A systematic review of the efficacy and safety of triple therapy in patients with type 2 diabetes mellitus not achieving target A1c goals despite existing dual therapy (metformin plus a sulfonylurea)

By

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ABSTRACT

Background. For adult patients with type 2 diabetes mellitus and an A1c >7.0% despite maximal oral hypoglycemic therapy with metformin and a sulfonylurea, the relative benefits and harms of triple therapy are unknown. In particular, it is unclear whether patients should commence insulin therapy, either alone or in combination with other agents, or whether desired glycemic control can be attained and maintained with other agents (exenatide, alpha-glucosidase inhibitors, and/or thiazolidinediones).

Objectives. To assess the efficacy—as measured by the change in A1c from baseline and by the proportion of patients attaining an A1c <7.0%; safety—as measured by the incidence of hypoglycemia and of treatment-related adverse events; treatment externalities—as measured by the effect on selected cardiovascular risk factors; and health outcomes—as measured by the effect on micro- or macro-vascular complications—of triple therapy. Economic considerations and effects on health-related quality of life are also assessed.

Methods. Eligible studies were identified by searching MEDLINE (1977-May 2007) with limits on subjects (humans), language (English), and publication (appearing in peer-reviewed literature). Inclusion criteria included, among others, that trials be randomized with both a minimum duration of follow-up (24 weeks) and an enrolled population (n=30); that at least one study arm investigate triple therapy; and that the authors report on key outcomes. Data extraction and assessment of study quality were undertaken by a single reviewer and made available for review.

Results. Eleven randomized controlled trials, enrolling 3,306 participants with a median follow-up duration of 24 weeks, were included. Overall, study methodologic quality was good. Trial participants were generally similar with respect to age, body mass index (BMI), duration of
diabetes, and baseline A1c making it possible to generalize the results of this review to a likely externally valid population.

A1c lowering varied from 0.2%-1.8% and from least effective (alpha-glucosidase inhibitors) to most effective (thiazolidinediones and insulin glargine). Generalizing these averaged results to patients at differing levels of baseline glycemic control is limited. Irrespective of the third agent chosen, less than half of all trial participants attained A1c <7.0%, though this may reflect inclusion of participants with advanced disease. Nevertheless, results suggest reconsideration of glycemic targets as well as the possible inappropriateness of certain treatment recommendations.

Third agents were generally safe and were well-tolerated. The incidence of serious adverse events was low (<3%) including severe hypoglycemia (1.5 events per 100 patient-years). Incidence of hypoglycemia appeared related to the sulfonylurea dose, suggesting a treatment recommendation, and to the ambient level of glycemic control, suggesting a shifting balance of benefits and harms with increasingly intensive therapy. The rarity of serious events precluded comparisons among particular agents. Treatment-related side effects, including their likelihood and severity, are discussed by drug class.

Few of the trials reported on micro- or macro-vascular endpoints, economic considerations, or effects on health-related quality of life. The paucity of such data in the included literature has implications for future research. A hypothetical outcomes table is generated to facilitate discussion about the diminishing returns of additional treatment.

Conclusions. The efficacy and safety of triple therapy in adults with type 2 diabetes mellitus has not been previously scrutinized in a systematic review. These results can supplement the existing body of knowledge and inform clinical practice. Further research is needed with
regard to micro- and macro-vascular outcomes as well as a reconsideration of treatment goals in this population in light of such outcomes. This review further illustrates the validity and necessity of similar analyses being performed along the treatment continuum for patients with type 2 diabetes, to improve both patient-provider decision-making and utilization of health care system resources.
INTRODUCTION

Two large-scale, randomized controlled trials (RCTs), the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have demonstrated significant reductions in rates of microvascular complications in patients who improve glycemic control with intensive therapy versus conventional therapy.

In the UKPDS, patients receiving intensive treatment (mean A1c=7.0%) compared to those receiving conventional treatment (mean A1c=7.9%) benefited from a relative risk reduction over 10 years of 12% for any diabetes-related endpoint and 10% for any diabetes-related death. However, aggregate measures were used and much of the reported risk reduction was due to an effect on microvascular endpoints. Furthermore, endpoints included intermediate outcomes such as need for retinal photocoagulation rather than health outcomes such as blindness.

The long-term benefit of intensive glycemic control on macrovascular outcomes in type 1 diabetes has also been shown. While observational data and a meta-analysis of prospective cohort studies support a similar benefit in type 2 diabetes, no RCT to date has shown such an effect.

Several professional societies have issued guidelines on glycemic control for patients with type 2 diabetes. Presently, the American Diabetes Association (ADA) recommends a glycated hemoglobin level (HbA1c or A1c) less than 7.0% for most patients, while the American Academy of Clinical Endocrinologists (AACE) and the European Association for the Study of Diabetes (EASD) both recommend an A1c less than 6.5%. One systematic review and an editorial argue that setting uniform targets for A1c for all patients is inappropriate. To treat
unwaveringly toward an A1c less than 7.0% is potentially harmful both for patients\textsuperscript{11,12} and for policy.\textsuperscript{13,14}

The artificiality in treatment goals should not obscure the important benefits of any reduction in A1c. While no threshold effect in terms of tight glycemic control and microvascular—and perhaps macrovascular—complication risk reduction has been observed,\textsuperscript{15} the incremental absolute benefits of intensive therapy decrease at lower A1c levels and these smaller benefits must be weighed against harms of increased risk of hypoglycemia, weight gain, and the cost of multiple drugs, among others.

NHANES 1999-2000 data suggests that only 37.0\% of participants maintain an A1c less than 7.0\% and 37.2\% of participants are above the recommended “take action” A1c of greater than 8.0\%.\textsuperscript{16} Indeed, population-based glycemic control has not improved substantially in the past decade, with the prevalence of patients whose A1c values exceed 8.0\% remaining stubbornly constant.\textsuperscript{17,18} In the UKPDS, fewer than 30\% of patients were able to achieve A1c levels less than 7.0\% on monotherapy\textsuperscript{19} and more than half of all patients ultimately required the addition of insulin.\textsuperscript{20} The decade between 1990 and 2000 was marked by an increase in the use of oral antidiabetic drugs in combination with each other, from <1\% to 29\%, and with insulin, from 4\% to 9\%.\textsuperscript{21}

The need for progressive therapy reflects the underlying pathophysiologic defect in type 2 diabetes—progressive pancreatic beta-cell dysfunction and increasing peripheral resistance to insulin. Reported failure rates for single oral agents of 5\% to 20\% per year mean that single oral therapy in type 2 diabetes seldom maintains glycemic control more than three years. Optimizing treatment decisions to reduce complications and spare remaining pancreatic endocrine function becomes of paramount importance.
Treatment inertia remains the norm in the United States (US). In one managed care study, for example, patients received only monotherapy despite 14-20 months of exposure to A1c levels greater than 8.0% until a second oral agent was added. Because the introduction of dual-agent therapy has the potential to lower A1c levels by only an additional 1.2%-2.0%, use of a third oral agent, whether another oral drug or insulin, is invariably required in many patients with advancing type 2 diabetes.

Several barriers prevent better glycemic control, including sub-optimal decision making. The decision to add therapies, including insulin, in patients inadequately controlled on monotherapy or dual oral therapy may often be delayed by the patient or by the provider. In the case of insulin, several reasons have been advanced including physician resistance to prescribing, patient reluctance, or the perception that insulin therapy implies severe disease, among others. While conventional barriers to insulin therapy—lingering concerns about hypoglycemia, complex regimens, and erratic absorptions—have been substantially overcome with the advent of insulin analogues, fear of hypoglycemia and injections remain a real obstacle. As a result, triple oral therapy appears a valid therapeutic step, appealing for many patients.

The introduction of new classes of blood-glucose lowering medications to supplement more established therapies—lifestyle interventions, insulin, sulfonylureas, and metformin—has increased the treatment options for type 2 diabetes. In addition, provider and patient uncertainty regarding the most appropriate way to proceed has increased. Despite the introduction of these new classes of medication for managing type 2 diabetes, recent studies suggest even currently available multi-drug therapies often do not allow patients to achieve better glycemic control.
The ADA and EASD recently released a consensus algorithm to guide disease management. The algorithm highlights both the tendency to treat toward an A1c level—or, to define any level above 7.0% as inadequate or suboptimal control—and the range of options for achieving the target goal. The uncertainty alluded to above is highly prevalent in an increasingly common clinical scenario: an adult patient with poorly controlled type 2 diabetes mellitus already on two oral agents (metformin plus a sulfonylurea) facing a choice among adding a third oral agent, initiating insulin, or taking no action.

While this choice is highly driven by patient and provider preferences and therefore amenable to shared decision-making, augmented by a decision aid, this choice and the subsequent creation of a decision aid benefit first from a systematic review of the existing literature regarding the incremental benefits and harms of the range of possible therapeutic agents.

METHODS

Key question. For adults (>19 years of age inclusive) with type 2 diabetes mellitus and an A1c >7.0% already on two oral agents (metformin plus a sulfonylurea), what are the benefits—in terms of glycemic control and of prevention of micro- and macro-vascular outcomes—and harms—in terms of treatment-related adverse events or intolerance due to side effects—of available add-on therapeutics including and compared to insulin?

Databases and Search Terms. To develop an appropriate search strategy, including which databases to search and which terms to input into search fields, a medical librarian with expertise in information retrieval was consulted and available during all phases of the review.
The author performed an electronic literature search of MEDLINE (1977 through May 2007) using the search strategy detailed in Table 1. Briefly, pilot testing was performed on a simplistic search strategy using the MeSH terms “Diabetes mellitus, type 2” and “hypoglycemic agents.” It was determined that, notwithstanding reasonable contraindications, metformin and a sulfonylurea was sufficiently common in studies of dual oral therapy that they be included in each subsequent search string as keywords. While “hypoglycemic agents” and “sulfonylurea compounds” lead to duplication, cataloging of studies including a sulfonylurea in dual oral therapy seem indexed by the latter term with newer studies by the former. Thus, both terms were included parenthetically in the search string with the Boolean operator “OR.”

This combination of keywords and MeSH terms were then appended to each possible permutation of the following keywords: exenatide (as a keyword rather than a substance name), acarbose or miglitol (alpha-glucosidase inhibitors), rosiglitazone or pioglitazone (thiazolidinediones), and insulin (again as a keyword). To ensure capture of articles in which insulin was part of the therapeutic regimen, an additional search was performed using the following MeSH terms: “diabetes mellitus, type 2” AND “hypoglycemic agents” AND “drug therapy, combination.” This search was also used as a rudimentary sensitivity analysis for the preceding searches. The search was restricted to English-language studies, conducted in human subjects, and appearing in the published literature.

The author also performed hand-searches of all bibliographies of articles returned that were retained on the basis of abstract as well as bibliographies of contemporaneous reviews returned by the search strategy. The number of trials returned by each search query, the number of articles initially included and excluded after abstract review, the number of articles added after hand-searching of relevant bibliographies, the number of articles retained for full review, and the
number of articles rejected after full review or included in the systematic review are detailed in
Table 2.

Pilot searching also included targeted keyword searches for articles concerning newer
agents like pramlintide (an amylin analog), sitagliptin and vildagliptin (DPP-IV inhibitors),
liraglutide (an oral GLP-1 receptor agonist), and repaglinide and nateglinide (meglitinides, rapid­
acting non-sulfonylurea insulin secretagogues). While evidence about these agents as
monotherapy and in combination therapy is certainly useful to guide clinical practice, it was felt
that the body of evidence for these agents in triple therapy was insufficient to warrant inclusion
at this time. In the case of the glinides, studies have shown no further antihyperglycemic effect
when added to a sulfonylurea.31

Article Selection and Review. The author evaluated all titles, abstracts, and keywords of
every record retrieved for inclusion or exclusion. Full articles were retrieved for further
assessment if the information given suggested that the study included patients with type 2
diabetes, used random allocation to comparison groups, included an arm of triple therapy, and
assessed one or more relevant clinical outcome measures for both efficacy and safety. If there
was any doubt regarding inclusion of the article from the information given in the title and
abstract or if no abstract was available, the full article was retrieved for clarification. The list of
included and excluded articles was made available for review. Differences of opinion were
resolved by consensus.

Inclusion and Exclusion Criteria. Guided by the focused clinical question, the author
generated inclusion and exclusion criteria summarized in Table 3.

Types of participants: Adult patients (>19 years of age inclusive) with type 2 diabetes
mellitus (according to appropriate diagnostic criteria at the time of the study) of any duration.
(other than newly diagnosed) who had not achieved satisfactory glycemic control on an existing stable regimen of metformin (maximally tolerated) and a sulfonylurea (at least half maximal dosing) prior to randomization were included. Any doses of any agent inconsistent with reasonable clinical practice were explained; any adjustments to dosages during the trial likewise needed to be explicit. Exclusion criteria included patients with type 1 diabetes mellitus, diabetes of secondary cause (eg, hemochromatosis), gestational diabetes, pre-diabetes/impaired glucose tolerance/impaired fasting glucose, or metabolic syndrome. Any studies occurring in the pediatric and/or adolescent patient populations (<18 years of age inclusive) were excluded.

Types of study settings: Any study conducted in the outpatient population or an otherwise ambulatory care setting, given that this is the setting in which the information is most applicable and the setting in which pilot testing of any decision aid would occur, were included. Exclusion criteria included studies conducted in or regarding inpatient, hospital, or intensive short-term management.

Types of study designs: Randomized controlled trials with follow-up periods of at least 24 weeks and an evaluable total study population of at least thirty participants were included. The guideline regarding number of participants in the final analysis was included because of the statistical difficulties associated with small sample sizes. At least one trial arm must include the investigation of an add-on third agent to existing dual oral therapy with metformin and a sulfonylurea. Other trial arms may include a placebo or an active comparator which need not also be “triple therapy.” Exclusion criteria included any non-randomized trial (prospective or retrospective cohort, case-control, case-series).

Types of outcomes: In order to be included, trials had to report both main outcome measures—change in HbA1c from baseline (placebo-subtracted or otherwise) AND measures of
treatment-related adverse events or side effects. Adverse events could include incidence of hypoglycemia and weight gain, as well as other side effects specific to particular agents.

Additional outcome measures which were not used as a basis for inclusion or exclusion but abstracted for reporting included other measures of glucose status (fasting plasma glucose, postprandial glucose), proportions attaining recommended A1c levels, cost-effectiveness data, any quality-of-life data reported using a validated instrument, and any diabetes-related morbidity or mortality.

In terms of general limitations, most were included because of logistical issues with the resources available to the systematic review and to the author. Because only published studies were included, the author acknowledges the potential publication bias created and the resultant tendency for studies to overestimate the efficacy of agents.

Quality assessment. Each trial was assessed by the author using a selection of the 17-item Maastricht-Amsterdam Criteria List,\(^{32}\) which includes criteria from previous work.\(^{33,34}\) The following factors were scored (total score range from 0-7):

1. Minimization of selection bias – a) was the randomization procedure adequate? b) was the allocation concealment adequate?
2. Minimization of performance bias – were a) the patients and b) the people administering the treatment blind to the intervention?
3. Minimization of attrition bias – a) were withdrawals and dropouts completely described? b) was analysis by intention-to-treat?
4. Minimization of detection bias – were a) outcome assessors blind to the intervention?

Based on these criteria, studies were subdivided into four categories: Excellent (total score 6-7): all quality criteria met: low risk of bias; Good (total score 4-5): one or more of the
quality criteria only partly met: moderate risk of bias; Fair (total score 2-3): one or more of the quality criteria not met: high risk of bias; Poor (total score 0-1): nearly all of the criteria not met: severe risk of bias. Studies were not excluded on the basis of methodological criteria. External validity was scored dichotomously; that is, either as likely valid or likely not valid to the proposed external population.

Data extraction. Data regarding inclusion criteria, quality criteria, and results were extracted solely by the author. The following information was collected:

1. General information: title, authors, reference, PMID.
2. Trial characteristics: design, duration, randomization (and method), allocation concealment (and method), blinding (patients, people administering treatment, outcome assessors), assessment of blinding; run-in period and lifestyle counseling or dietary reinforcement.
3. Intervention(s): Placebo or active comparator, add-on agent (dose, route timing), existing regimen of metformin and sulfonylurea (dose, route, timing), and protocol specifying adjustments to both.
4. Patients: sampling (method), exclusion criteria, the total number of participants and the number randomized in each comparison group, as well as intention-to-treat (ITT) population for safety analysis and the evaluable population (per protocol population) for efficacy analysis. Patient characteristics including age, BMI, and duration of type 2 diabetes.
5. Outcomes: Changes in HbA1c from baseline changes from baseline and proportions of the study population experiencing drug-related adverse events and/or side effects—particularly hypoglycemia and effect on weight; other measures of glucose control
including, but not limited to, fasting plasma glucose, postprandial glucose, and proportion of subjects treated achieving A1c < 7.0%; risk reduction of microvascular or macrovascular complications.

6. Results: whether or not a power calculation was performed and whether the analysis included adjustments including, but not limited to, intention-to-treat and last observation carried forward.

RESULTS

Efficacy. The change in A1c from baseline was the primary outcome measure for efficacy. All trials, per inclusion criteria, reported on this endpoint. Taken collectively, add-on agents, in addition to existing metformin and sulfonylurea therapy, lowered A1c by 0.2-1.8%. Alpha-glucosidase inhibitors, acarbose and miglitol, were the least effective drug class achieving modest reductions in A1c of approximately 0.5%. Thiazolidinediones, pioglitazone and rosiglitazone, and triple therapy regimens containing insulin glargine were the most effective, lowering A1c by 0.9-1.8%.

The proportion of patients attaining an A1c < 7.0% was a secondary outcome measure for efficacy. Eight of eleven trials (8/11, 72.7%) reported on this endpoint. In none of the eleven trial arms considered (excluding placebo and non-triple therapy comparators) did the proportion exceed 50%. Proportions were comparable irrespective of the add-on agent and ranged from 24%-49%.

Safety. Hypoglycemia was one of the principal outcome measures for safety. Hypoglycemia was reported either as a proportion or as a rate in all but one study (10/11, 90.9%). In terms of overall hypoglycemia, proportions ranged from 28%-53% and rates from 2.7-7.7
events per patient-year. Trials generally categorized hypoglycemic events either as mild-moderate (subjects reported symptoms consistent with hypoglycemia and may have documented levels of plasma glucose <70mg/dl) or as severe (requiring the assistance of another person to obtain treatment, including intravenous glucose or intramuscular glucagon). Definitions were similar across all studies. Because of the rarity of the event, a comparison of the incidence of severe hypoglycemia across treatment groups was not made. The overall incidence rate of severe hypoglycemia, calculated from 68,064 patient-weeks of follow-up among the ten trials reporting, was 1.5 events per 100 patient-years.

Drug-related adverse events, specific to particular agents or to a drug class, were a second principal outcome measure for safety. In general, all third agents were safe and well-tolerated. The incidence of severe events was low (<3%) irrespective of agent and this finding was robust. Less than half of severe adverse events were deemed-treatment related and few led to participant withdrawal from the trial. Particular agent specific effects, their incidence and their management, are discussed further by drug class.

_Treatment externalities._ While glycemic control remains the cornerstone of therapy in type 2 diabetes, increasing importance is placed on proper management and amelioration of other cardiovascular risk factors: weight, blood pressure, lipid profile, and tobacco status. All but one trial (10/11, 90.9%) reported on the effect of a third agent on weight. Exenatide was associated with weight loss of 1.6-2.5kg. This effect was independent of glycemic effect and treatment-related gastrointestinal side effects. Acarbose and miglitol were associated with modest weight reductions of 0.3-0.8kg, though these drugs are generally regarded as weight neutral. The thiazolidinediones and regimens containing insulin were both associated with weight gain, from 3.0-3.5kg and from 1.8-2.9kg, respectively.
Six of eleven trials (54.5%) reported on the effect on lipid profile but few of these reached statistical significance. In general, neither exenatide nor the alpha-glucosidase inhibitors had a significant effect on lipid profile, likely related to their respective underlying mechanisms of action. Rosiglitazone had unfavorable effects on lipids (increased total cholesterol (TC), low density lipoprotein (LDL), and triglycerides (TG)) while insulin glargine had favorable effects on lipids (decreased TC, LDL, and TG; increased high density lipoprotein (HDL)). None of the trials reported on blood pressure; trials which commented on a possible favorable effect were difficult to interpret in light of the significant number of trial participants receiving concomitant antihypertensives.

*Health outcomes.* Only 1/13 (7.7%) trials reported on micro- or macro-vascular endpoints. The UKPDS was the only trial in which measurement of these endpoints was included in the protocol and the only trial with a sufficient duration of follow-up to capture these events. The UKPDS reported data concerning "any diabetes-related endpoint" and microvascular disease. The relative risks for acarbose compared with placebo were 1.00 (95% CI 0.81-1.23) and 0.91 (95% CI 0.61-1.35), respectively. Interpretation of this and other measures in this trial were complicated by the high overall loss to follow-up (56.9%).

Few trials (2/13, 15.4%) reported cost considerations. In one trial the authors found a significant difference in cost of care between insulin plus metformin ($3.20/day) and triple therapy ($10.40/day) despite similar effects on A1c.\(^6\) In another trial, the authors estimated the total mean cost of glycemic control over 24 weeks to be $235 lower among subjects treated with insulin glargine ($1,368) compared with subjects treated with rosiglitazone ($1,603).\(^6\)

Similarly few (3/13, 23.1%) trials reported on health related quality-of-life using validated instruments (two trials reported their results elsewhere). In each case, comparisons
were primarily to gauge quality of life with either exenatide, a glitazone, or insulin monotherapy compared to a triple therapy regimen containing basal insulin. Few differences were found in each pairwise comparison and the clinical relevance is of such findings is unknown.\textsuperscript{46,79,80}

*Characteristics of included studies.* 49 studies were retained for full review of which 11 are included in this review. Excluded studies tended to be of insufficient sample size or duration, were nonrandomized, or did not include a triple therapy treatment arm. The studies that were included had good internal validity. The population to whom these results are externally valid are best described as a middle-aged to elderly population, overweight, with a relatively long duration of diabetes, and a baseline A1c above 8.0%, already on metformin and a sulfonylurea.

**SUPPLEMENTARY RESULTS AND DISCUSSION BY AGENT OR DRUG CLASS**

*Exenatide.* Three articles fulfilled inclusion criteria. Study designs were similar. Patients continued maximally tolerated metformin plus a sulfonylurea and were randomized either to exenatide or placebo,\textsuperscript{35} to exenatide or insulin glargine,\textsuperscript{36} or to exenatide or insulin aspart.\textsuperscript{37} Study populations were similar with respect to age, body mass index (BMI), duration of diabetes, and baseline A1c. Withdrawal rates were differential in two trials: 19.4% (exenatide) versus 9.7% (insulin glargine), 9.5% (exenatide) versus 0.7% (insulin glargine) due to adverse events\textsuperscript{36}; 21.3% (exenatide) versus 10.1% (biphasic insulin), 7.9% (exenatide) versus 0.0% (biphasic insulin) due to adverse events.\textsuperscript{37}

Exenatide, as an add-on to existing metformin and sulfonylurea therapy, lowered A1c by 0.8-1.1% from baseline, superior to placebo and non-inferior to either insulin regimen tested. Exenatide demonstrated comparable efficacy in two parallel phase III RCTs, one in which exenatide was added to sulfonylurea monotherapy,\textsuperscript{38} the other in which it was added to metformin monotherapy.\textsuperscript{39} 46 patients in a phase II study already on and continuing metformin
and sulfonylurea therapy also experienced A1c lowering. However, this study was not designed to assess differences among various treatment groups.

Change in A1c over time shows the greatest reduction in A1c occurs at 12-16 weeks post-initiation and decreases slightly thereafter. Improvements in glycemic control have been sustained up to 82 weeks in open-label extensions of the phase III RCTs. Additional gains in A1c reduction seem likely attributable to the dose escalation of all patients to the 10ug twice daily dose at the start of the open-label extensions.

From one-third to nearly one-half of exenatide-treated patients attained A1c levels less than 7%. Again, the pivotal phase III trials observed similar proportions as did their open-label extensions. Limitations to the latter analysis include the lack of a comparator group and self-selection bias, though the authors attempted to control for both in their analyses.

Weight loss of 1.6-2.5kg was an important treatment externality. Weight loss was statistically significant as early as two weeks post-initiation of exenatide treatment. Weight loss was similar when exenatide was added either to sulfonylurea or to metformin monotherapy. Reduction in body weight was progressive in three 82-week completer cohorts, with losses of 4.0-5.3kg.

Beneficial changes in lipid profiles and in blood pressure were noted in the open-label trials but not in their randomized predecessors. Additional trials controlling for these factors are needed.

The most common adverse events were gastrointestinal, including nausea (33.0-57.1%), vomiting (13.7-17.4%), and diarrhea (8.5-17.4%). All side effects appear dose-dependent and gradual dose escalation has been shown to attenuate these effects. Incidence of treatment-emergent nausea was generally of mild-to-moderate intensity and peaked during the initial weeks.
of dosing then decreased thereafter. Studies generally included a *post hoc* analysis of weight change stratified by whether or not the patient had experienced nausea, in addition to calculating a Pearson’s correlation coefficient. Gastrointestinal side effects were not a significant cause of the weight reduction observed in patients receiving exenatide.

Hypoglycemic events were reported both as a proportion (27.8%) and as a rate (4.7-7.3 events per patient-year). One trial’s study design enabled an assessment of the influence of concurrent sulfonylurea dosing on risk of hypoglycemia. The overall incidence of hypoglycemia was lower among those patients randomized to the minimum recommended dose of sulfonylurea compared to those randomized to the maximally effective dose with small attenuation of the effects on glycemic control.

The increased hypoglycemia observed is likely a composite of background sulfonylurea susceptibility and superimposed exenatide effect. This conjecture is supported by low rates of hypoglycemia in the exenatide plus metformin monotherapy trial compared with the others in which a sulfonylurea was part of the treatment regimen. A proactive approach to sulfonylurea dose reduction will likely limit the incidence of hypoglycemia in exenatide-treated patients. For example, 33% (84/253) of exenatide-treated patients had their sulfonylurea dose reduced with resultant decrease in rates of hypoglycemia but without attendant compromise of reductions in A1c.

Anti-exenatide antibodies were detected in 43-49% of patients by study’s end in each of the three trials and were generally of low titer. The presence or absence of antibodies had no predictive effect on the magnitude of an individual’s glycemic response or on the incidence of adverse events. The clinical significance of the development of antibodies is unknown at this time.
None of the trials reported on micro- or macro-vascular endpoints, cost data, or health-related quality of life (HRQOL). One trial\textsuperscript{36} used validated instruments to measure quality-of-life but results are reported elsewhere.\textsuperscript{46} In the per protocol population (\(n=455\)), both exenatide and insulin glargine were associated with significant improvements in patient-reported outcomes. The negatives of an additional daily injection and a higher rate of gastrointestinal adverse events were likely balanced by the positives of weight loss in patients treated with exenatide. Whether these gains in patient satisfaction are clinically meaningful in terms of adherence is not known.

Two cost-effectiveness analyses have also been reported elsewhere.\textsuperscript{47,48} Although exenatide was generally associated with an increase in direct medical costs, the gains in quality-adjusted life years (QALYs) translated into mean incremental cost-effectiveness ratios (ICERs) commonly regarded as cost effective.

\textit{Acarbose and miglitol.} Three articles fulfilled inclusion criteria. Study designs were similar in two. Patients continued metformin plus a sulfonylurea and were randomized either to acarbose or placebo\textsuperscript{49} or to miglitol or placebo.\textsuperscript{50} The third study was embedded within the larger UKPDS trial.\textsuperscript{51} Randomization was not stratified according to preexisting therapy, so imbalances may exist between the acarbose and placebo treatment arms within any given preexisting therapy group (i.e., metformin plus sulfonylurea). However, analyses are performed and results are reported in such a way as to permit a comparison. Biases due to inter-group variability are likely greater than intra-group variability, randomization appears successful, and selection bias is minimal.

Study populations were similar in two.\textsuperscript{50,51} One study population differs from the other two trials most importantly in terms of mean BMI: 24.8 (acarbose)\textsuperscript{99} versus 27.7 (acarbose)\textsuperscript{50} and 29.8 (acarbose).\textsuperscript{51} This study population is also internally homogeneous with respect to
demographics; standard deviations are small.\textsuperscript{49} Withdrawal rates were nondifferential in all trials. 56.9\% overall loss to follow-up within the metformin plus sulfonylurea treatment group was observed in the UKPDS trial; analyses were performed by allocated therapy (intention-to-treat) and by actual therapy.\textsuperscript{51}

Acarbose or miglitol, as an add-on to existing metformin and sulfonylurea therapy, lowered A1c by 0.5-0.55\% from baseline at 24 weeks, and 0.20\% (allocated therapy) or 0.32\% (actual therapy) from baseline at 3 years. Neither of these latter differences was statistically significant. A greater initial reduction in median A1c was observed in the UKPDS trial though it did not achieve statistical significance; thereafter, A1c levels rose steadily to the three-year endpoint. None of the included trials reported the proportion of acarbose-treated patients attaining A1c levels less than 7\%. One trial divided acarbose-treated patients into responders (reduction in A1c >0.5\%) and non-responders (reduction in A1c <0.5\%); no significant predictors of treatment effect were found.

A critical review of acarbose\textsuperscript{52} and a Cochrane meta-analysis\textsuperscript{53} of published, placebo-controlled studies in which an alpha-glucosidase inhibitor was studied either as monotherapy or combination therapy found comparable reductions in A1c (0.68-0.77\%). The latter study found a larger effect on A1c for patients with higher baseline A1c (-0.12\% decrease for every +1.0\% baseline A1c) and an inverse relationship with study duration (the less effect on A1c the longer the follow-up period).\textsuperscript{53}

Smaller prospective trials where acarbose was added to metformin plus a sulfonylurea have yielded conflicting results. In one placebo-controlled study (n=28), no significant improvements in A1c levels after four months were detected in patients randomized to acarbose; however, a relatively low-dose (150mg/d) of acarbose was used.\textsuperscript{54} Two open label studies, one in
Thailand\textsuperscript{55} \((n=36)\) and the other in the US\textsuperscript{56} \((n=11)\), found significant differences in A1c from baseline; however, both studies also found significant decreases in body weight, not usually associated with acarbose therapy. Positive results of the magnitude reported in these studies (1.0-1.4\%) are likely attributable as much to dietary reinforcement as to acarbose. In the latter trial, the high baseline A1c of enrolled subjects (13.6\%) also calls into question whether or not patients were fully optimized on existing therapy. Another study in which placebo or acarbose were compared to bedtime NPH insulin\textsuperscript{57} \((n=29)\) found decreases in A1c of 0.8\% when acarbose was added to failing metformin-sulfonlurea therapy.

Modest weight loss of 0.3-0.54kg was reported in two trials.\textsuperscript{49,51} Differences in the Chinese diet coupled with dietary reinforcement during the run-in phase probably explains the former study consistent with results reported elsewhere.\textsuperscript{58} Overall, acarbose and miglitol are generally regarded as weight neutral. No significant differences in hypoglycemic events or in lipid profiles were observed in any of the trials.

The most common adverse events were gastrointestinal, including flatulence (30.0-62.2\%), diarrhea (11.0-16.0\%), and abdominal pain (1.0-4.0\%).\textsuperscript{49-51} The occurrence of side effects appears to be dose dependent and gradual dose escalation may attenuate these effects somewhat. In the UKPDS trial, side effects were often the reason given for noncompliance: flatulence (30\%) and diarrhea (16\%). The authors note that most of the patients who discontinued acarbose therapy did so during the first year, suggesting that once tolerance is established, adherence is easier to maintain.\textsuperscript{51}

None of the trials reported on cost data or on health-related quality of life (HRQOL). The UKPDS reported data concerning “any-diabetes related endpoint” and microvascular disease.
The relative risks for acarbose compared with placebo were 1.00 (95% CI 0.81-1.23) and 0.91 (95% CI 0.61-1.35), respectively.\textsuperscript{51}

Though improvements in glycemic control are comparatively modest, alpha-glucosidase inhibitors' place in diabetic pharmacotherapy must be considered given their weight and hypoglycemic “neutrality” as well as their effects on postprandial glucose levels and non-dependence on residual beta-cell function.

Rosiglitazone and pioglitazone. Three articles fulfilled inclusion criteria. Study designs were similar. Patients continued metformin plus a sulfonylurea and were randomized either to rosiglitazone or placebo,\textsuperscript{59} to rosiglitazone or insulin glargine,\textsuperscript{60} or to a glitazone (rosiglitazone or pioglitazone) or premixed insulin (continuing only metformin).\textsuperscript{61} Study populations were similar with respect to age, body mass index (BMI), and duration of diabetes. The mean baseline A1c was higher in one trial, owing to the exclusion criteria of those with an A1c less than 8.0%.\textsuperscript{61} Withdrawal rates were differential in one study (19.9% (rosiglitazone) versus 37.0% (placebo), 67.6% of the latter figure owing to hyperglycemia or loss of glycemic control).\textsuperscript{59}

Rosiglitazone or pioglitazone, as an add-on to existing metformin and sulfonylurea therapy, lowered A1c by 0.9-1.77% from baseline, superior to placebo and non-inferior to either insulin regimen (though neither trial was set-up to demonstrate non-inferiority). A planned subgroup analysis in one study found that when baseline A1c exceeded 9.5%, the reduction in A1c with insulin glargine was significantly greater than with rosiglitazone, suggesting adding a glitazone may be beneficial when baseline A1c is modestly elevated, but inappropriate at higher levels.\textsuperscript{60}

One study design permitted treatment switches: patients failing three oral drugs, rather than being withdrawn, were transferred to insulin/metformin therapy, or if on insulin plus
metformin, were switched to a multiple-injection regimen.\(^6\) 13.3% (13/98) of patients on triple oral therapy were switched to metformin/insulin by study’s end (A1c mean (SD) pre-switch 9.85 (1.70); post-switch 8.06 (1.36). 2.4% (2/90) of patients on insulin were switched to basal-bolus therapy by study’s end; both patients experienced slight increases in A1c.

The efficacy of rosiglitazone or pioglitazone, as an add-on to metformin plus a sulfonylurea, has been demonstrated elsewhere and corroborates the findings above. Rosiglitazone was added to existing therapy, including metformin plus a sulfonylurea (n=4247), in a large six-month observational study in Germany. The triple therapy treatment group experienced a 1.3% reduction in A1c with 48.0% achieving an A1c <7.0%, despite a higher baseline A1c, BMI, and longer duration of diabetes.\(^6\) Several smaller prospective trials involving rosiglitazone have reported similar results: an A1c reduction of 1.8% in a minority population (n=48),\(^6\) 0.97% at a lower dose (4mg/d) and in a reasonably well-controlled population (mean (SD) baseline A1c 7.54 (0.9)) (n=30),\(^6\) and 1.1% in a population of Greek diabetic patients (n=38).\(^6\)

Pioglitazone lowered A1c by 1.5% with 61% of patients achieving A1c levels <6.5% in an aggressive treat-to-target prospective open-label study (n=54)\(^6\) and a retrospective cohort conducted by chart review (n=45) with comparison to a previous study\(^6\) found pioglitazone lowered A1c by 2.1\%.\(^6\)

Rosiglitazone and pioglitazone have also been compared to various insulin regimens in several smaller prospective trials. Reductions in A1c have again been similar: 1.8% (rosiglitazone) versus 1.5% (insulin glargine) (n=20);\(^6\) 0.9% (rosiglitazone) versus 1.2% (premixed (70/30) insulin with evening meal) (n=17);\(^6\) 1.9% (pioglitazone) versus 2.3% (NPH
insulin qhs) \((n=62)\).\(^{70}\) This latter trial was randomized but was excluded for insufficient follow-up (16 weeks).

Weight gain of 3.0-3.5kg was reported in all three trials.\(^{59-61}\) This weight gain does not seem to blunt reductions in glycemic control and is largely independent of the fluid retention well-known to this drug class. Effect on lipids was reported in all three trials; effect was either non-significant or effects favored the insulin-included regimen. However, of the three trials, all but one involved rosiglitazone and this remaining study involved 50% of patients on each agent.\(^{61}\) A well-done randomized trial\(^{71}\) and a retrospective cohort conducted by chart review\(^{72}\) focused on comparing the two members of the TZD drug class and their respective effects on lipid profiles. Overall, pioglitazone has demonstrated more favorable effects (greater increases in HDL, more modest increases in LDL, and decreases in TGs) than has rosiglitazone.

Hypoglycemic events were reported both as a proportion\(^{59,60}\) (48.0-53.0%) and as a rate\(^{61}\) (3.4 events per patient-year). Incidence has generally been lower and of greater variation in other reported studies (0.0-37.0%)\(^{64-66,70}\), though studies also vary widely in their definition of and recording of hypoglycemic events. In both trials in which an insulin-containing regimen was used as an active comparator, the incidence of hypoglycemia in the TZD-containing regimen was significantly less. One trial did not report adverse events other than those related to hypoglycemia.\(^{61}\) Otherwise, the most common significant adverse event was mild to moderate edema (8.0-12.5%), a side effect well-known to this drug class. Incidence has been of greater variation in other reported studies (0.78-19%).\(^{62-67,70}\) The liver toxicity which led to the market recall of troglitazone, the first member of this drug class, has not been appreciable outside of rare case reports with either of these agents.
None of the trials reported on micro- or macro-vascular endpoints. A recently published meta-analysis of randomized trials has caused both alarm in the health-care community and criticism of the Food and Drug Administration (FDA). The meta-analysis found in those patients taking rosiglitazone compared with controls, the odds ratio for myocardial infarction was 1.43 (95% CI, 1.03-1.98, p=0.03) and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98-2.74, p=0.06). Limitations of the analysis include lack of a time-to-event analysis and the fact the analysis pools trials not designed to investigate the outcomes of interest (e.g., myocardial infarction and death from cardiovascular causes). Because the event is relatively rare, confidence intervals are wide and differential misclassification could bias the results. The largest trials, which are included in the analysis, yield somewhat conflicting information. The population in the former trial differs importantly from the population addressed herein, dealing with primary prevention in patients with impaired glucose tolerance.

Given the effect of rosiglitazone on lipids and on edema in the setting of susceptibility to congestive heart failure, a biologically plausible mechanism exists for the effect seen; the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial may provide further support or refutation. It is important to note that pioglitazone, with its more favorable effect on lipids, has shown a trend toward benefits in terms of a composite end-point representing coronary and peripheral vascular events (hazard ratio, 0.90, p=0.095) and a secondary endpoint consisting of myocardial infarction, stroke, and death from any cause (hazard ratio, 0.84, p=0.027). However, no similar pooled analysis has been undertaken; thus what effect may exist cannot yet be said to represent a “class effect.”

Two of the trials reported on cost data; in both cases, cost of care analysis demonstrated superiority for the insulin-included regimen. None of the trials reported on health-related quality
of life. One trial used validated instruments to measure quality-of-life but results are reported elsewhere. This study found both rosiglitazone and insulin glargine groups showed improvements in HRQOL, although subjects treated with insulin glargine experienced significantly greater improvements in several dimensions, notably total symptom score and overall perception of general health.

**Insulin.** Two articles fulfilled inclusion criteria, in addition to those studies already a part of the review that included a “triple therapy with insulin” arm. Concerning the two additional trials, study designs were similar. Patients continued maximally tolerated metformin plus a sulfonylurea and were randomized either to a bedtime dose of NPH insulin or to a morning dose of insulin glargine. In both trials, the comparison arm was premixed insulin (70% NPH/30% regular) dosed twice daily as monotherapy. Neither trial included a placebo arm, therefore differences are from baseline as opposed to placebo-subtracted from baseline.

Study populations were similar with respect to age, body mass index (BMI), duration of diabetes, and baseline A1c. Patients randomized to premixed insulin had a significantly lower BMI (mean (SD) = 28.5 (3.8)) than patients randomized to bedtime NPH plus oral hypoglycemic agents (OHAs) (mean (SD) = 33.2 (6.4)) in one trial. Withdrawal rates were differential in the other trial: 4.0% (glargine + OHAs) versus 15.0% (premixed insulin). In the latter group, the most common reasons for withdrawal were unwillingness to continue (12/28, 42.9%), lack of efficacy (5/28, 17.9%), and unspecified (9/28, 32.1%).

Insulin, as an add-on to existing metformin and sulfonylurea therapy, lowered A1c by 0.8-1.7% from baseline. Insulin glargine was the add-on agent in three trials. Mean doses ranged from 25.0-38.5U/d with reduction in A1c from 1.1-1.7%. NPH insulin was the add-on agent in one trial (mean dose 25.8U/d, A1c reduction 0.8%). Twice-daily insulin
aspart was the add-on agent in the remaining trial (mean dose, 24.4U/d, A1c reduction 0.9%). Three of the trials were designed to test the non-inferiority of other agents, exenatide in two and rosiglitazone in the other. Therefore, treatment effects with insulin in these particular trials must be interpreted in light of their respective study designs. Still, trial conditions represent efficacy more than effectiveness, so the observed effects with insulin should not necessarily be taken as the lower range of effects that would be observed in other settings. In two of the trials, insulin plus oral hypoglycemics were compared to premixed insulin dosed twice daily as monotherapy. Reduction in A1c with insulin monotherapy exceeded triple therapy with NPH in one study (-1.2% versus -0.8%), but was less than triple therapy with glargine in another study (-1.31% versus 1.64%).

From one-fourth to one-half of insulin-treated patients attained A1c levels less than 7%. Proportions were consistent among glargine-treated patients (48-49%) in three trials and were consistently higher than patients on other insulin-containing regimens, whether used in combination or as monotherapy. Some of the difference could be explained by the varying use of forced titration, and the aggressiveness or lack thereof, in the trials.

Better glycemic control and an increased proportion of patients attaining A1c levels less than recommended not surprisingly came at the expense of an increased incidence of hypoglycemia. One trial performed an additional analysis in which it was revealed that more patients reached an A1c<7% without confirmed nocturnal hypoglycemia with glargine (46%) than with premixed insulin (29%). A similar effect (55.2% versus 30.2%) was seen in a planned subgroup analysis of the original study conducted in patients >65 years of age (n=130), reported elsewhere.
Modest weight gain of 1.3-2.9 kg is an important treatment externality. Weight gain was more than was observed with exenatide, but less than with rosiglitazone and with premixed insulin monotherapy. Several studies have suggested that metformin, in particular, is important for ameliorating the weight gain seen with combination insulin therapy.

Hypoglycemia was the most common and important side effect. Severe hypoglycemia requiring medical assistance was rare. Hypoglycemic events were reported as a rate in all trials and ranged from 2.7-7.7 events per patient-year. These rates were higher than with rosiglitazone, comparable to exenatide, and less than observed with premixed insulin monotherapy. Again, incidence of hypoglycemia tends to be related to the study design and reflect how insulin is dosed and subsequently titrated.

None of the trials reported on lipids or on micro- or macro-vascular endpoints. One trial reported on cost, and showed a distinct and significant cost advantage for triple therapy with once-daily glargine compared to triple therapy with rosiglitazone.

DISCUSSION

Summary of findings. Eleven randomized controlled trials, enrolling 3,306 participants with a median follow-up duration of 24 weeks, were included. Overall, study methodologic quality was good. Trial participants were generally similar with respect to age, body mass index (BMI), duration of diabetes, and baseline A1c making it possible to generalize the results of this review to a likely externally valid population.

A1c lowering varied from 0.2%-1.8% and from least effective (alpha-glucosidase inhibitors) to most effective (thiazolidinediones and insulin glargine). Generalizing these averaged results to patients at differing levels of baseline glycemic control is limited. Irrespective
of the third agent chosen, less than half of all trial participants attained A1c <7.0%, though this may reflect inclusion of participants with advanced disease. Nevertheless, results suggest reconsideration of glycemic targets as well as the possible inappropriateness of certain treatment recommendations.

Third agents were generally safe and were well-tolerated. The incidence of serious adverse events was low (<3%) including severe hypoglycemia (1.5 events per 100 patient-years). Incidence of hypoglycemia appeared related to the sulfonylurea dose, suggesting a treatment recommendation, and to the ambient level of glycemic control, suggesting a shifting balance of benefits and harms with increasingly intensive therapy. The rarity of serious events precluded comparisons among particular agents.

Few of the trials reported on micro- or macro-vascular endpoints, economic considerations, or effects on health-related quality of life. The paucity of such data in the included literature has implications for future research.

**Efficacy.** Interpretation of efficacy measures is confounded by several factors. First, all results are reported as population means, irrespective of baseline A1c. Only two studies\(^{35,60}\) reported an analysis of change in A1c from baseline stratified by baseline A1c. In the trial involving exenatide,\(^{35}\) participants whose baseline A1c >9.0% experienced significantly greater effects than those whose A1c <9.0% (-1.5% versus -0.5%, respectively). While published quantitative results were unavailable for the rosiglitazone versus insulin glargine trial,\(^{60}\) the authors state that when baseline A1c >9.5%, reduction in A1c with insulin glargine was significantly greater than with rosiglitazone (in patients with A1c <9.5% there was no significant difference between treatment groups). This suggests adding a glitazone may be beneficial when baseline A1c is modestly elevated but inappropriate at higher levels.
Second, interventions in these trials are initiated at wide-ranging levels of existing glycemic control. Typical inclusion criteria admitted participants whose baseline A1c was between 7.0%-11.0%. Without stratified analysis, the magnitude of A1c lowering is difficult to generalize for a patient with an A1c of 8.0% on metformin and sulfonylurea and for another with an A1c of 10.0%. Any algorithm predicated on a single treatment recommendation without accounting for this is not sufficiently evidence-based.

Third, unrealized potential exists for these and future studies to clarify whether add-on therapy demonstrates a linear relationship or a curvilinear relationship based on baseline A1c. If diminishing returns are observed irrespective of agent, then shared-decision making—eliciting patient values regarding route of administration, likelihood of adverse event, and cost among others—should be a highly effective approach.

Safety. In those trials evaluating hypoglycemia, rates seemed related to two factors. First, hypoglycemia seemed to vary with background sulfonylurea dose. In a trial investigating exenatide, the overall incidence of hypoglycemia was lower among those randomized to a minimally effective sulfonylurea dose than those randomized to a maximally tolerated sulfonylurea dose (35% versus 21%, respectively) with small attenuation of the effects on glycemic control as measured by change in A1c (-0.9% versus -0.6%, respectively). In a second trial investigating exenatide, 33% of exenatide-treated patients had their sulfonylurea dose reduced: hypoglycemia rates decreased following sulfonylurea dose reductions from 26.9 events per patient year to 6.1 events per patient year with observed reductions in A1c similar between those on stable sulfonylurea doses and those on reduced sulfonylurea doses (-0.99% versus -0.93%, respectively). In the trial investigating rosiglitazone add-on therapy, doses of glyburide/metformin were decreased due to hypoglycemia in 18 patients (10.0%), decreasing
rates of hypoglycemia without sacrificing efficacy. This suggests a proactive approach to sulfonlurea dosing in limiting the incidence of hypoglycemia and has implications for practice.

Second, hypoglycemia seemed to vary with ambient A1c levels; that is, with increasingly tight control, there was an increased incidence of hypoglycemia. In the above-mentioned trial investigating rosiglitazone, hypoglycemia was associated with lower final A1c levels particularly in patients achieving levels <6.5%. This is not a novel finding: the trade-off between hypoglycemia and tight control is well-known to clinicians and given this, care should be taken with target goals in certain populations such as the elderly and those prone to being hypoglycemic unaware among other vulnerable cohorts.

*Implications.* While proportion of patients achieving an A1c less than 7.0% was reported in many of the studies (8/11, 72.7%), the proportion of patients achieving this level of control was less than half in all studies. It is interesting to note that the treatment goals and measures of quality care rely on guidelines and recommendations, though these targets were rarely achieved in the trials included in this systematic review. This should not be regarded as failure, though it may suggest an inappropriateness of the guidelines. Regardless, it should refocus the discussion on the benefits of incremental reductions in A1c, particularly as it relates to risk reduction of micro- and macro-vascular endpoints.

To illustrate the diminishing returns expected to be observed with increasingly intensive glycemic control, a hypothetical outcomes table was generated based upon a Markov decision model, itself constructed from the Rochester cohort study of diabetic patients and the Wisconsin Epidemiologic Study of Diabetic Retinopathy to provide estimates of the rates of progression to end-stage outcomes. The table assumes the clinical situation posed in the background and rationale section of this review: A fifty-five-year-old, overweight
(BMI=30kg/m²) adult with long-standing diabetes (10-years post-diagnosis) and an A1c=8.0% on maximally-tolerated metformin plus glipizide.

The table then inputs the upper limit of demonstrated effectiveness of various third agents reviewed herein as well as the proportion of patients experiencing treatment-related adverse events. The absolute risk reductions in lifetime risk for blindness due to diabetic retinopathy and for end-stage renal disease due to diabetic nephropathy are extrapolated from the model. These are then used to calculate the number needed to treat (NNT) to prevent one health outcome—blindness or end-stage renal disease—as opposed to intermediate outcomes so prevalent in the literature.

While not reflected in the outcomes table, in patients with later onset, moderate glycemic control prevents most end-stage complications caused by microvascular disease. Given these diminishing returns, the question needs to be reframed away from which agents to choose, given relative comparable efficacy (NNT range, 91-333), and toward what target level is appropriate. In the same thread, patients with an elevated baseline A1c above a certain threshold may reflect advanced disease, diminished beta-cell secretory capacity and increasing peripheral resistance. In this instance, it may be inappropriate to recommend an agent other than insulin.

Cost data was taken from the current Drug Topics 2006 Red Book (October 2006). Values listed reflect average wholesale prices where cost for individual subjects was based upon the maximum daily dose administered in trials. Calculations do not include the cost of lab monitoring, supplies, or increased frequency of self-monitoring of blood glucose levels. They also do not comment on whether metformin or sulfonylurea dose might be able to be lowered or dropped and the resultant effect on overall cost of treatment. Differences in cost from a health
systems perspective are important given that improved medical resource utilization resulting from better glycemic control may ultimately yield cost-savings.

Limitations of the literature. An insufficient trial duration (for purposes of this review, less than 24 weeks) was an important exclusion criterion. Despite this, only one trial (the UKPDS) had a follow-up period longer than one year and the eleven trials included had a median follow-up of 24 weeks. While several agents have reported efficacy past a year, these extended trials are open-label and thus introduce important biases into the interpretation of their results.

Most trials are conducted long enough to demonstrate the effectiveness of the agent, but do not address how long that agent is effective. Given that the pathophysiologic defect in type 2 diabetes mellitus is progressive, the duration of effectiveness—expressed as a period free of complications, or the period of time spent above an A1c level known to place a patient at increased risk of complications—is an important consideration in treatment-decisions. Few studies, both included and excluded, performed Kaplan-Meier analysis on time to treatment failure, however that may be defined, or time to treatment switch (to insulin or to another agent).

Limitations of this analysis. While information regarding effect on fasting plasma glucose and postprandial glucose levels were abstracted when available, this review was not designed to address the differential effect of each agent on these two outcomes and the effect that may have on glycemic control in general.

In those trials which performed analyses stratified by baseline A1c, those with higher A1c at baseline often realized more pronounced reductions in A1c. Whether or not this can be explained by the mechanistic targeting of fasting and/or postprandial glucose levels and the relative contributions of each at varying levels of glycemic control cannot be stated from this review. The more poorly controlled the patient is, the more the fasting glucose concentration
contributes to overall hyperglycemia, whereas in better-controlled patients, postprandial glycemia plays a more major role. 84

Guidelines on type 2 diabetes conflict with one another about indications for treatment and preferred regimens, and most recommendations are based on less than sufficient evidence. For example, it is unclear in the case of combination therapy whether sulfonylurea or metformin or both should be continued. Studies on insulin posed a formidable challenge as general practice and the bulk of the literature is either insulin as monotherapy after oral therapy has failed or insulin with either continued metformin or a sulfonylurea after treatment failure with two oral agents. 85 This review was again not designed to address the efficacy of any particular regimen or to discriminate among them. 86 The constraints of the systematic review were that studies regarding insulin would only be admitted if insulin was part of a triple therapy regimen. The results of this review are not generalizable to those with higher A1c values many of whom may need additional injections of short-acting insulin if levels of A1c remain above target despite optimization of basal insulin.

This review does not address agents in the drug development pipeline. Limited keyword searching suggested no articles would have met inclusion criteria; but, the changing armamentarium does curtail the lifespan of any review. However, it does nothing to diminish the importance of optimizing treatment decisions informed by rigorous evaluation of the evidence and supplemented by shared decision-making between patient and provider. The failure to implement already available interventions aggressively and effectively is a major barrier to quality care, not remedied by the influx of new medications.
REFERENCES


54 Rodier M, Richard JL, Monnier L, Mirouze J. Effect of long term acarbose (Bay g 5421) therapy on metabolic control of non insulin dependent (type II) diabetes mellitus. *Diabetes Metab* 1998; 14:12-4 [PMID: 3292303]


Table 1. MEDLINE queries including keywords and MeSH terms

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LIMITS

SUBJECTS: “Humans” LANGUAGE: “English” AGES: “All adults (19+ years)” PUBLICATION TYPE: “Clinical trial” OR “Randomized controlled trial”
Table 2. Inclusion and exclusion applied to stages of article review and collection

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<td><strong>Study population</strong></td>
<td>Adults (&gt;19 years of age inclusive) with type 2 diabetes mellitus of any duration with an A1c &gt; 7.0% on an existing, stable regimen of metformin plus a sulfonylurea</td>
<td>Adults with type 1 diabetes mellitus, diabetes of secondary cause, gestational diabetes, pre-diabetes, or metabolic syndrome; trial conducted in the pediatric or adolescent population (&lt;18 years of age inclusive)</td>
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<td>Studies conducted in or regarding inpatient, hospital, or intensive short-term management or comparable settings</td>
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<td><strong>Study design</strong></td>
<td>Randomized-controlled trials with follow-up at least 24 weeks and an evaluable total study population of at least thirty participants; at least one trial arm must include the investigation of an add-on third agent to existing dual therapy with metformin and a placebo; must include an active control or placebo though can be open label</td>
<td>Non-randomized trials, doses of metformin and/or sulfonylurea inconsistent with clinical practice, inadequate final sample size or follow-up period; drugs which have been withdrawn from or are not available in the US market (i.e., troglitazone)</td>
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<td><strong>Reported outcomes</strong></td>
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<td>Any trial which did not report one or both of these key measures</td>
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<tr>
<td>DRUG CLASS</td>
<td>Reference</td>
<td>Agent Dosage</td>
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<tr>
<td>EXENATIDE</td>
<td><strong>Kendall DM, Riddle MC, Rosenstock J, et al</strong></td>
<td>Exenatide 10ug bid</td>
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<td>Placebo N/A</td>
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<td><strong>Heine RJ, Van Gaal LF, Johns D, et al</strong></td>
<td>Exenatide 10ug bid</td>
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<tr>
<td></td>
<td></td>
<td>Placebo N/A</td>
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<tr>
<td></td>
<td><strong>Nauck MA, Duran S, Kim D, et al</strong></td>
<td>Exenatide 10ug bid</td>
</tr>
<tr>
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<td>Placebo N/A</td>
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<td></td>
<td><strong>α-GLUCOSIDASE INHIBITORS</strong></td>
<td>Acarbose, 100mg tid</td>
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<tr>
<td></td>
<td><strong>Lam KSL, Tiu SC, Tsang MW, et al</strong></td>
<td>Placebo N/A</td>
</tr>
<tr>
<td></td>
<td><strong>Standl E, Schernthaner G, Rybka J, et al</strong></td>
<td>Miglitol, 100 mg tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo N/A</td>
</tr>
<tr>
<td></td>
<td><strong>Holman RR, Call CA, Turner RC</strong></td>
<td>Acarbose, 100mg tid</td>
</tr>
<tr>
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<td>Placebo N/A</td>
</tr>
<tr>
<td>GLITAZONES</td>
<td>Patients</td>
<td>Rosiglitazone, 4mg bid</td>
</tr>
<tr>
<td>------------</td>
<td>----------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Dailey III GE, Noor MA, Park JS, et al</td>
<td>Rosiglitazone, 4mg bid</td>
<td>MET (&gt;1500mg/d) + SU (&gt;7.5mg/d)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>MET (&gt;1500mg/d) + SU (&gt;7.5mg/d)</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>MET (=max) + SU (=max)</td>
</tr>
<tr>
<td></td>
<td>Insulin 70/30 bid (63U/d)</td>
<td>MET (=max)</td>
</tr>
<tr>
<td>Schwartz S, Sievers R, Strange P, et al</td>
<td>Rosiglitazone, 4mg bid</td>
<td>MET (=max) + SU (&gt;half-max)</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine (38.5U/d)</td>
<td>MET (=max) + SU (&gt;half-max)</td>
</tr>
<tr>
<td>Rosenstock J, Sugimoto D, Strange P, et al</td>
<td>Rosiglitazone, 4mg bid</td>
<td>MET (=max) + SU (&gt;half-max)</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine (38.5U/d)</td>
<td>MET (x=1895mg/d) + SU (&gt;half-max)</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine (28.2U/d)</td>
<td>MET (x=1895mg/d) + SU (&gt;half-max)</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine (28.2U/d)</td>
<td>MET (x=1895mg/d) + SU (&gt;half-max)</td>
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Table 5. Reported outcomes of included studies

<table>
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<tr>
<th>DRUG CLASS</th>
<th>Reference</th>
<th>Intervention Comparison</th>
<th>Change in A1c (%)</th>
<th>Proportion attaining A1c &lt; 7%</th>
<th>Hypoglycemia (% or events/pt-yr)</th>
<th>Weight change (kg)</th>
<th>Side effects</th>
<th>Lipids</th>
<th>Micro-/macrovascular</th>
<th>Cost data or CEA</th>
<th>HRQOL</th>
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</thead>
<tbody>
<tr>
<td><strong>EXENATIDE</strong></td>
<td>Kendall DM, Riddle MC, Rosenstock J, et al</td>
<td>Exenatide</td>
<td>-0.8</td>
<td>34</td>
<td>27.8%</td>
<td>-1.6</td>
<td>Nausea (49%), vomiting (14%), diarrhea (17%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>+0.2</td>
<td>9</td>
<td>12.6%</td>
<td>-0.9</td>
<td></td>
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<tr>
<td>Heine RJ, Van Gaal LF, Johns D, et al</td>
<td>Exenatide</td>
<td>-1.11</td>
<td>46</td>
<td>7.3 c/p-yr</td>
<td>-2.3</td>
<td>Nausea (57%), vomiting (17%), diarrhea (9%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Insulin glargine</td>
<td>-1.11</td>
<td>48</td>
<td>6.3 c/p-yr</td>
<td>+1.8</td>
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<tr>
<td>Nauck MA, Duran S, Kim D, et al</td>
<td>Exenatide</td>
<td>-1.04</td>
<td>32</td>
<td>4.7 c/p-yr</td>
<td>-2.5</td>
<td>Nausea (33%), vomiting (15%), diarrhea (10%)</td>
<td>R; NS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Insulin aspart</td>
<td>-0.89</td>
<td>24</td>
<td>5.6 c/p-yr</td>
<td>+2.9</td>
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<td><strong>α-GLUCOSIDASE INHIBITORS</strong></td>
<td>Lam KSL, Tiu SC, Tsang MW, et al</td>
<td>Acarbose</td>
<td>-0.5</td>
<td>NR</td>
<td>R; NS</td>
<td>-0.54</td>
<td>Flatulence (62%), diarrhea (11%)</td>
<td>R; NS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>+0.1</td>
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<td>+0.42</td>
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<td>Standl E, Schernthaner G, Rybka J, et al</td>
<td>Miglitol</td>
<td>-0.55</td>
<td>NR</td>
<td>R; NS</td>
<td>NR</td>
<td>Flatulence (30%), diarrhea (14%)</td>
<td>R; NS</td>
<td>NR</td>
<td>NR</td>
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<td></td>
<td>Placebo</td>
<td>-0.20</td>
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<tr>
<td>Holman RR, Cull CA, Turner RC</td>
<td>Acarbose, ITT popn</td>
<td>-0.2</td>
<td>NR</td>
<td>NR</td>
<td>-0.3</td>
<td>Flatulence (30%), diarrhea (16%)</td>
<td>NR</td>
<td>RR 0.91 (95%CI: 0.61-1.35)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Acarbose, PP popn</td>
<td>-0.32</td>
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<td>-0.8</td>
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<td><strong>GLITAZONES</strong></td>
<td>Dailey III GE, Noor MA, Park JS, et al</td>
<td>Rosiglitazone</td>
<td>-0.9</td>
<td>42</td>
<td>53%</td>
<td>+3.0</td>
<td>Mild-moderate edema (8%)</td>
<td>R; NS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>+0.1</td>
<td>14</td>
<td>25%</td>
<td>+0.03</td>
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<td>Schwartz S, Sievers R, Strange P, et al</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>-1.77</td>
<td>31</td>
<td>48%</td>
<td>+3.5</td>
<td>NR</td>
<td>NR</td>
<td>R; favored insulin+met</td>
<td>NR</td>
<td>R; favored insulin+met</td>
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<tr>
<td></td>
<td>70/30 bid + MET</td>
<td>-1.96</td>
<td>32</td>
<td>67%</td>
<td>+2.9</td>
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<tr>
<td>Study</td>
<td>Treatment</td>
<td>Weight</td>
<td>Rate/yr</td>
<td>Rate change</td>
<td>Adverse Effect</td>
<td>Preferred Medication</td>
<td>Preferred Medication</td>
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<tr>
<td><em>Rosenstock J, Sugimoto D, Strange P, et al</em></td>
<td>Rosiglitazone</td>
<td>-1.51</td>
<td>49</td>
<td>3.4e/yr</td>
<td>+3.0</td>
<td>Mild-mod edema (12.5%)</td>
<td>R; favored insulin</td>
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<tr>
<td>Insulin</td>
<td>-1.66</td>
<td>48</td>
<td>7.7e/yr</td>
<td>+1.6</td>
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<td>NR</td>
<td>NR</td>
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<td>glargine</td>
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<tr>
<td>NPH qhs + MET + SU</td>
<td>-0.8</td>
<td>36</td>
<td>2.7e/yr</td>
<td>+1.3</td>
<td>NR</td>
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<td>70/30 bid monotherapy</td>
<td>-1.2</td>
<td>42</td>
<td>4.3e/yr</td>
<td>+4.2</td>
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<td>NR</td>
<td>R; NS</td>
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<td><em>Janka H, Plewe G, Riddle MC, et al</em></td>
<td>Glargine + MET +SU</td>
<td>-1.64</td>
<td>49</td>
<td>4.1e/yr</td>
<td>+1.4</td>
<td>URI (16%), headache (10%), GI sx (10%)</td>
<td>NR</td>
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<tr>
<td>70/30 bid monotherapy</td>
<td>-1.31</td>
<td>39</td>
<td>9.9e/yr</td>
<td>+2.1</td>
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Table 6. Outcomes table

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<tr>
<th>Therapy Conditions</th>
<th>No additional therapy</th>
<th>+Exenatide</th>
<th>+α-glucosidase inhibitor</th>
<th>+TZD</th>
<th>+Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute HbA1c reduction</td>
<td>+0.8%</td>
<td>-1.0%</td>
<td>-0.5%</td>
<td>-1.5%</td>
<td>-1.7%</td>
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<tr>
<td>NNT (to prevent one microvascular complication: blindness)</td>
<td>N/A</td>
<td>ARR = 0.8%</td>
<td>ARR = 0.4%</td>
<td>ARR = 1.0%</td>
<td>ARR = 1.1%</td>
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<tr>
<td>NNT = 125</td>
<td>NNT = 250</td>
<td>NNT = 100</td>
<td>NNT = 91</td>
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</tr>
<tr>
<td>NNT (to prevent one microvascular complication: ESRD)</td>
<td>N/A</td>
<td>ARR = 0.7%</td>
<td>ARR = 0.3%</td>
<td>ARR = 1.0%</td>
<td>ARR = 1.1%</td>
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<tr>
<td>NNT = 143</td>
<td>NNT = 333</td>
<td>NNT = 100</td>
<td>NNT = 91</td>
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<tr>
<td>Likelihood of adverse event</td>
<td>N/A</td>
<td>Nausea: 33%-57% (30%-62%)</td>
<td>Flatulence: 9%-17% (11%-16%)</td>
<td>Mild-mod edema: 9%-17% (11%-16%)</td>
<td>Severe hypoglycemia: 1.5 events per 100 patient-years</td>
</tr>
<tr>
<td>Cost considerations</td>
<td>No additional therapy: BYETTA $0.00/mo</td>
<td>Acarbose: $207.00/mo</td>
<td>Miglitol: $97.36/mo</td>
<td>Rosiglitazone: $183.42/mo</td>
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<tr>
<td>N/A</td>
<td>PRECOSE: $207.00/mo</td>
<td>ACTOS: $195.77/mo</td>
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<td>$0.00/mo</td>
<td>300 mg daily</td>
<td>45 mg daily</td>
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<tr>
<td>Miglitol: $97.36/mo</td>
<td>100 mg daily</td>
<td>8 mg daily</td>
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<tr>
<td>Rosiglitazone: $183.42/mo</td>
<td>$152.29/mo</td>
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