1998† | 50 | SU + metformin vs. SU alone | 591 | 3 years | –0.6% |
| Defronzo and Goodman 1995† | 46 | Glyburide + metformin vs. glyburide alone | 632 | 29 weeks | –1.6% |
| **AGIs** | | | | | |
| Lin et al. 2003 | 131 | SU + acarbose vs. SU + placebo | 69 | 24 weeks | –1.1% |
| Phillips et al. 2003 | 132 | Metformin + acarbose vs. metformin + placebo | 81 | 24 weeks | –1.0% |
| Van Gaal et al. 2001 | 133 | Metformin + miglitol vs. metformin + placebo | 152 | 32 weeks | –0.4% |
| Chiasson et al. 2001 | 58 | Metformin + miglitol vs. either alone | 324 | 36 weeks | –1.4% vs. miglitol<br>–0.5% vs. metformin |
| Standl et al. 2001† | 178 | Metformin/glyburide + miglitol vs. metformin/glyburide + placebo | 154 | 24 weeks | –0.4% |
| Willms and Ruge 1999† | 177 | SU + acarbose vs. SU + metformin vs. SU + placebo | 89 | 12 weeks | –1.0% (+ acarbose)<br>–1.2% (+ metformin) |
| Holman et al. 1999† | 176 | Variety of treatments + acarbose vs. variety of treatments + placebo | 973 | 3 years | –0.2% |
| Rosenstock et al. 1998† | 174 | Metformin + acarbose vs. metformin + placebo | 148 | 24 weeks | –0.7% |
| Scorpiglione et al. 1999† | 175 | Variety of treatments + acarbose vs. variety of treatments + placebo | 250 | 12 months | –0.1% (*P* = NS) |
| Johnston et al. 1994† | 179 | SU + miglitol vs. SU + placebo | 192 | 14 weeks | –0.8% |
| Costa and Pinol 1997† | 173 | Glibenclamide + acarbose vs. glibenclamide + placebo | 65 | 6 months | –0.8% |
| Coniff et al. 1995† | 122 | Tolbutamide + acarbose vs. either alone | 290 | 24 weeks | –0.4% (vs. tolbutamide)<br>–0.8% (vs. acarbose)<br>Note: Acarbose dose 200 mg three times a day (above FDA maximum) |
| Chiasson et al. 1994† | 115 | Metformin or SU + acarbose vs. metformin or SU + placebo | 354 | 1 year | –0.8 to –0.9% |

*Continued on next page*

cle.[70–73] Some investigators have also demonstrated a reduction of hepatic glucose production,[44,72] although not to as significant a degree as with metformin. PPAR-γ is most highly expressed in fat cells, and TZD therapy is associated with prominent effects on circulating fat-derived factors that influence insulin sensitivity, such as free fatty acids, adiponectin, and tumor necrosis factor-α.[74] TZD action in muscle tissue may indeed derive indirectly through these effects.

Since our original report, many more studies indicate that TZDs have beneficial effects on a variety of cardiovascular risk determinants, including cytokines and inflammatory markers,[75–77] lipids,[78–81] blood pressure,[78,82,83] endothelial function,[78,84–87] and certain cellular and molecular events that control the atherosclerotic process.[88–91] Recently, pioglitazone has been shown to have better effects than rosiglitazone on plasma lipids,[92] although the ultimate role of the lipid changes induced by TZDs remains uncertain, given these agents' apparent potential widespread vascular benefit. Provocative data regarding a suppressive effect on carotid intimal media thickness,[93] a surrogate for atherosclerosis, as well as coronary artery restenosis after angioplasty[94,95] have also emerged.

**Table 3. Antidiabetic Oral Agent Combination Therapy: Published, Randomized, Controlled Trials, cont'd**

| Authors and Year | Reference | Randomization | *N* | Study Length | A1C Results* |
|---|---|---|---|---|---|
| **TZDs** | | | | | |
| Hanefeld et al. 2004 | 134 | SU + pioglitazone vs. SU + metformin | 639 | 52 weeks | Equivalent efficacy |
| Jovanovic et al. 2004 | 33 | Repaglinide + pioglitazone vs. either alone | 246 | 24 weeks | –1.6% vs. repaglinide<br>–2.0% vs. pioglitazone |
| Nagasaka et al. 2004 | 135 | SU + pioglitazone vs. SU + metformin | 78 | 4 months | Equivalent efficacy |
| Kerenyi et al. 2004 | 136 | Glibenclamide + rosiglitazone vs. glibenclamide alone | 340 | 26 | –0.8% |
| Yang et al. 2003 | 137 | SU + rosiglitazone vs. SU + metformin | 211 | 12 weeks | Equivalent efficacy |
| Vongthavaravat et al. 2002 | 138 | SU + rosiglitazone vs. SU alone | 348 | 26 weeks | –1.1% |
| Gomez-Perez et al. 2002 | 139 | Metformin + rosiglitazone vs. metformin + placebo | 116 | 26 weeks | –1.5% |
| Rosenstock et al. 2002 | 39 | Troglitazone + nateglinide vs. either alone | 599 | 16 weeks | –0.9% vs. troglitazone<br>–1.1% vs. nateglinide |
| Kipnes et al. 2001 | 140 | SU + pioglitazone vs. SU + placebo | 560 | 16 weeks | –1.3% |
| Miyazaki et al. 2001 | 141 | SU + pioglitazone vs. SU + placebo | 23 | 16 weeks | –1.7% |
| Einhorn et al. 2000† | 180 | Metformin + pioglitazone vs. metformin + placebo | 328 | 16 weeks | –0.8% |
| Fonseca et al. 2000† | 181 | Metformin + rosiglitazone vs. metformin + placebo | 348 | 26 weeks | –1.2% |
| Wolffenbuttel et al. 2000† | 182 | SU + rosiglitazone vs. SU + placebo | 574 | 26 weeks | –1.0% |
| Buysschaert et al. 1999† | 183 | SU + troglitazone vs. SU + placebo | 259 | 16 weeks | –0.2%<br>Note: Troglitazone dose not maximal (200 mg daily) |
| Horton et al. 1998† | 166 | Glyburide + troglitazone vs. either alone | 552 | 1 year | –2.7% |
| Iwamoto et al. 1996† | 184 | SU + troglitazone vs. SU + placebo | 291 | 12 weeks | –0.9% |
| **Non-SU Secretagogues** | | | | | |
| Fonseca et al. 2003 | 142 | Rosiglitazone + nateglinide vs. rosiglitazone + placebo | 402 | 24 weeks | –0.8% |
| Raskin et al. 2003 | 143 | Metformin + repaglinide vs. metformin + mateglinide | 192 | 16 weeks | Repaglinide –1.3% vs. nateglinide –0.7% |
| Marre et al. 2002 | 144 | Metformin + mateglinide vs. metformin + placebo | 461 | 24 weeks | –0.6% |
| Raskin et al. 2000† | 171 | Troglitazone + repaglinide vs. either alone | 256 | 22 weeks | –1.3% vs. troglitazone<br>–0.9% vs. repaglinide |
| Moses et al. 1999† | 170 | Metformin + repaglinide vs. either alone | 83 | 3 months | –1.1% vs. metformin<br>–1.0% vs. repaglinide |
| Horton et al. 2000† | 37 | Metformin + nateglinide vs. either alone | 701 | 24 weeks | –0.6% vs. metformin<br>–0.9% vs. metformin |

*Unless otherwise indicated, values represent the absolute percent reduction in A1C of combination therapy vs. monotherapy.
†Studies included in our original report.[12]

Long-term outcomes studies with TZDs are not yet available. In some retrospective analyses thus far presented mainly in abstract form, benefit is suggested on cardiovascular outcomes, but the data are inconsistent and fraught with interpretative challenges.[96–99] The results of prospective outcome studies underway will be necessary in order to determine whether these effects yield measurable clinical benefits and indeed improve the macrovascular complications of type 2 diabetes.

Recent reports also suggest that TZDs may "preserve" β-cell function. The most convincing data come from the Troglitazone in the Prevention of Diabetes study[100] of diabetes prevention that tested troglitazone or placebo in relatively young women with a history of gestational diabetes mellitus. Progression to type 2 diabetes was reduced by > 50% in women on active treatment, likely a reflection of improved β-cell function that accompanied increased insulin sensitivity. Whether such preservation of insulin secretory capacity occurs in patients once diabetes is established is less clear. To date, small, short-term studies suggest benefit on markers of β-cell function.[101–103] Convincing data from long-term clinical trials with adequate methodology are still lacking.

Published trials since our original report have confirmed that the A1C-lowering effect of the TZDs is equivalent[104] and typically in the same range as that achieved by the SUs or metformin, in both placebo-controlled and head-to-head studies[39, 105–108] (Tables 1 and 2). These agents are also approved as monotherapy and in combination with most other agents, including metformin—a combination that is increasingly popular and now available in a single proprietary product (rosiglitazone/metformin) (Table 3).

Side effects include weight gain and edema, which have precluded their widespread use for patients with heart failure. Recently, more concern has arisen regarding the potential effect of TZDs in heart failure patients. A consensus statement from the American Diabetes Association and the American Heart Association addressed this issue and endorsed the FDA's current recommendation that the drugs not be used in patients with advanced heart failure symptoms (class III or IV New York Heart Association classification).[109] Caution was also advised in patients with less severe heart failure. In a recent retrospective study of Medicare beneficiaries, decreased mortality was observed in diabetic patients prescribed a TZD after a hospitalization for heart failure.[68]

Randomized studies are needed to confirm these data before any change in practice is considered. Troglitazone, the TZD primarily associated with idiosyncratic hepatocellular injury, has been off the market for several years. Although the remaining agents have not been shown to pose a similar risk, recommendations still exist regarding periodic surveillance of liver function for patients on TZDs.

### α-Glucosidase Inhibitors

α-Glucosidase inhibitors (AGIs) act by inhibiting an enzyme on the enterocyte brush border that breaks down complex starches, delaying intestinal absorption of carbohydrate and particularly attenuating postprandial blood glucose elevations.[110,111] Current members of this drug class include acarbose and miglitol.

In placebo-controlled trials, AGIs have usually been shown to reduce A1C by only 0.5–1%[112–122] and are therefore generally considered less efficacious than other classes. Additional studies since our last report continue to confirm this trend, both in placebo-controlled and head-to-head trials[18,58,123–126] (Tables 1 and 2). AGIs are approved for use as monotherapy and in combination with sulfonylureas and metformin (Table 3).

Side effects include abdominal bloating and cramping, frequently leading to cessation of drug use. The AGIs' more modest efficacy and higher incidence of side effects have limited their widespread use in the United States, although, interestingly, they remain very popular in other countries, particularly Germany and Japan.

In post hoc analysis of data from the Study to Prevent Non-Insulin Dependent Diabetes Mellitus trial, acarbose was observed to have an impressive effect on the risk of myocardial infarction (hazard ratio = 0.09).[127] These data support the view, based on epidemiological studies, that postprandial hyperglycemia has a greater influence on cardiovascular outcomes than does fasting glucose. No long-term outcomes data are available on vascular end points in type 2 diabetic patients, however.

## MONOTHERAPY STRATEGIES

Clinical trial research published since our original report does not compel any change in the prevailing view that most of the available oral agents are appropriate as initial therapy, barring, of course, any contraindications that might exist in specific patient circumstances. Most classes of drugs are equally efficacious in reducing A1C, with the exception of the AGIs and nateglinide. This conclusion is now garnered from newer studies, both when a specific agent is compared to placebo (Table 1) or when two drugs are compared to each other (Table 2).

Actual medication choice should incorporate not only consideration of glucose-lowering efficacy and contraindications, but also the myriad of other clinical features of individual patients. These include comorbidities, the capacities and tolerances of the patient, anticipated side effects, the degree of glucose control desired, concurrent drug therapy, dosing frequency, and cost.

Most endocrinologists continue to prefer metformin as the optimal first-line agent, particularly in obese patients, as long as no contraindications are present. First-line therapy with TZDs is becoming increasingly popular, but in the absence of convincing outcomes data and in light of side effects and cost, such a choice cannot yet be considered evidence based. Cardiovascular outcomes

studies and investigations exploring the effects of TZDs on β-cell function should be available over the next 1–2 years. The results of these may indeed alter recommendations regarding the optimal initial approach to this disease.

Primary therapy with secretagogues is no longer as popular. In certain patients, particularly those in whom there appears to be a greater degree of pancreatic dysfunction as opposed to insulin resistance, or in those with contraindications for the other agents (e.g., advanced heart failure), their use as initial therapy is logical. Patients with erratic meal schedules and those with marked postprandial glucose excursions may do best with the rapid-acting non-SU secretagogues. The AGIs may best benefit those patients with mild hyperglycemia, particularly those with demonstrable postprandial excursions who are able to tolerate the significant side effect profile of drugs in this class.

## COMBINATION STRATEGIES

As discussed above, diabetes is a complex disorder that involves multiple pathophysiological defects. Data from the UKPDS suggested that a ~ 50% loss of β-cell function was already present in newly diagnosed type 2 diabetic patients.[128] As the disease progresses, further functional decline in β-cell output is apparent. As a result, only 50% of patients were adequately controlled on monotherapy 3 years after diagnosis; by 9 years, this figure had fallen to 25%. Thus, combination therapy involving agents with complementary mechanisms of action is not only logical but frequently necessary to achieve control.

Published trials since our original report confirm the additive beneficial effects on glucose control of agents from different therapeutic classes[19,33,39,58–60,129–145] (Table 3). Typically, the A1C reduction resembles the effect of the added individual agent when used as monotherapy. Few studies, however, suggest an actual "synergistic" effect. Precisely how various regimens function together metabolically remains incompletely understood but is an area of great interest that warrants further inquiry.

Over the past several years, the availability of several combination products incorporating SUs with metformin or metformin with a TZD have been marketed. These convenient formulations may enhance compliance. Their availability raises the potential for starting patients at the outset with two drugs. Such an approach is logical and will likely result in quicker achievement of target glucose levels, particularly in those with the greatest degree of baseline glycemia.

## EMERGING THERAPIES

Additional pharmacological agents will likely soon become available for the management of patients with type 2 diabetes. These include other PPAR-agonists with additional effects on PPAR-α and PPAR-δ, and consequently better lipid effects than current TZDs.[146] Several agents are in late-phase trials, although several others have been dropped at this stage because of toxicity concerns.

Modulation of the incretin system is another area of active investigation by several pharmaceutical companies. Incretin mimetics include glucagon-like peptide-1 agonists and the dipeptidyl peptidase-IV inhibitors,[147,148] which augment endogenous incretin levels. These drugs improve glucose-dependent insulin secretion while simultaneously suppressing glucagon secretion, delaying gastric emptying, and decreasing appetite. Modest decreases in body weight are described with their use.

Obesity, the principle cause of type 2 diabetes, remains an important target for possible drug therapy. Available antiobesity drugs have limited effectiveness on body weight; clearly, newer therapeutic options are needed. One such agent, rimonabant,[149] modulates the endogenous cannabinoid system and appears to be furthest along in development. We suspect that future weight loss agents with more substantive effects on body weight will likely play an increasingly important role in the future therapy of obese type 2 diabetic patients.

## CONCLUSIONS

During the past 5 years, oral agent options for patients with type 2 diabetes have remained relatively static, and there is a paucity of new information from diabetes clinical trials that would significantly affect the way we should prescribe these drugs. In contrast, over the next several years, as the results of key clinical trials are revealed, the optimal therapeutic approach will likely be better defined, specifically regarding the best initial therapy for drug-naive patients. Such a choice may arise from studies exploring the cardiovascular and β-cell impact of various agents, particularly the insulin sensitizers. Other emerging concepts being addressed by ongoing investigations involve the notion of earlier treatment, perhaps even in the prediabetic state, more aggressive progression to combination strategies, and more liberal use of insulin sooner in the disease course.

It is unlikely, however, that any study result will alter the realization that the ideal drug choice for a specific individual is a complex decision that needs to be made by each practitioner, taking into account the risks and benefits of each agent and the requirements, capacities, and unique clinical features of each patient. Moreover, the actual selection may not be as important as an overall comprehensive approach to care that involves not only glycemic management, but also aggressive modification of other cardiovascular risk factors. To what extent emerging drug classes will affect this therapeutic approach to type 2 diabetic patients remains unclear.

## REFERENCES

[1]Ferrannini E: Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. *Endocr Rev* 19:477–490, 1998

[2]Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-

dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 329:1988–1992, 1993

[3]Shulman GI: Cellular mechanisms of insulin resistance. *J Clin Invest* 106:171–176, 2000

[4]Kahn SE: The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 46:3–19, 2003

[5]LeRoith D: Beta-cell dysfunction and insulin resistance in type 2 diabetes: role of metabolic and genetic abnormalities. *Am J Med* 113 (Suppl. 6A):3S–11S, 2002

[6]Robertson RP, Harmon J, Tran PO, Poitout V: Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes* 53 (Suppl. 1):S119–S124, 2004

[7]The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993

[8]Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995

[9]The U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998

[10]American Diabetes Association: Standards of medical care in diabetes (Position Statement). *Diabetes Care* 28 (Suppl. 1):S4–S36, 2005

[11]American Association of Clinical Endocrinologists: Medical guidelines for the management of diabetes mellitus. *Endocr Pract* 8 (Suppl. 1):41–65, 2002

[12]Inzucchi S: Oral antihyperglycemic therapy for type 2 diabetes. *JAMA* 287:360–372, 2002

[13]Doar JW, Thompson ME, Wilde CE, Sewell PF: Diet and oral antidiabetic drugs and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. *BMJ* 1:498–500, 1976

[14]Turner RC: The U.K. Prospective Diabetes Study: a review. *Diabetes Care* 21 (Suppl. 3):C35–C38, 1998

[15]Schade DS, Jovanovic L, Schneider J: A placebo-controlled, randomized study of glimepiride in patients with type 2 diabetes mellitus for whom diet therapy is unsuccessful. *J Clin Pharmacol* 38:636–641, 1998

[16]Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT: Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM: results of two multicenter, randomized, placebo-controlled clinical trials. *Diabetes Care* 20:597–606, 1997

[17]Luis Bautista J, Bugos C, Dirnberger G, Atherton T: Efficacy and safety profile of glimepiride in Mexican American patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther* 25:194–209, 2003

[18]Fischer S, Patzak A, Rietzsch H, Schwanebeck U, Kohler C, Wildbrett J, Fuecker K, Temelkova-Kurktschiev T, Hanefeld M: Influence of treatment with acarbose or glibenclamide on insulin sensitivity in type 2 diabetic patients. *Diabetes Obes Metab* 5:38–44, 2003

[19]Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D, the Glyburide/Metformin Initial Therapy Study Group: Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab* 4:201–208, 2002

[20]Rosenstock J, Samols E, Muchmore DB, Schneider J: Glimepiride, a new once-daily sulfonylurea: a double-blind placebo-controlled study of NIDDM patients. *Diabetes Care* 19:1194–1199, 1996

[21]Zimmerman BR: Sulfonylureas. *Endocrinol Metab Clin North Am* 26:511–521, 1997

[22]Simonson DC, Ferrannini E, Bevilacqua S, Smith D, Barrett E, Carlson R, DeFronzo RA: Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 33:838–845, 1984

[23]Kilo C, Meenan A, Bloomgaren Z: Glyburide versus glipizide in the treatment of patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 14:801–812, 1992

[24]Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, Kiowski W, Amann FW, Gruber D, Harris S, Burger W: Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 20:403–405, 1999

[25]Johnson JA, Majumdar SR, Simpson SH, Toth EL: Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 25:2244–2248, 2002

[26]Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr: Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 33:119–124, 1999

[27]Jollis JG, Simpson RJ Jr, Cascio WE, Chowdhury MK, Crouse JR 3rd, Smith SC Jr: Relation between sulfonylurea therapy, complications, and outcome for elderly patients with acute myocardial infarction. *Am Heart J* 138:S376–S380, 1999

[28]Klamann A, Sarfert P, Launhardt V, Schulte G, Schmiegel WH, Nauck MA: Myocardial infarction in diabetic vs non-diabetic subjects: survival and infarct size following therapy with sulfonylureas. *Eur Heart J* 21:220–229, 2000

[29]Davis TM, Parsons RW, Broadhurst RJ, Hobbs MS, Jamrozik K: Arrhythmias and mortality after myocardial infarction in diabetic patients: relationship to diabetes treatment. *Diabetes Care* 21:637–640, 1998

[30]Halkin A, Roth A, Jonas M, Behar S: Sulfonylureas are not associated with increased mortality in diabetics treated with thrombolysis for acute myocardial infarction. *J Thromb Thrombolysis* 12:177–184, 2001

[31]Jovanovic L, Dailey G 3rd, Huang WC, Strange P, Goldstein BJ: Repaglinide in type 2 diabetes: a 24-week, fixed-dose efficacy and safety study. *J Clin Pharm* 40:49–57, 2000

[32]Goldberg RB, Einhorn D, Lucas CP, Rendell MS, Damsbo P, Huang WC, Strange P, Brodows RG: A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. *Diabetes Care* 21:1897–1903, 1998

[33]Jovanovic L, Hassman DR, Gooch B, Jain R, Greco S, Khutoryansky N, Hale PM: Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. *Diabetes Res Clin Pract* 63:127–134, 2004

[34]Derosa G, Mugellini A, Ciccarelli L, Crescenzi G, Fogari R: Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther* 25:472–484, 2003

[35]Madsbad S, Kilhovd B, Lager I, Mustajoki P, Dejgaard A, the Scandinavian Repaglinide Group: Comparison between repaglinide and glipizide in type 2 diabetes mellitus: a 1-year multicentre study. *Diabet Med* 18:395–401, 2001

[36]Hanefeld M, Bouter KP, Dickinson S, Guitard C: Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 23:202–207, 2000

[37]Horton ES, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S: Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 23:1660–1665, 2000

[38]Saloranta C, Hershon K, Ball M, Dickinson S, Holmes D: Efficacy and safety of nateglinide in type 2 diabetic patients with modest fasting hyperglycemia. *J Clin Endocrinol Metab* 87:4171–4176, 2002

[39]Rosenstock J, Shen SG, Gatlin MR, Foley JE: Combination therapy with nateglinide and a thiazolidinedione improves glycemic control in type 2 diabetes. *Diabetes Care* 25:1529–1533, 2002

[40]Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338:867–872, 1998

[41]Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Inzucchi SE, Schumann WC, Petersen KF, Landau BR, Shulman GI: Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 49:2063–2069, 2000

[42]Bailey CJ, Turner RC: Metformin. *N Engl J Med* 334:574–579, 1996

[43]Cusi K, DeFronzo RA: Metformin: a review of its metabolic effects. *Diabetes Rev* 6:89–130, 1998

[44]Yu JG, Kruszynska YT, Mulford MI, Olefsky JM: A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. *Diabetes* 48:2414–2421, 1999

[45]Johansen K: Efficacy of metformin in the treatment of NIDDM: a meta-analysis. *Diabetes Care* 22:33–37, 1999

[46]DeFronzo RA, Goodman AM: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995

[47]Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F, Cohen JM, Grandmottet P, Vague P, Safar ME, Eschwege E: The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. *Diabetes Care* 19:920–926, 1996

[48]Mather KJ, Verma S, Anderson TJ: Improved endothelial function with metformin in type 2 diabetes mellitus. *J Am Col Cardiol* 37:1344–1350, 2001

[49]Hundal RS, Inzucchi SE: Metformin: new understandings, new uses. *Drugs* 63:1879–1894, 2003

[50]U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998

[51]Olsson J, Lindberg G, Gottsater M, Lindwall K, Sjostrand A, Tisell A, Melander A: Increased mortality in type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. *Diabetologia* 43:558–560, 2000

[52]Kao J, Tobis J, McClelland RL, Heaton MR, Davis BR, Holmes DR Jr, Currier JW: Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. *Am J Cardiol* 93:1347–1350, 2004

[53]Dornan T, Heller S, Peck G, Tattersall R: Double-blind evaluation of efficacy and tolerability of metformin in NIDDM. *Diabetes Care* 14:342–344, 1991

[54]Nagi D, Yudkin J: Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects; a study of two ethnic groups. *Diabetes Care* 16:621–629, 1993

[55]Grant PJ: The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. *Diabetes Care* 19:64–66, 1996

[56]Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL: Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 103:491–497, 1997

[57]Hoffmann J, Spengler M: Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. *Am J Med* 103:483–490, 1997

[58]Chiasson JL, Naditch L, the Miglitol Canadian University Investigator Group: The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care* 24:989–994, 2001

[59]Goldstein BJ, Pans M, Rubin CJ: Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. *Clin Ther* 25:890–903, 2003

[60]Marre M, Howlett H, Lehert P, Allavoine T: Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in type 2 diabetic patients inadequately controlled on metformin. *Diabet Med* 19:673–680, 2002

[61]Lord JM, Flight IH, Norman RJ: Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 327:951–953, 2003

[62]De Leo V, la Marca A, Petraglia F: Insulin-lowering agents in the management of polycystic ovary syndrome. *Endocr Rev* 24:633–667, 2003

[63]Tsilchorozidou T, Prelevic GM: The role of metformin in the management of polycystic ovary syndrome. *Curr Opin Obstet Gynecol* 15:483–488, 2003

[64]Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, the DPP Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002

[65]Masoudi FA, Wang Y, Inzucchi SE , Setaro JF, Havranek EP, Foody JM, Krumholz HM: Metformin and thiazolidinedione use in Medicare patients with heart failure. *JAMA* 290:81–85, 2003

[66]Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD, the DARTS/MEMO Collaboration: Contraindications to metformin therapy in patients with type 2 diabetes: a population-based study of adherence to prescribing guidelines. *Diabet Med* 18:483–488, 2001

[67]Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH: Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 162:434–437, 2002

[68]Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM: Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 111:583–590, 2005

[69]Mudaliar S, Henry RR: New oral therapies for type 2 diabetes mellitus: the glitazones or insulin sensitizers. *Annu Rev Med* 52:239–257, 2001

[70]Frias JP, Yu JG, Kruszynska YT, Olefsky JM: Metabolic effects of troglitazone therapy in type 2 diabetic, obese, and lean normal subjects. *Diabetes Care* 23:64–69, 2000

[71]Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J: Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. *N Engl J Med* 331:1188–1193, 1994

[72]Maggs DG, Burant CF, Buchanan TA, Cline G, Gumbioner B, Hsueh WA, Inzucchi S, Kelly D, Nolan J, Olefsky JM, Polonsky KS, Silver D, Valiquett TR, Shulman GI: Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. *Ann Intern Med* 128:176–185, 1998

[73]Petersen KF, Krssak M, Inzucchi S, Cline GW, Dufour S, Shulman GI: Mechanism of troglitazone action in type 2 diabetes. *Diabetes* 49:827–831, 2000

[74]Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA: The hormone resistin links obesity to diabetes. *Nature* 409:307–312, 2001

[75]Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI: Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 106:679–684, 2002

[76]Chu NV, Kong AP, Kim DD, Armstrong D, Baxi S, Deutsch R, Caulfield M, Mudaliar SR, Reitz R, Henry RR, Reaven PD: Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care* 25:542–549, 2002

[77]Boyle PJ: What are the effects of peroxisome proliferator-activated receptor agonists on adiponectin, tumor necrosis factor-alpha, and other cytokines in insulin resistance? *Clin Cardiol* 27 (7 Suppl. 4):IV11–IV16, 2004

[78]Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA: Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 134:61–71, 2001

[79]Gegick CG, Altheimer MD: Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 7:162–169, 2001

[80]Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE, the Pioglitazone 026 Study Group: The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Art Dis* 12:413–423, 2001

[81]Lawrence JM, Reid J, Taylor GJ, Stirling C, Reckless J: Favorable effects of pioglitazone and metformin compared with gliclazide on lipoprotein subfractions in overweight patients with early type 2 diabetes. *Diabetes Care* 27:41–46, 2004

[82]Fullert S, Schneider F, Haak E, Rau H, Badenhoop K, Lubben G, Usadel KH, Konrad T: Effects of pioglitazone in nondiabetic patients with arterial hypertension: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 87:5503–5506, 2002

[83]Grossman E: Rosiglitazone reduces blood pressure and urinary albumin excretion in type 2 diabetes. *J Hum Hypertens* 17:5–6, 2003

[84]Uwaifo GI, Ratner RE: The roles of insulin resistance, hyperinsulinemia, and thiazolidinediones in cardiovascular disease. *Am J Med* 115 (Suppl. 8A):12S–19S, 2003

[85]Paradisi G, Steinberg HO, Shepard MK, Hook G, Baron AD: Troglitazone therapy improves endothelial function to near normal levels in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:576–580, 2003

[86]Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor C, Logerfo FW, Horton ES, Veves A: The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. *Metabolism* 52:173–180, 2003

[87]Sidhu JS, Cowan D, Kaski JC: The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. *J Am Coll Cardiol* 42:1757–1763, 2003

[88]Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y: Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 86:3452–3456, 2001

[89]Levi Z, Shaish A, Yacov N, Levkovitz H, Trestman S, Gerber Y, Cohen H, Dvir A, Rhachmani R, Ravid M, Harats D: Rosiglitazone (PPAR gamma-agonist) attenuates atherogenesis with no effect on hyperglycaemia in a combined diabetes-atherosclerosis mouse model. *Diabetes Obes Metab* 5:45–50, 2003

[90]Marx N, Kehrle B, Kohlhammer K, Grub M, Koenig W, Hombach V, Libby P, Plutzky J: PPAR activators as antiinflammatory mediators in human T lymphocytes: implications for atherosclerosis and transplantation-associated arteriosclerosis. *Circ Res* 90:703–710, 2002

[91]de Dios ST, Bruemmer D, Dilley RJ, Ivey ME, Jennings GL, Law RE, Little PJ: Inhibitory activity of clinical thiazolidinedione peroxisome proliferator activating receptor-gamma ligands toward internal mammary artery, radial artery, and saphenous vein smooth muscle cell proliferation. *Circulation* 107:2548–2550, 2003

[92]Derosa G, Cicero AF, Gaddi A, Ragonesi PD, Fogari E, Bertone G, Ciccarelli L, Piccinni MN: Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. *Clin Ther* 26:744–754, 2004

[93]Sidhu JS, Kaposzta Z, Markus HS, Kaski JC: Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. *Arterio Thromb Vasc Biol* 24:930–934, 2004

[94]Takagi T, Yamamuro A, Tamita K, Yamabe K, Katayama M, Mizoguchi S, Ibuki M, Tani T, Tanabe K, Nagai K, Shiratori K, Morioka S, Yoshikawa J: Pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus: an intravascular ultrasound scanning study. *Am Heart J* 146:E5, 2003

[95]Takagi T, Yamamuro A, Tamita K, Yamabe K, Katayama M, Morioka S, Akasaka T, Yoshida K: Impact of troglitazone on coronary stent implantation using small stents in patients with type 2 diabetes mellitus. *Am J Cardiol* 89:318–322, 2002

[96]Teirstein PS, Kao JA, Castarella P, Huppe G, Sirkin K, Grise M, Giap H, Koka A, Tripuraneni P: Insulin sensitizers are associated with improved outcomes in diabetic patients undergoing brachytherapy. *J Am Coll Cardiol* 43 (Suppl. A):1025–1041, 2002

[97]Koro CE, Fu Q, Dirani RG, Fedder DO: Beneficial effects of thiazolidinediones on myocardial infarction risk in patients with type 2 diabetes (Abstract). *Diabetes* 53 (Suppl. 2):A247, 2004

[98]Mulestein JB, Pearson RR, Horne BD, Bair TL, Thomas H, Lappe DL, Anderson JL, Jones HU, Lavasani F, Einhorn D, Renlund DG: Use of either metformin or thiazolidinedione is associated with improved survival among patients with type 2 diabetes from a registry of 16,203 diabetic patients. *J Am Coll Cardiol* 43 (Suppl. A):810–815, 2004

[99]Sauer WH, Berlin JA, Kimmel SE: Insulin sensitizing drug use is associated with a reduced risk of myocardial infarction in type 2 diabetics (Abstract). *Circulation* 108 (Suppl IV):IV–767, 2003

[100]Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 51:2796–2803, 2002

[101]Juhl CB, Hollingdal M, Porksen N, Prange A, Lonnqvist F, Schmitz O: Influence of rosiglitazone treatment on beta-cell function in type 2 diabetes: evidence of an increased ability of glucose to entrain high-frequency insulin pulsatility. *J Clin Endocrinol Metab* 88:3794–3800, 2003

[102]Goke B, Lubben G, Bates PC: Coefficient of beta-cell failure in patients with type 2 diabetes treated with pioglitazone or acarbose. *Exp Clin Endocrinol Diabetes* 112:115–117, 2004

[103]Ovalle F, Bell DS: Clinical evidence of thiazolidinedione-induced improvement of pancreatic beta-cell function in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 4:56–59, 2002

[104]Khan MA. St Peter JV. Xue JL: A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 25:708–711, 2002

[105]Herz M, Johns D, Reviriego J, Grossman LD, Godin C, Duran S, Hawkins F, Lochnan H, Escobar-Jimenez F, Hardin PA, Konkoy CS, Tan MH: A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. *Clin Ther* 25:1074–1095, 2003

[106]Scherbaum WA, Goke B, the German Pioglitazone Study Group: Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study. *Horm Metab Res* 34:589–595, 2002

[107]Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, Shestakova M, Herz M, Johns D, Schluchter BJ, Festa A, Tan MH: Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab* 88:1637–1645, 2003

[108]Miyazaki Y, Matsuda M, DeFronzo RA: Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. *Diabetes Care* 25:517–523, 2002

[109]Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R: Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 108:2941–2948, 2003

[110]Goke B, Herrmann-Rinke C: The evolving role of alpha-glucosidase inhibitors. *Diabetes Metab Rev* 14 (Suppl. 1):S31–S38, 1998

[111]Lebowitz HE: α-glucosidase inhibitors as agents in the treatment of diabetes. *Diabetes Rev* 6:132–145, 1998

[112]Hanefeld M, Fischer S, Schulze J, Spengler M, Wargenau M, Scholberg K, Fucker K: Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. *Diabetes Care* 14:732–737, 1991

[113]Hotta N, Kabuta H, Sano T, Matsumae H, Yamada H, Kitazawa S, Sakamoto N: Long-term effect of acarbose on glycaemic control in non-insulin-dependent diabetes mellitus: a placebo-controlled double-blind study. *Diabet Med* 10:134–138, 1993

[114]Santeusanio F, Ventura MM, Contandini S, Compagnucci P, Moriconni V, Zaccarini P: Efficacy and safety of two different doses of acarbose in non-insulin-dependent diabetic patients treated by diet alone. *Diabetes Nutr Metab* 6:147–154, 1993

[115]Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, Ryann EA, Tan MH, Wolever TM: The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: a multicenter controlled clinical trial. *Ann Intern Med* 121:928–935, 1994

[116]Coniff RF, Shapiro JA, Robbins D, Kleinfield R, Seaton TB, Beisswenger P, McGill JB: Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM: a placebo-controlled dose-comparison study. *Diabetes Care* 18:817–824, 1995

[117]Braun D, Schonherr U, Mitzkat H-J: Efficacy of acarbose monotherapy in patients with type 2 diabetes: a double-blind study conducted in general practice. *Endocrinol Metab* 3:275–280, 1996

[118]Fischer S, Hanefeld M, Spengler M, Boehme K, Temelkova-Kurktschiev T: European study on dose-response relationship of acarbose as a first-line drug in non-insulin-dependent diabetes mellitus: efficacy and safety of low and high doses. *Acta Diabetol* 35:34–40, 1998

[119]Johnston PS, Feig PU, Coniff RF, Krol A, Kelley DE, Mooradian AD: Chronic treatment of African-American type 2 diabetic patients with alpha-glucosidase inhibition. *Diabetes Care* 21:416–422, 1998

[120]Scott R, Lintott CJ, Zimmet Campbell L, Bowen K, Welborn T: Will acarbose improve the metabolic abnormalities of insulin-resistant type 2 diabetes mellitus? *Diabetes Res Clin Pract* 43:179–185, 1999

[121]Hasche H, Mertes G, Bruns C, Englert R, Genthner P, Heim D, Heyen P, Mahla G, Schmidt C, Schulze-Schleppinghof B, Steger-Johannsen G: Effects of acarbose treatment in type 2 diabetic patients under dietary training: a multicentre, double-blind, placebo-controlled, 2-year study. *Diabetes Nutr Metab* 12:277–285, 1999

[122]Coniff RF, Shapiro JA, Seaton TB, Bray GA: Multicenter, placebo-controlled trial comparing acarbose with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. *Am J Med* 98:443–451, 1995

[123]Josse RG, Chiasson JL, Ryan EA, Lau DC, Ross SA, Yale JF, Leiter LA, Maheux P, Tessier D, Wolever TM, Gerstein H, Rodger NW, Dornan JM, Murphy LJ, Rabasa-Lhoret R, Meneilly GS: Acarbose in the treatment of elderly patients with type 2 diabetes. *Diabetes Res Clin Pract* 59:37–42, 2003

[124]Drent ML, Tollefsen AT, van Heusden FH,

Hoenderdos EB, Jonker JJ, van der Veen EA: Dose-dependent efficacy of miglitol, an alpha-glucosidase inhibitor, in type 2 diabetic patients on diet alone: results of a 24-week double-blind placebo-controlled study. *Diabetes Nutr Metab* 15:152–159, 2002

[125]Salman S, Salman F, Satman I, Yilmaz Y, Ozer E, Sengul A, Demirel HO, Karsidag K, Dinccag N, Yilmaz MT: Comparison of acarbose and gliclazide as first-line agents in patients with type 2 diabetes. *Curr Med Res Opin* 16:296–306, 2001

[126]van de Laar FA, Lucassen PL, Kemp J, van de Lisdonk EH, van Weel C, Rutten GE: Is acarbose equivalent to tolbutamide as first treatment for newly diagnosed type 2 diabetes in general practice? A randomised controlled trial. *Diabetes Res Clin Pract* 63:57–65, 2004

[127]Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, the STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003

[128]Turner RC, Cull CA, Frighi V, Homan R, the UKPDS Group: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA* 281:2005–2012, 1999

[129]Blonde L, Rosenstock J, Mooradian AD, Piper BA, Henry D: Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. *Diabetes Obes Metab* 4:368–375, 2002

[130]Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S: Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. *Diabet Med* 18:828–834, 2001

[131]Lin BJ, Wu HP, Huang HS, Huarng J, Sison A, bin Abdul Kadir DK, Cho CG, Sridama W, the Writing Group for the Asian Study of Acarbose With Sulfonylureas: Efficacy and tolerability of acarbose in Asian patients with type 2 diabetes inadequately controlled with diet and sulfonylureas. *J Diabetes Complications* 17:179–185, 2003

[132]Phillips P, Karrasch J, Scott R, Wilson D, Moses R: Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. *Diabetes Care* 26:269–273, 2003

[133]Van Gaal L, Maislos M, Schernthaner G, Rybka J, Segal P: Miglitol combined with metformin improves glycaemic control in type 2 diabetes. *Diabetes Obes Metab* 3:326–331, 2001

[134]Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH, the QUARTET Study Group: One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes Care* 27:141–147, 2004

[135]Nagasaka S, Aiso Y, Yoshizawa K, Ishibashi S: Comparison of pioglitazone and metformin efficacy using homeostasis model assessment. *Diabet Med* 21:136–141, 2004

[136]Kerenyi Z, Samer H, James R, Yan Y, Stewart M: Combination therapy with rosiglitazone and glibenclamide compared with upward titration of glibenclamide alone in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 63:213–223, 2004

[137]Yang J, Di F, He R, Zhu X, Wang D, Yang M, Wang Y, Yuan S, Chen J: Effect of addition of low-dose rosiglitazone to sulphonylurea therapy on glycemic control in type 2 diabetic patients. *Chin Med J* 116:785–787, 2003

[138]Vongthavaravat V, Wajchenberg BL, Waitman JN, Quimpo JA, Menon PS, Ben Khalifa F, Chow WH, the 125 Study Group: An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. *Curr Med Res Opin* 18:456–461, 2002

[139]Gomez-Perez FJ, Fanghanel-Salmon G, Antonio Barbosa J, Montes-Villarreal J, Berry RA, Warsi G, Gould EM: Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. *Diabetes Metab Res Rev* 18:127–134, 2002

[140]Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL: Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med* 111:10–17, 2001

[141]Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino LJ, DeFronzo RA: Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 24:710–719, 2001

[142]Fonseca V, Grunberger G, Gupta S, Shen S, Foley JE: Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improves overall glycemic control. *Diabetes Care* 26:1685–1690, 2003

[143]Raskin P, Klaff L, McGill J, South SA, Hollander P, Khutoryansky N, Hale PM, the Repaglinide vs. Nateglinide Metformin Combination Study Group: Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. *Diabetes Care* 26:2063–2068, 2003

[144]Marre M, Van Gaal L, Usadel KH, Ball M, Whatmough I, Guitard C: Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab* 4:177–186, 2002

[145]Garber AJ, Donovan DS Jr, Dandona P, Bruce S, Park JS: Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. *J Clin Endocrinol Metab* 88:3598–3604, 2003

[146]Blaschke F, Bruemmer D, Law RE: Will the potential of peroxisome proliferator-activated receptor agonists be realized in the clinical setting? *Clin Cardiol* 27 (7 Suppl. 4):IV3–IV10, 2004

[147]Ahren B: Gut peptides and type 2 diabetes mellitus treatment. *Curr Diab Rep* 3:365–372, 2003

[148]Deacon CF: Therapeutic strategies based on glucagon-like peptide 1. *Diabetes* 53:2181–2189, 2004

[149]Bays HE: Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes Res* 12:1197–1211, 2004

[150]Fonseca VA, Valiquett TR, Huang SM, Ghazzi MN, Whitcomb RW: Troglitazone monotherapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled study. *J Clin Endocrinol Metab* 83:3169–3176, 1998

[151]Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A, the Rosiglitazone Clinical Trials Study Group: Once- and twice-dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes Care* 24:308–315, 2001

[152]Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI, the Rosiglitazone Clinical Trials Study Group: Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 86:280–288, 2001

[153]Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL: Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *Diabetes Care* 23:1605–1611, 2000

[154]Rosenstock J, Corrao PJ, Goldberg RB, Kilo C: Diabetes control in the elderly: a randomized, comparative study of glyburide versus glipizide in non-insulin-dependent diabetes mellitus. *Clin Ther* 15:1031–1040, 1993

[155]Carlson RF, Isley WL, Ogrinc FG, Klobucar TR: Efficacy and safety of reformulated, micronized glyburide tablets in patients with non-insulin-dependent diabetes mellitus: a multicenter, double-blind, randomized trial. *Clin Ther* 15:788–796, 1993

[156]Birkeland KI, Furuseth K, Melander A, Mowinckel P, Vaaler S: Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide: glycemic control and insulin secretion during 15 months. *Diabetes Care* 17:45–49, 1994

[157]Dills DG, Schneider J: Clinical evaluation of glimepiride versus glipizide in NIDDM in a double-blind comparative study. *Horm Metab Res* 28:426–429, 1996

[158]Kitbachi AE, Kaminska E, Fisher JN, Sherman A, Pitts K, Bush A, Bryer-Ash M: Comparative efficacy and potency of long-term therapy with glipizide or glyburide in patients with type 2 diabetes mellitus. *Am J Med Sci* 319:143–148, 2000

[159]Tessier D, Maheux P, Khalil A, Fulop T: Effects of gliclazide versus metformin on the clinical profile and lipid peroxidation markers in type 2 diabetes. *Metab Clin Exp* 48:897–903, 1999

[160]Campbell IW, Menzies DG, Chalmers J, McBain AM, Brown IR: One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. *Diabetes Metab* 20:394–400, 1994

[161]Hermann LS: Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: a double-blind controlled study. *Diabetes Care* 17:1100–1109, 1994

[162]Clarke BF, Campbell IW: Comparison of metformin and chlorpropamide in non-obese, maturity-onset diabetics uncontrolled by diet. *BMJ* 2:1576–1578, 1997

[163]Hoffmann J, Spengler M: Efficacy of 24-week monotherapy with acarbose, glibenclamide, or placebo in NIDDM patients. *Diabetes Care* 17:561–566, 1994

[164]Segal P, Feig PU, Schernthaner G, Ratzmann KP, Rypka J, Petzinna D, Berlin C: The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone. *Diabetes Care* 20:687–691, 1997

[165]Kirk JK, Pearce KA, Michielutte R, Summerson JH: Troglitazone or metformin in combination with sulfonylureas for patients with type 2 diabetes? *J Fam Pract* 48:879–882, 1999

[166]Horton ES, Whitehouse F, Ghazzi MN, Venable TC, Whitcomb RW: Troglitazone in combination with sulfonylureas restores glycemic control in patients with type 2 diabetes. *Diabetes Care* 21:1462–1469, 1998

[167]Marbury T, Huang WC, Strange P, Lebowitz H: Repaglinide versus glyburide: a one-year comparison trial. *Diabetes Res Clin Pract* 43:155–166, 1999

[168]Landgraf R, Bilo HJ, Muller PG: A comparison of repaglinide and glibenclamide in the treatment of type 2 diabetic patients previously treated with sulphonylureas. *Eur J Clin Pharm* 55:165–171, 1999

[169]Wolffenbuttel BH, Landgraf R: A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care* 22:463–477, 1999

[170]Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, Donnelly T, Moffitt P, Hopkins H: Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 22:119–124, 1999

[171]Raskin P, Jovanovic L, Berger S, Schwartz S, Woo V, Ratner R: Repaglinide/troglitazone combination therapy: improved glycemic control in type 2 diabetes. *Diabetes Care* 23:979–983, 2000

[172]Erle G, Lovise S, Stocchiero C, Lora L, Coppini A, Marchetti P, Merante D: A comparison of preconstituted, fixed combinations of low-dose glyburide plus metformin versus high-dose glyburide alone in the treatment of type 2 diabetic patients. *Acta Diabetol* 36:61–65, 1999

[173]Costa B, Pinol C: Acarbose in ambulatory treatment of non-insulin-dependent diabetes mellitus associated to imminent sulfonylurea failure: a randomized-multicentric trial in primary healthcare. *Diabetes Res Clin Pract* 38:33–40, 1997

[174]Rosenstock J, Brown A, Fischer J, Jain A, Littlejohn T, Nadeau D, Sussman A, Taylor T, Krol A, Magner J: Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. *Diabetes Care* 21:2050–2055, 1998

[175]Scorpiglione N, Belfiglio M, Carinci F, Cavaliere D, De Curtis A, Franciosi M, Mari E, Sacco M, Tognoni G, Nicolucci A: The effectiveness, safety and epidemiology of the use of acarbose in the treatment of patients with type II diabetes mellitus: a model of medicine-based evidecce. *Eur J Clin Pharmacol* 43:179–185, 1999

[176]Holman RR, Cull CA, Turner RC: A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UKPDS 44). *Diabetes Care* 22:960–964, 1999

[177]Willms B, Ruge D: Comparison of acarbose and metformin in patients with type 2 diabetes mellitus insufficiently controlled with diet and sulphonylureas: a randomized, placebo-controlled study. *Diabet Med* 16:755–761, 1999

[178]Standl E, Schernthaner G, Rybka J, Hanefeld M, Raptis SA, Naditch L: Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pract* 51:205–213, 2001

[179]Johnston PS, Coniff RF, Hoogwerf BJ, Santiago JV, Pi-Sunyer FX, Krol A: Effects of the carbohydrase inhibitor miglitol in sulfonylurea-treated NIDDM patients. *Diabetes Care* 17:20–29, 1994

[180]Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL: Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther* 22:1395–1409, 2000

[181]Fonseca V, Rosenstock J, Patwardhan R, Salzman A: Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 283:1695–1702, 2000

[182]Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan RN: Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients. *Diabet Med* 17:40–47, 2000

[183]Buysschaert M, Bobbioni E, Starkie M, Frith L: Troglitazone in combination with sulphonylurea improves glycaemic control in type 2 diabetic patients inadequately controlled by sulphonylurea therapy alone. *Diabet Med* 16:147–153, 1999

[184]Iwamoto Y, Kosaka K, Kuzuya T, Akanuma Y, Shigeta Y, Kaneko T: Effect of combination therapy of troglitazone and sulphonylureas in patients with type 2 diabetes who were poorly controlled by sulphonylurea therapy alone. *Diabet Med* 13:365–370, 1996

*Bonnie Kimmel, MD, is a senior resident in general internal medicine at the Yale Primary Care Residency Program in Waterbury and New Haven, Conn. Silvio E. Inzucchi, MD, is a professor of medicine and clinical director of the Section of Endocrinology at Yale University School of Medicine and director of the Yale Diabetes Center at Yale-New Haven Hospital in New Haven, Conn.*

***Note of disclosure:*** *Dr. Inzucchi has served on advisory boards for Takeda, Pfizer, and Novartis. He has received honoraria for speaking engagements from Takeda, GlaxoSmithKline, and Bristol-Myers Squibb. These companies market oral pharmaceutical products for the treatment of diabetes.*