



# How to select and combine oral agents for patients with type 2 diabetes mellitus

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Combination therapy;  
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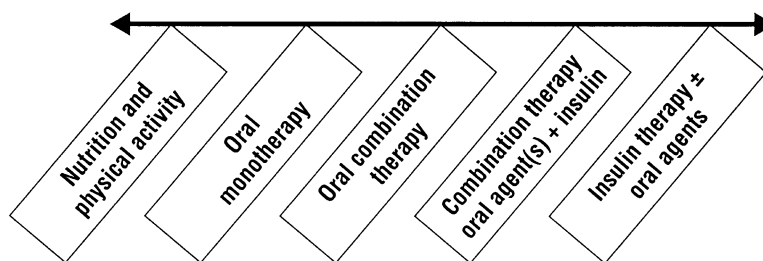
The increased number of oral agents available to treat patients with type 2 diabetes mellitus (DM) has presented clinicians with choices about how to combine them when monotherapy is not adequate to achieve glycemic targets. Initial studies focused on whether a combination of 2 active drugs was better than a single active agent plus placebo. Several factors need to be considered before results of combination regimens from a given protocol can be compared with results from a different study regimen. Some of these factors include population characteristics, baseline control and prior therapies, length of study, and outcomes (glycemic and nonglycemic). Additional factors to be considered are costs and side effects. These studies generally demonstrate that combination therapy is more likely than monotherapy to achieve glucose control in patients not at glycemic targets. The data also demonstrate that inadequate glucose control with a given medication does not necessarily indicate drug failure; indeed, adding a new agent to an existing regimen is typically better than using the new agent as monotherapy. More recent studies have begun to compare regimens each containing 2 drugs (usually with 1 medication in common). Outcomes beyond glycemic control have been measured, including traditional (e.g., lipid profiles, albuminuria) and nontraditional (e.g., high-sensitivity C-reactive protein, plasminogen activator inhibitor type-1) markers. However, modifying traditional markers with these medications has not yet been shown to improve outcomes; modifying nontraditional markers is even less certain. None of these trials have been extended long enough to report on hard clinical end points. Nonetheless, certain combinations may end up being preferable because they have better impact on nonglycemic end points while maintaining equivalent degrees of glucose control. Finally, the costs of multiple medications for DM need to be weighed in the decision-making process faced by clinicians. © 2005 Elsevier Inc. All rights reserved.

In the past decade, >6 new oral medications for the treatment of diabetes mellitus (DM) in 5 different classes have become available to healthcare professionals. The rationale for combining medications stemmed from the UK Prospective Diabetes Study (UKPDS) data, which demonstrated that glycemic control generally worsened

over time and was not achieved by single-drug therapy.<sup>1</sup> The rapid increase in pharmacologic options for treating type 2 DM and the risk for complications from gradually deteriorating control of DM has produced 2 major changes: (1) the replacement of an abrupt stepwise transition from a single oral agent directly to pure insulin therapy, and (2) the recognition that in many patients, combinations of oral agents can achieve target glycemic levels (in conjunction with healthy lifestyle behaviors involving nutrition and physical activity). However, reports on combining oral agents have raised new questions. Variations between available studies limit direct

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**Figure 1** Spectrum of therapies for type 2 diabetes mellitus.

**Table 1** Factors to consider in evaluating studies of combination therapies

- Baseline control
- Size of study
- Duration of diabetes mellitus
- Regimens before randomization
- Length of study
- Comparisons—baseline or placebo
- Glycemic end points
- Nonglycemic end points
- Clinical outcomes
- Side effects—degree and impact
- Costs
- Peer review status

comparisons and impair clinicians' abilities to select appropriate combinations of oral agents. Differences in study design, markers of therapeutic efficacy, costs, and untoward side effects all must be considered when evaluating these new regimens. To optimize the combination of oral medications for patients with type 2 DM, practicing clinicians must comprehend the available data, as well as be aware of what data are as yet unavailable.

Combination therapy with multiple oral agents falls within a spectrum of DM care (**Figure 1**) that attains glycemic targets by relying, at one end, on diet and exercise, and at the other end, on different types of insulin. Between these 2 ends of the spectrum lie strategies that use oral monotherapy or oral agents in combination with insulin. Recent reviews have summarized studies examining monotherapy or add-on therapy (i.e., adding an active agent or placebo to a monotherapy regimen).<sup>2</sup> Because most of these add-on studies show benefit, they will not be reviewed here. This article also will not include studies that have examined the addition of insulin to oral regimens, but will focus on regimens using multiple oral agents without the use of insulin. An underlying assumption is that patients will have received proper diabetes education and will have maximized their ability to make healthy choices regarding nutrition and physical activity. The initial discussion suggests some of the factors that clinicians should consider when evaluating data presented on combination regimens. The subsequent discussion summarizes recent studies that have compared 2 active regimens and ends with some general information on costs.

## Evaluating and comparing combination therapy trials

Choosing a combination of oral agents should depend on results from available research. Although it would be advantageous if clinicians could compare published clinical trials that use different regimens, the various ways in which these trials have been organized, implemented, and conducted make direct comparisons difficult. Available research should be viewed in the context of how it applies to a specific patient and his or her healthcare provider. As clinicians attempt to place different trials in context, they need to consider several variables. **Table 1** provides a list of factors that may vary across trials and that should be considered before comparing one regimen with another.

### Baseline control

Although current guidelines recommend modifying treatment regimens to achieve a hemoglobin (Hb) A<sub>1c</sub> value  $\leq 7.0\%$ ,<sup>3</sup> most clinical trials have used a range of HbA<sub>1c</sub> values for inclusion. Depending on this range, one might expect to see greater or lesser changes from baseline as a new medication is added. Generally, patients with worse glucose control will likely have a greater difference (baseline to end of study) after adding an agent than those who are just above the threshold for desirable control. For example, metformin had greater absolute reductions in fasting plasma glucose (FPG) in patients with higher concentrations of glucose at baseline.<sup>4</sup>

## Power and applicability

Conclusions from studies using smaller numbers of patients do not have the same statistical power as those based on studies with larger populations. However, larger sample sizes can result in statistically significant differences that may not be clinically relevant. Separate from the sample size, a multicenter study will have greater applicability than a single-site investigation. Beyond identifying the sites where a study was conducted, it is also important to know the age, sex, and ethnic/racial composition of the cohort, because those variables also may influence the relevance of the results.

The entire sample size for a study is not always used for measuring all parameters. Within studies, portions of the results may be based on a smaller subset. The subset may be random or may be based on participation from specific centers. The applicability of findings from smaller subsets to larger study populations or to the universe of patients with DM must be considered carefully.

## Onset/duration of DM

Type 2 DM appears to result from a combination of insulin resistance and impaired  $\beta$ -cell secretion. Even if a genetic predisposition for insulin resistance is present, the resistance may only become evident under certain environmental conditions (e.g., those that promote weight gain and obesity). Although many patients who manifest insulin resistance compensate by augmenting endogenous secretion of insulin, those who cannot maintain the hyperinsulinemic state will face gradual declines in insulin concentrations and subsequent hyperglycemia.

As the pathophysiology of the progression of type 2 DM becomes clearer, the benefit of specific drug combinations may depend on the degree or "stage" of either insulin resistance or  $\beta$ -cell secretion. Patients with severe glucose intolerance and poor  $\beta$ -cell mass (or  $\beta$ -cell exhaustion) would not be expected to have a large response to adding a sulfonylurea. Conversely, thiazolidinediones (TZDs; also known as glitazones) may not demonstrate much efficacy in patients with relatively normal indices of insulin sensitivity. Patients with recently diagnosed type 2 DM may be more likely to have some  $\beta$ -cell reserves, whereas those with a longer duration of disease may have less insulin-secretory capacity.

## Prior regimen

In addition to baseline control, evaluating studies of combination therapies should consider the potential impact of previous regimens as well as the duration of washout periods. Patients who were suboptimally controlled (and therefore eligible for a particular trial) with a combination of medications would be expected to have significant deterioration in glucose control if randomized to a study proto-

col arm receiving a single agent plus placebo. Conversely, patients receiving monotherapy who are subsequently randomized to a 2-drug arm would be more likely to improve their glucose control. In a post hoc analysis of a particular combination therapy protocol, these factors were shown to be relevant<sup>5</sup> (see "Comparisons in Study Design").

## Study duration

Depending on a drug's mechanism of action, changes in glycemic control can be observed within several days or up to several weeks. As a result, combination regimens should only be compared after sufficient time has elapsed for maximal benefits to be realized for all agents used in the study. Trials of longer duration may also demonstrate whether improved control is intermittent or sustained over time. Documented ability to maintain glycemic control will be an increasingly important consideration, because certain groups of patients (e.g., some ethnic populations, obese children) are developing type 2 DM at earlier ages and can be expected to initiate and continue oral agents for longer periods of time. Sustained glycemic control will also likely be needed to demonstrate benefits on clinical outcomes. Because trials that have been evaluating various combinations for sufficient time to detect differences in clinical outcomes have not yet been published, the results and conclusions of current studies must be placed in context as demonstrating an impact on glycemic control without complete knowledge of the impact on clinical outcomes.

## Comparisons in study design

After the introduction of new oral agents, initial studies emphasized the benefits of adding a new agent to an older agent versus using a placebo with an older agent ("new plus old" vs. "placebo plus old"). These studies demonstrated the efficacy of combination therapy over monotherapy, and were necessary to evaluate drug interactions and to ensure that the therapeutic agents in the combination did not inadvertently counteract each other. Results from these studies were typically expressed as the difference between the new regimen (new plus old) versus the older agent with placebo (placebo plus old). This manner of expressing results can be misleading, because the natural history of type 2 DM is to worsen over time.<sup>1</sup> Thus, patients in the control group (placebo plus old) will typically have poorer glycemic control over time, which may appear to enhance the benefits of the experimental regimen (new plus old). Clinicians choose between active regimens, not placebo therapy. Thus, as the results of these early studies are reviewed, it is probably more clinically relevant to compare changes in outcome variables from baseline rather than changes versus placebo. Nonetheless, these studies have served a necessary function by confirming the continued deterioration in glucose control in those receiving

monotherapy and by demonstrating that combination therapy with agents involving different mechanisms augments glycemic control. With the observation that new regimens were better than no addition, the next critical question became how to determine whether the new change is better than other possible changes.

Recently, pharmaceutical companies have begun to compare regimens involving 2 active agents (with 1 agent in common to both regimens). However, even in a trial comparing 2 regimens, dose equivalency between the add-on drugs may need to be considered. Although this often is difficult to determine (it can be the pharmacologic equivalent of comparing apples and oranges), maximal doses of either add-on medication would seem to be the preferable approach.

### Glycemic control

The priority of initial studies involving medications for DM has been, and will likely continue to be, glucose control. However, the optimal way to measure and express glucose control may vary based on mechanism of action. At present, studies may choose to express impact on hyperglycemia by measuring FPG, postprandial glucose (PPG), or HbA<sub>1c</sub>. Comparing regimens or studies using FPG and PPG can be problematic, depending on the agents used. It may be problematic to use PPG to compare a long-acting insulin secretagogue (which has a greater effect on FPG) with a short-acting insulin secretagogue (which predominantly affects PPG). Conversely, a combination regimen using an insulin sensitizer may be more beneficial on FPG values without demonstrating as large an impact on PPG control. Recognizing particular times of day (or types of glycemic patterns) when specific combinations are maximally beneficial may help clarify which patients benefit most. Two patients with the same HbA<sub>1c</sub> may benefit from different combinations if one has predominantly elevated morning FPG values but fairly small PPG excursions, and the other begins the day in good control but has very high PPG excursions. Thus, despite the problems of comparing regimens by examining glucose concentrations at specific times of day, an awareness of when combination regimens exert their benefit can be helpful in selecting a course of therapy based on a patient's glycemic profile and the time of day when glucose concentrations are highest.

As a measure of mean blood glucose concentrations over an 8- to 12-week period, HbA<sub>1c</sub> has now become the "gold standard" for reflecting integrated glucose control. The recognition and establishment of target HbA<sub>1c</sub> values that minimize risk for microvascular complications created a new way of analyzing data and a new benchmark for reporting results. The percentage of patients who achieve HbA<sub>1c</sub> values below goals established by the American Diabetes Association (ADA)<sup>3</sup> (7.0%) or the American Association of Clinical Endocrinologists (AACE)<sup>6</sup> (6.5%) has been used as an indicator of success in the most recent clinical trials involving combination therapy.

### Nonglycemic markers

Beyond measures of glycemic control, recent trials have begun to include other markers or risk factors related to complications. Although there is great merit in studying and reporting these variables, improvement in some markers (e.g., lipids and urine microalbumin) has been more clearly linked to complications than have other "nontraditional" biochemical markers (e.g., C-peptide, proinsulin, plasminogen activator inhibitor type-1 [PAI-1], or high-sensitivity C-reactive protein [hs-CRP]). In addition to biochemical markers, other quantifiable markers such as carotid artery intimal medial thickness have also been measured.<sup>7,8</sup> After traditional markers were found to be linked to complications, studies demonstrated that improving most traditional markers reduced diabetes-related complications. As combination therapies are evaluated for clinical effectiveness, a crucial question will become whether certain combination regimens are more effective than others on clinical outcomes predicted by either traditional or nontraditional markers. Ultimately, certain combination regimens may, in fact, be more relevant for their impact on nonglycemic end points than on glucose control.

### Study end points

Studies of combination therapy rarely follow patients beyond 1 to 2 years. Just as the definitive goal of lipid-lowering medication studies has been a reduction in cardiovascular events, optimal studies of combination therapies need to include clinical outcomes on, at a minimum, microvascular complications. Virtually the only large study to date to consider the effect of combining medications on clinical outcomes was the UKPDS<sup>9</sup>; this portion was designed as an add-on study and did not compare 2 active therapy combinations. Large long-term prospective studies will be needed to demonstrate the impact of combination therapies and establish clinical benefits to patients.

### Side effects

The benefits of combination therapy must be weighed against the risk of side effects. For combination regimens involving insulin secretagogues (especially sulfonylureas), the major side effect has been the frequency and severity of hypoglycemia. However, for many patients, weight gain is as much an unwanted result of combination therapy as are other reported negative effects. Patients often feel caught in a double bind when they are told by providers about the importance of weight loss but are prescribed a combination drug regimen that causes them to gain, rather than lose, weight. Weight gain is a greater problem with some combination regimens than others, but it may be a crucial factor affecting adherence to a treatment plan.

## Costs

Clinical trials involving combination regimens do not typically evaluate or report the differences in costs between regimens. However, patients are increasingly concerned about the cost of their pharmaceutical regimens; this is especially true of individuals living on fixed incomes, such as the elderly. Some studies have reported the cost of combination therapies compared with the cost of living with and treating long-term complications.<sup>10</sup> However, the cost of complications is greatly influenced by which healthcare system bears that burden; the costs of diabetes-related complications in Germany, for example, may not be the same as in the United States. From a cost perspective, combination oral regimens should be evaluated not only with other oral regimens but with the addition of insulin. Although many patients prefer to avoid even once-daily insulin, in the short run the cost of adding insulin or replacing oral agents with multiple injections of insulin is often less expensive than using multiple oral agents. The question as to whether combination oral agent therapy or insulin has greater benefits in the long run, beyond glucose control, will only be addressed by randomized prospective studies.

## Peer review status

Publication in peer-reviewed journals currently remains the optimal way to ensure as objective an evaluation of the research project as possible. Even then, negative results or perceptions of a company's product may cause delays in publication,<sup>11</sup> and research outcomes (rather than the importance of the project) may determine whether the project is submitted for publication. Potentially more problematic than the peer-review process for journal publication, committees reviewing abstracts for national meetings are sometimes forced to make decisions based on limited information. Although attempts are made to scrutinize studies submitted for presentation at national meetings, it is difficult to undertake an in-depth analysis of a research project from a half-page abstract. Certainly, national meetings are important forums for releasing new information and are appropriate references for new research. However, time delays of several years between presentation and publication in peer-reviewed journals should raise a question about the willingness of the authors to subject their work to the peer-review process. In addition, clinicians may want to determine whether an abstract was published without being accepted for presentation, a procedure that some societies have adopted in recent years. Finally, the practice of some corporations to present research projects without peer review or access to public query, with data listed as being "on file" at a corporate location, is of potential concern. Overall, as results of combination regimens are announced, it is critical to determine whether the findings are available for review, have been presented as an abstract at a recent national meeting, or have been published in full detail in a

peer-reviewed journal. Although some of these issues may be resolved as data become available through publicly accessible databases, evaluations of combination therapy trials will likely continue to be influenced by the mediums in which data are communicated, analyzed and presented.

## Other factors

As combination therapy strategies transition from the rigor of clinical trial protocols to the real world of clinical practice, issues distinguishing efficacy from effectiveness become increasingly important.<sup>12</sup> Findings from specific combinations cannot be extrapolated to all combinations. Additional factors that may influence the results of specific combination therapy regimens in clinical settings include age, body mass index, sex, ethnicity, and other concurrent medications.

The difficulties in implementing the results of clinical trials that take years to complete and whose designs were created when a different state of the art was in place are not inconsequential. Even as current studies report on the benefits of 2-drug combinations, clinical practice has moved to usage of 3- and 4-drug regimens to optimize the therapeutic approach to type 2 DM. In addition, new drug classes are being introduced (e.g., incretins) and new delivery systems (e.g., inhaled insulin) are creating new markets for using previously established classes of medications. The delay between the initial release of new products, their various implementations in clinical settings, and the documentation in clinical trials of the benefit for different regimens will potentially create barriers to the use of evidence-based medicine for the treatment of type 2 DM.

## Examples of relevant trials

### Early studies and the "drug failure" misnomer

With the approval of metformin in the United States, one of the early studies reporting the benefits of combination therapy enrolled patients who had failed on therapy using only glyburide. The observation that patients taking glyburide plus metformin improved their HbA<sub>1c</sub> values compared with those taking metformin alone indicated that the glyburide had not failed but instead continued to provide additional benefit.<sup>13</sup> The concept that patients not achieving adequate control should have other agents added to their present regimen (rather than changing to a different form of monotherapy) has become a fundamental principle of combination therapy in diabetes treatment. The use of the word "failure" thus becomes a misnomer. Monotherapy does not fail; rather, a single drug becomes inadequate to achieve glycemic goals but should be continued as part of the new combination. The only caveat would be for patients who do not benefit from an initial monotherapy course.<sup>14</sup> Although that specific circumstance (adding a second drug when an

initial drug has not had any significant impact as monotherapy) has not been studied, it would seem unlikely that continuing a drug with little to no evidence of response would provide additional benefits as part of a combination regimen.

One of the earliest studies to consider combination therapy is also among the few studies to report clinical outcomes. The UKPDS created an arm of its protocol in which 537 nonobese patients who were taking sulfonylureas and had persistently elevated FPG values were randomized to receive continued sulfonylurea therapy or sulfonylurea plus metformin. These patients had demonstrated poor control (on monotherapy) for ~7 years, and although the median follow-up period was 6.6 years, most received <4 years of combination therapy.<sup>9</sup> Poor control was allowed in this study because the relation between improved control and reduction of risk for complications was not known at that time.

The results of this portion of the UKPDS were surprisingly disappointing. The combination of metformin and sulfonylurea did not demonstrate decreased risk for DM end points, DM-related deaths, all-cause mortality, myocardial infarction, or stroke. There was a statistically nonsignificant decrease in microvascular complications.<sup>9</sup> Several possible explanations have been suggested for the lack of effect of combination therapy, including the small numbers of events and too short a period involving combination therapy. In addition, it may be that prolonged poor glycemic control (>7 years) may have increased the risk of complications beyond the benefits of what combination therapy could achieve during the study period.

Combination therapy was reexamined in 1997 with troglitazone, the first TZD approved by the US Food and Drug Administration (FDA). Following a 2-week washout and 3 months of monotherapy (either metformin or troglitazone), 26 patients received both agents together for 3 months. The results of this study demonstrated that the combination of 2 drugs with different mechanisms was better at decreasing FPG, HbA<sub>1c</sub>, and PPG (in response to a mixed meal) than either drug alone.<sup>15</sup> Although troglitazone is no longer approved for use in the United States, the study was important because of its methodologies and the unambiguous impact of using 2 drugs versus 1 drug.

### Studies of active combination therapies with an agent in common

The approval of  $\alpha$ -glucosidase inhibitors brought to the market a fourth drug class, creating the possibility of combining this class with sulfonylureas, biguanides, or TZDs. Investigators compared adding either metformin or acarbose in patients who were already taking sulfonylureas. This industry-sponsored study involved 89 patients and lasted 12 weeks. The results showed similar benefits regarding changes in HbA<sub>1c</sub>, PPG, and weight loss from baseline in the acarbose/sulfonylurea group and the metformin/

sulfonylurea group when compared with the placebo/sulfonylurea group.<sup>16</sup>

The availability of short-acting insulin secretagogues has focused attention on the role of PPG control. Raskin and colleagues<sup>17</sup> compared nateglinide versus repaglinide in a group of nearly 200 patients treated with metformin. Results from this industry-sponsored study showed improved FPG and HbA<sub>1c</sub> values during the 16 weeks of the study. The group on repaglinide and metformin had a greater reduction in HbA<sub>1c</sub> (1.28%) compared with the group on nateglinide and metformin (0.67%).

More recently, as other TZDs received approval from the FDA—rosiglitazone and pioglitazone were approved in 1999—studies began to examine their use as a component of combination therapy. In one protocol, patients inadequately controlled on sulfonylureas were randomized to have either pioglitazone or metformin added. In the other protocol, patients inadequately controlled on metformin were randomized to add either pioglitazone or gliclazide. Both protocols studied >600 patients and spanned 2 years. These industry-sponsored studies examined HbA<sub>1c</sub> values, FPG, and the percentage of patients achieving HbA<sub>1c</sub> <7.0%. In addition, they recorded side effects, weight change, lipid profiles, insulin, C-peptide, and proinsulin levels.

In the study comparing metformin with pioglitazone in sulfonylurea patients, the results after 1 year demonstrated no difference in FPG or HbA<sub>1c</sub> values.<sup>18</sup> Although there appears to be a transient benefit of metformin midway through the study, statistical analysis specific to this time point was not provided in the publication. Overall, no difference was observed in the 2 combination regimens (pioglitazone plus sulfonylurea vs. metformin plus sulfonylurea) regarding the percentage of patients with HbA<sub>1c</sub> <7.0%. Despite the similar degree of glucose control, the use of pioglitazone plus sulfonylurea resulted in a greater decrease in triglycerides (TG), a greater increase in high-density lipoprotein (HDL) cholesterol, and a greater decrease in urine albumin/creatinine when compared with metformin plus a sulfonylurea. Not surprisingly, adding pioglitazone resulted in greater frequency of edema and adding metformin resulted in greater frequency of gastrointestinal (GI) side effects (each 10% to 15%).

The results from the second year of this study were recently presented by Moules and colleagues<sup>19</sup> in abstract form and confirmed no significant differences between either regimen regarding FPG or HbA<sub>1c</sub> values. In a separate abstract, Mariz and coworkers<sup>20</sup> reported that patients taking pioglitazone plus a sulfonylurea continued to have lower TG and higher HDL cholesterol values than those taking metformin plus a sulfonylurea. However, the combination of pioglitazone plus a sulfonylurea had a less beneficial impact on low-density lipoprotein (LDL) cholesterol than the regimen using metformin plus a sulfonylurea.

In the study comparing the addition of pioglitazone or gliclazide to metformin, Edwards and associates<sup>21</sup> reported

a small but statistically significant difference in HbA<sub>1c</sub> values for patients completing  $\geq 18$  months of therapy. There also was a small difference in FPG ( $-1.8$  mmol/L for pioglitazone plus metformin vs.  $-1.1$  mmol/L for gliclazide plus metformin). The percentage of patients achieving HbA<sub>1c</sub>  $< 7.0\%$  was greater (30.6%) for the pioglitazone/metformin group than for the gliclazide/metformin group (25.2%).

As in the study by Hanefield and colleagues,<sup>18</sup> which compared pioglitazone/sulfonylurea to metformin/sulfonylurea, the glitazone regimen in the study by Mariz and associates<sup>20</sup> had a beneficial effect on lipid profiles. In the Mariz group's study, the addition of pioglitazone to metformin resulted in a greater decrease in TG and increase in HDL cholesterol than did the addition of gliclazide to metformin.<sup>20</sup> However, the combination of pioglitazone plus metformin had a less beneficial impact on LDL cholesterol compared with the combination of metformin plus gliclazide. As in the study by Hanefield and associates,<sup>18</sup> the addition of pioglitazone resulted in greater frequency of edema (11%), whereas the addition of gliclazide resulted in an equivalent frequency of hypoglycemia (11%). The weight gain in the pioglitazone group was greater than the sulfonylurea group, but the results were not statistically significant.

Rosiglitazone, the other major TZD currently on the US market, has also been studied in combination with other glucose-lowering medications. The design of this industry-sponsored trial was different from other combination therapy studies. Patients were required to wash out of their current DM regimen for 2 weeks. Whereas 28% to 30% of patients had been on no pharmacologic therapy before enrolling, 49% to 51% of patients had been on monotherapy and 20% to 21% had already been on combination therapy.<sup>22</sup> After washout, metformin was started in all patients ( $n = 709$ ) and increased to 1,000 mg/day. At that point, the patients were randomized to receive either additional metformin (up to the maximal dose) or increasing doses of rosiglitazone. This study was a variation of the model of new plus old versus placebo plus old, because it used different doses of metformin in each arm. Outcome variables included FPG and HbA<sub>1c</sub> values, as well as PPG and indices of insulin sensitivity. Lipid profiles and weights were also measured, as were side effects. Of interest, this study also analyzed, from a subset of  $\sim 40$  patients, blood samples for the nontraditional vascular risk markers PAI-1, hs-CRP, and matrix metalloproteinase-9.

After 24 weeks, no statistical difference was noted in the overall HbA<sub>1c</sub> values between the 2 regimens. However, there was a difference in FPG ( $-38.5$  mg/dL [2.1 mmol/L] for rosiglitazone plus metformin vs.  $-19.9$  mg/dL [1.1 mmol/L] for metformin alone) and also in fasting insulin concentrations. The regimen using the maximum dose of rosiglitazone with half maximal metformin resulted in a greater percentage of patients achieving HbA<sub>1c</sub>  $< 7.0\%$  (55% vs. 45%) and also  $< 6.5\%$  (39% vs. 26%) compared

with those on maximal doses of metformin alone.<sup>22</sup> The addition of rosiglitazone caused a mean weight gain of 1.8 kg; the use of maximal metformin resulted in a mean weight loss of 1.8 kg. Edema was more common in patients taking rosiglitazone (4.7%), and 6.8% of patients randomized to receive maximum metformin had to discontinue participation because of GI-related side effects.

The use of the combination regimen (rosiglitazone plus metformin vs. metformin alone) appeared to benefit nontraditional vascular markers in the small subset of patients studied. PAI-1 and hs-CRP decreased more in the rosiglitazone plus metformin arm than in the metformin monotherapy arm.<sup>23</sup> As mentioned previously, although it is tempting to speculate about these findings, it must be emphasized that there are no long-term prospective studies determining whether decreasing nontraditional risk markers provides clinical benefit. In addition, this study evaluated a combination of a maximal dose of a TZD plus a submaximal dose of metformin compared with a maximal dose of metformin alone. Therefore, the question remains as to whether the regimens were of equal potency.

## Considerations regarding cost and adherence

As combination therapy becomes increasingly common, the ramifications of cost and ease of use will need to be carefully considered. Unfortunately, these issues are neither trivial nor easily resolved. Factors affecting cost of medications now include generic versus brand name, special (e.g., extended release) formulations, tier of coverage in a given health plan, combination pills that incorporate fixed doses of medications, and the potential "wild card" of purchasing medications through the Internet. Although it is difficult to arrive at any simple conclusions, some broad observations may be relevant. **Figure 2** shows the costs for a 1-month supply of sulfonylureas and short-acting insulin secretagogues, according to an Internet Web site in 2004.<sup>24</sup> A general rule for these medications is that newer medications are more expensive than older medications. However, generic sulfonylureas are not always less expensive than brand-name medications, and some long-acting formulations are relatively less expensive.

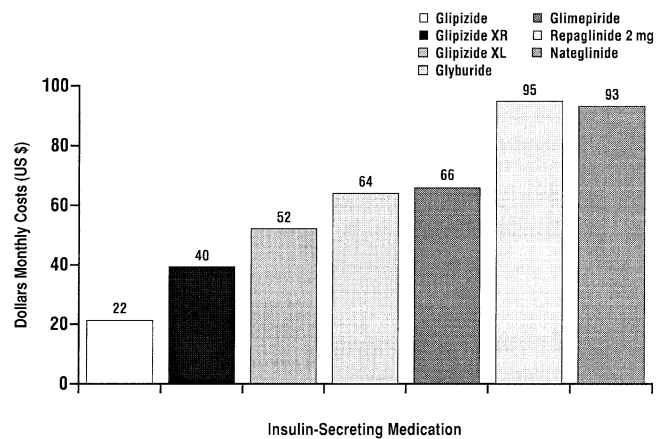
In **Figure 3**,<sup>24</sup> the costs of other medications are shown. Generic metformin is the least expensive in this group, although an extended-release branded form of metformin is quite comparable in price to the shorter-acting brand-name form. TZDs are consistently more expensive than non-TZD drugs; the difference between the 2 glitazone brands may be relevant to some patients but also may be offset by local pricing or other factors. There can also be significant differences between these 2 agents depending on third-party formularies.

A comparison of combination pill formulations with monotherapy shows that the monthly costs for combination therapy (not surprisingly) are higher (**Figure 4**).<sup>24</sup> A single

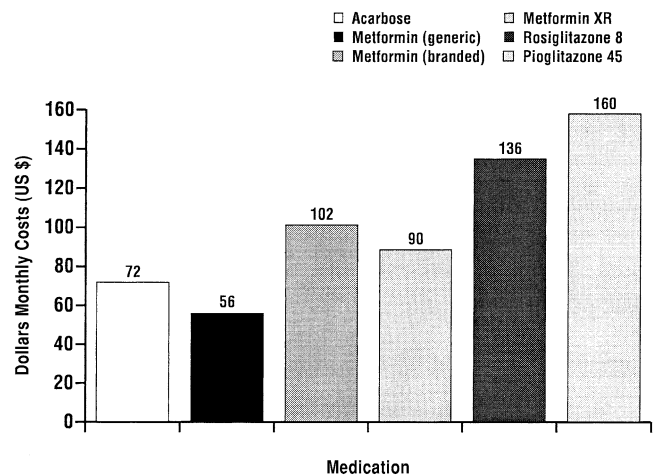
combination pill can be less expensive than using 2 generic equivalents; for example, generic metformin 2,000 mg plus rosiglitazone 8 mg would total \$226, whereas a single combination pill providing the equivalent dosages would be \$182. Regarding the costs of different combination pills, the product combining a TZD with metformin is more expensive (~50%) than combining a sulfonylurea with metformin. However, the differences in formulations in these combinations make it more difficult to compare them. For some patients, the allure of combination therapy is less an issue of price and more an issue of decreasing the total daily number of pills taken. Although most combination pills help patients decrease their total pill count, some regimens offer no advantage. For example, a total daily dose of glipizide 20 mg and metformin 2,000 mg would still require 4 pills (each pill contains glipizide 5 mg and metformin 500 mg) compared with taking 2 pills of a brand-name extended-release glipizide 10 mg and 2 pills of metformin 1,000 mg.

Proceeding beyond 2-drug regimens to 3-drug regimens increases cost considerations with less information on clinical outcomes. The right side of Figure 4 shows the dramatic increase in costs for patients using 3 different medications, because no triple-combination pills are currently available. The estimates show how quickly the cost of treating hyperglycemia can increase to >\$300 per month. Obviously, the use of additional medications to control blood pressure and hyperlipidemia only further increases the costs. As the field of combination therapy continues to be evaluated, it will be important to measure the benefits of clinical outcomes against the costs to the healthcare system as well as to patients for out-of-pocket expenses. Given the chronic nature of type 2 DM, the financial impact of years of medical therapy expenses is substantial. For example, if one considers the results of the trial comparing rosiglitazone plus half-maximal metformin to full-dose metformin, the cost of metformin 1000 mg plus rosiglitazone 8 mg (\$181) is essentially double the cost of metformin 2,000 mg (\$90).<sup>24</sup>

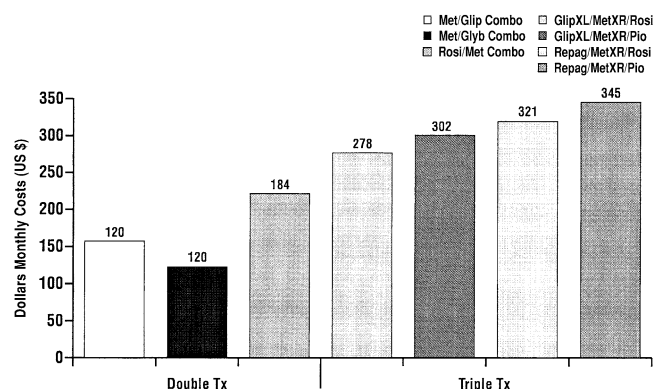
Although studies evaluating the cost-effectiveness of different combination therapies are critically important, there are several barriers to conducting them. Higher prices of newer products under patent protection make it more difficult to demonstrate a positive cost/benefit outcome compared with combinations using lower-priced generic drugs. Because generic drugs have no patent protection, manufacturers of these products are not likely to conduct expensive long-term clinical trials. This leaves 3 potential sources for these studies: governmental health agencies (e.g., Veterans Administration [VA], National Institutes of Health [NIH]), nongovernmental associations (e.g., ADA), and managed care organizations. The first 2 types of organizations have cooperated in large prospective clinical trials; managed care organizations have more commonly participated by reporting on large pharmacy and clinical databases. Because managed care organizations have a vested interest in under-



**Figure 2** Monthly costs of sulfonylureas versus short-acting insulin secretagogues. Values are shown in US dollars. XL = extended-life; XR = extended-release. (Adapted from [www.drugstore.com](http://www.drugstore.com).<sup>24</sup>)



**Figure 3** Monthly costs of thiazolidinediones versus nonthiazolidinediones. Values are shown in US dollars. XR = extended-release. (Adapted from [www.drugstore.com](http://www.drugstore.com).<sup>24</sup>)



**Figure 4** Monthly costs of monotherapy versus combination formulations. Values are shown in US dollars. Glip = glipizide; Glyb = glyburide; Met = metformin; Pio = pioglitazone; Repag = repaglinide; Rosi = rosiglitazone; XL = extended-life; XR = extended-release. (Adapted from [www.drugstore.com](http://www.drugstore.com).<sup>24</sup>)

**Table 2** Potential combination regimens for type 2 diabetes mellitus

	Sulfonylureas	Secretagogues	Metformin	Glitazones	Glucosidase inhibitors
Sulfonylureas	XXXXXXXX	? Benefit	✓	✓	✓
Secretagogues	? Benefit	XXXXXXXX	✓	✓	? Increase in hypoglycemia
Metformin	✓	✓	XXXXXXXX	✓	? Increased GI side effects
Glitazones	✓	✓	✓	XXXXXXXX	
Glucosidase inhibitors	✓	? Increase in hypoglycemia	? Increased GI side effects		XXXXXXXX

XXXXXXXX = unity areas of overlap, not combinations; ✓ = studies using this regimen have been conducted, either in comparison with single active drug plus placebo, or in comparison with another 2-drug regimen; GI = gastrointestinal.

standing the cost–benefit ratio of medical therapies, it would seem advantageous for them to participate more actively in evaluating optimal strategies for cost-effective healthcare. There is a tremendous need and potential for clinical research programs that would cooperatively share de-identified information from third-party payers to examine and determine optimal approaches to chronic diseases like type 2 DM.

## Summary

Just as other fields (e.g., hypertension, infectious disease) changed dramatically with the availability of combination medications, the treatment of type 2 DM has been radically altered by the relatively rapid release into the clinical arena of drugs with distinct mechanisms of actions. Initial studies demonstrating benefit over placebo have been followed by studies demonstrating additive benefit to monotherapy. The next level of investigation, which has only recently begun, focuses on evaluating different 2-drug combination regimens (**Table 2**). Although many combinations have been examined in some fashion, other agents cannot be combined because of overlapping therapeutic actions or side effects. For instance, a study combining a longer-acting sulfonylurea and a shorter-acting secretagogue is unlikely to be undertaken given the similar mechanisms of action. Similarly, the potential for severe postprandial hypoglycemia would seem too high to prompt a study of a short-acting secretagogue and a glucosidase inhibitor. Lastly, the combination of metformin and acarbose would likely cause excessive GI side effects and not be tolerable.

From a clinical perspective, these studies suggest relatively similar benefits in glucose control for any particular 2-combination regimen. Of great interest, the recent studies involving TZDs raise the strong possibility that combination regimens may have advantages with regard to nonglycemic risk factors. However, beyond the beneficial effects on risk factors, it is the adverse effect of a particular regimen that may end up determining which combination regimen is chosen for a specific patient. Individual concerns over hy-

poglycemia, GI side effects, or edema may tip the scale away from one permutation and toward another.

Most of the recent studies have spanned <2 years, and nearly all have evaluated surrogate markers of diabetes-related complications without having reported on concrete clinical outcomes. The impact on markers and risk factors appears quite promising. However, longer-term clinical trials are needed to confirm the clinical benefit of combination therapy. Until head-to-head comparisons are available, clinicians will be faced with the challenge of comparing different studies conducted by different investigators with different patients in different settings. As combination studies proceed, appropriate control groups using alternative combination regimens should be included to ensure that optimal regimens are identified. Additional comparisons to insulin therapy (with or without oral agents) will likely be needed to help configure a cost/benefit approach. Potential problems associated with combination therapy (e.g., monetary costs, side effects) should be identified and openly discussed. As these questions are answered, subsequent studies evaluating >2 agents will likely be undertaken to determine an optimal approach to the treatment of type 2 DM.

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