

# Oral Agents for Type 2 Diabetes: An Update

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**T**ype 2 diabetes is a multifactorial metabolic disease characterized by abnormalities at multiple organ sites. These defects include insulin resistance and insulin deficiency.<sup>1,2</sup> 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.<sup>3</sup> The latter is an apparent progressive process with both functional defects in islet cell function and, eventually, apparent loss of  $\beta$ -cell mass.<sup>4,5</sup> These defects are intimately linked, with derangements in one system exacerbating those in the others.<sup>6</sup> 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.<sup>7-9</sup> 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.<sup>10,11</sup> 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,<sup>12</sup> 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

## 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.

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<sub>1c</sub> (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.

## 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  $\beta$ -cell,<sup>13</sup> 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.<sup>14</sup> Therefore,  $\beta$ -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%.<sup>9,15,16</sup> Several published SU studies

completed since our original report was published confirm these points (Tables 1 and 2).<sup>17–20</sup> 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<sup>9,15,21,22</sup> and hypoglycemia.<sup>9,21,23</sup> 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.<sup>24</sup> 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,<sup>25–27</sup> but not in others,<sup>28–30</sup> 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.<sup>9</sup>

### 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,<sup>31–35</sup> whereas the latter appears to be less efficacious<sup>36–39</sup> (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<sup>40,41</sup>—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.<sup>40,42–44</sup> 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.<sup>40,42,45</sup> Other nonglycemic benefits have been reported, including modest lowering of lipid levels,<sup>46,47</sup> and improvements in fibrinolysis,<sup>47</sup> inflammatory markers, and endothelial function.<sup>48</sup>

Numerous studies during the past several years have continued to demonstrate a benefit of metformin on these cardiovascular risk markers.<sup>49</sup> 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.<sup>50</sup> 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.<sup>50</sup> Such a finding appeared to be confirmed in a more recent retrospective analysis.<sup>51</sup> Another group of investigators has suggested a cardiovascular benefit in patients undergoing percutaneous coronary intervention.<sup>52</sup>

In placebo-controlled trials, metformin consistently lowers A1C by 1–2%.<sup>19,46,50,53–58</sup> 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<sup>59,60</sup> (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.<sup>61–63</sup>

Since our original report, the results from the Diabetes Prevention Program<sup>64</sup> 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%.<sup>64</sup> 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<sup>42</sup> 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*
<b>SUs</b>					
Luis Bautista et al. 2003	17	Glimepiride 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%
<b>Metformin</b>					
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	Metformin 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%
<b>AGIs</b>					
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%
Santeusano 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%
<b>TZDs</b>					
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%
<b>Non-SU Secretagogues</b>					
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.<sup>12</sup> 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
<b>SUs</b>					
van de Laar et al. 2004	126	Tolbutamide vs. acarbose	96	30 weeks	Tolbutamide more efficacious (A1C -1.8 vs. -1.1% [ <i>P</i> 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
<b>Metformin</b>					
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	Metformin 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% [ <i>P</i> < 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
<b>AGIs</b>					
Fischer et al. 2003	18	Acarbose vs. glibenclamide	77	16 weeks	Glibenclamide more efficacious (A1C -1.3 vs. 0.0% [ <i>P</i> < 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% [ <i>P</i> 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)
<b>TZDs</b>					
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
<b>Non-SU Secretagogues</b>					
Jovanovic et al. 2004	33	Repaglinide vs. pioglitazone	246	24 weeks	Equivalent efficacy
Derosa et al. 2003	34	Repaglinide vs. glimepiride	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% [ <i>P</i> < 0.05])
Horton et al. 2000*	37	Nateglinide vs. metformin	701	24 weeks	Metformin more efficacious (A1C -0.8 vs. -0.5% [ <i>P</i> < 0.01])
Raskin et al. 2000*	171	Repaglinide vs. troglitazone	256	22 weeks	Repaglinide more efficacious (A1C -0.8 vs. -0.4% [ <i>P</i> < 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
Wolffenbittel 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.<sup>12</sup>

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.<sup>65-67</sup> Despite this, complication rates are few, suggesting that current pre-

scribing 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.<sup>68</sup>

#### TZDs

TZDs are activators of the nuclear transcription factor peroxisome proliferator-

activated receptor- $\gamma$  (PPAR- $\gamma$ ) and modulate the activity of a host of genes that regulate carbohydrate and lipid metabolism.<sup>69</sup> 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*
<b>SUs + Metformin</b>					
Marre et al. 2002	60	Metformin + glibenclamide vs. either alone	411	16 weeks	-1.0% vs. metformin -0.9% vs. glibenclamide
Garber et al. 2003	145	Glyburide + metformin vs. either alone	485	16 weeks	-0.5% vs. glyburide -0.7% vs. metformin
Goldstein et al. 2003	59	Glipizide + metformin vs. either alone	247	18 weeks	-1.1% vs. glipizide -1.0% vs. metformin
Garber et al. 2002	19	Glyburide + metformin vs. either alone	800	20 weeks	-0.3% vs. glyburide -0.5% vs. metformin
Blonde et al. 2002	129	Glyburide + metformin vs. either alone	639	16 weeks	-1.7% vs. glyburide -1.9% vs. metformin
Charpentier et al. 2001	130	Metformin + glimepiride 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%
<b>AGIs</b>					
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 -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) -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) -0.8% (vs. acarbose) 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%

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cle.<sup>70-73</sup> Some investigators have also demonstrated a reduction of hepatic glucose production,<sup>44,72</sup> although not to as significant a degree as with metformin. PPAR- $\gamma$  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- $\alpha$ .<sup>74</sup> 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,<sup>75-77</sup> lipids,<sup>78-81</sup> blood pressure,<sup>78,82,83</sup> endothelial function,<sup>78,84-87</sup> and certain cellular and molecular events that control the atherosclerotic process.<sup>88-91</sup> Recently,

pioglitazone has been shown to have better effects than rosiglitazone on plasma lipids,<sup>92</sup> 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,<sup>93</sup> a surrogate for atherosclerosis, as well as coronary artery restenosis after angioplasty<sup>94,95</sup> 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*
<b>TZDs</b>					
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 -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 -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%
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%
<b>Non-SU Secretagogues</b>					
Fonseca et al. 2003	142	Rosiglitazone + nateglinide vs. rosiglitazone + placebo	402	24 weeks	-0.8%
Raskin et al. 2003	143	Metformin + repaglinide vs. metformin + nateglinide	192	16 weeks	Repaglinide -1.3% vs. nateglinide -0.7%
Marre et al. 2002	144	Metformin + nateglinide 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 -0.9% vs. repaglinide
Moses et al. 1999†	170	Metformin + repaglinide vs. either alone	83	3 months	-1.1% vs. metformin -1.0% vs. repaglinide
Horton et al. 2000†	37	Metformin + nateglinide vs. either alone	701	24 weeks	-0.6% vs. metformin -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.<sup>12</sup>

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.<sup>96–99</sup> 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”  $\beta$ -cell function. The most convincing data come from the Troglitazone in the Prevention of Diabetes study<sup>100</sup> 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  $\beta$ -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  $\beta$ -cell function.<sup>101–103</sup> 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<sup>104</sup> and typically in the same range as that achieved by the SUs or metformin, in both placebo-controlled and head-to-head studies<sup>39, 105–108</sup> (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 con-

sensus 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).<sup>109</sup> 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.<sup>68</sup>

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.

### $\alpha$ -Glucosidase Inhibitors

$\alpha$ -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.<sup>110,111</sup> 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%<sup>112–122</sup> 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<sup>18,58,123–126</sup> (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).<sup>127</sup> 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  $\beta$ -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  $\beta$ -cell function was already present in newly diagnosed type 2 diabetic patients.<sup>128</sup> As the disease progresses, further functional decline in  $\beta$ -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<sup>19,33,39,58–60,129–145</sup> (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 metaboli-

cally 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- $\alpha$  and PPAR- $\delta$ , and consequently better lipid effects than current TZDs.<sup>146</sup> 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,<sup>147,148</sup> 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 anti-obesity drugs have limited effectiveness on body weight; clearly, newer therapeutic options are needed. One such agent, rimonabant,<sup>149</sup> 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-naïve patients. Such a choice may arise from studies exploring the cardiovascular and  $\beta$ -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.

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**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.