

Enhanced Glycemic Control with Combination Therapy for Type 2 Diabetes in Primary Care

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ABSTRACT

Type 2 diabetes mellitus is an increasingly common medical problem for primary care clinicians to address. Treatment of diabetes has evolved from simple replacement of insulin (directly or through insulin secretagogues) through capture of mechanisms such as insulin sensitizers, alpha-glucosidase inhibitors, and incretins. Only very recently has recognition of the critical role of the gastrointestinal system as a major culprit in glucose dysregulation been established. Since glycated hemoglobin A_{1c} reductions provide meaningful risk reduction as well as improved quality of life, it is worthwhile to explore evolving paths for more efficient use of the currently available pharmacotherapies.

Because diabetes is a progressive disease, even transiently successful treatment will likely require augmentation as the disorder progresses. Pharmacotherapies with complementary mechanisms of action will be necessary to achieve glycemic goals. Hence, clinicians need to be well informed about the various noninsulin alternatives that have been shown to be successful in glycemic goal attainment. This article reviews the benefits of glucose control, the current status of diabetes control, pertinent pathophysiology, available pharmacological classes for combination, limitations of current therapies, and suggestions for appropriate combination therapies, including specific suggestions for thresholds at which different strategies might be most effectively utilized by primary care clinicians.

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INTRODUCTION

Globally, the World Health Organization (WHO) reports that as many as 220 million individuals have diabetes.¹ The Framingham Offspring Study

database indicates that the incidence of type 2 diabetes mellitus (DM2) has doubled in the US from the 1970s through the 1990s.² In the US, it was estimated in 2010 that nearly 26 million individuals had diabetes, of which 7.0 million (27%) were undiagnosed.³ Furthermore, the prevalence of diabetes (driven largely by DM2) is projected to reach 12.0% by 2050, affecting more than 48 million individuals.⁴ Disconcertingly, almost half of deaths in this population occur before the age of 70 years, and the WHO projects that the number of diabetes deaths will double between 2005 and 2030. Clinicians also increasingly recognize the additional burden of DM2 in children and adolescents.⁵ Most patients with DM2 are appropriately managed within the primary care sector, with the occasional need for consultation by diabetologists.

Since DM2 is associated with increased mortality, increased risk of macrovascular disease (ie, stroke and myocardial infarction), and increased microvascular disease (ie, retinopathy, nephropathy, and neuropathy), there are numerous challenges worthy of intervention for risk reduction. Healthy diet, regular physical activity, maintaining a normal body weight, and avoiding tobacco use can prevent or delay the onset of diabetes.

Good control of glucose (glycated hemoglobin A_{1c} [HbA_{1c}] <7%) in patients with DM2 has been shown to reduce microvascular disease and improve quality of life.⁶ Despite the salutary effects attributable to good glucose control, only about half of patients with diabetes are at the currently recognized treatment goal.⁷ In addition to glycemic control, comprehensive DM2 care requires attention to blood pressure, lipids, and lifestyle factors (ie, diet, exercise, and abstinence from smoking), leading to complex medication and lifestyle treatment regimens. Failure to attain glycemic goals may reflect the competing demands of attaining multiple goals at the same time.

Currently, the most widely recognized measure for glycemic control is HbA_{1c}, although exceptions, such as for persons with hemoglobinopathy, do exist. Recommendations from the American Diabetes Association (ADA) suggest an HbA_{1c} goal <7.0%.⁶ Ultimately, as diabetes progresses, most patients will require insulin therapy. However, the purpose of this communication is to focus upon ways primarily to capitalize on non-insulin combination therapies to achieve glycemic goals.

Guidelines from the European Association for the Study of Diabetes (EASD) concur with the concept that utilization of polypharmacy, especially early combination therapy, is one of the greatest advances in DM2 disease management.⁸ Skillful application of combination treatments will be necessary to attain and maintain adequate glucose control in the majority of DM2 patients.⁹ For diabetic patients who “deselect” injection therapy (ie, those who are unwilling or unable to use parenteral treatments), it will be particularly necessary to capitalize upon the complementary therapeutic effects of multiple oral agents.

CONCERNS ABOUT THE CURRENT STATUS OF DIABETES CONTROL

The current status of diabetes control is far from optimal. According to the most recent National Health and Nutrition Examination Survey (NHANES) data, between 2003 and 2006 only 57.1% of adults with diabetes surveyed had achieved the recommended HbA_{1c} target of 7.0% or lower.⁷ Other surveys have shown that 30% or more patients with diabetes have an HbA_{1c} greater than 8.0%.^{10,11} The complexity of multifaceted goal achievement is perhaps best reflected by 2003-2006 data from NHANES that showed the dismally low composite of only 12.2% of patients with diabetes achieving all

three primary goals for HbA_{1c} (<7.0%), blood pressure (<130/80 mm Hg), and low-density lipoprotein cholesterol (<100 mg/dL).⁷

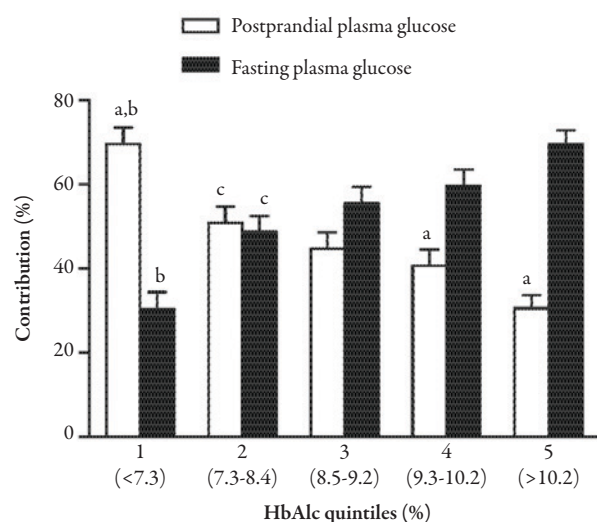
Additionally, despite consistent confirmation of treatment benefits, clinicians have been historically somewhat sluggish in advancement of pharmacotherapy to attain appropriate glucose goals. In a 2000-2002 study of 30 academic primary care and diabetes/endocrinology clinics in the US, among patients with HbA_{1c} values above goal only 40.4% had their current treatment regimens adjusted at the most recent clinic visit.¹² Similarly, a study from Kaiser Permanente (Northwest) data from 1994-2002 demonstrated that patients may not receive appropriate augmentation of therapy promptly: among patients on metformin monotherapy ($n=354$), the average amount of time between their first HbA_{1c} reading >8.0% and treatment augmentation or substitution was 14 months; for patients on sulfonylurea monotherapy ($n=2517$), the average duration was 20 months.¹³ Thus, there remains a great, unmet need for prompt and effective intensification of diabetes management. Early combination therapy offers promise in this regard.

Recognizing that many patients with DM2 languish for protracted periods with glucose levels well above the recognized toxic threshold, the most recent ADA/EASD algorithm has provided a pathway for more prompt control of hyperglycemia by indicating the propriety of introducing insulin as an early agent in combination therapy with metformin to achieve glucose management goals.¹⁴ We do not dispute the advantages of prompt control or the efficiency of goal attainment with insulin. Rather, we see great opportunity for improved recognition of the prompt glycemic control that can be attained with skillful combination of non-insulin therapies, and advancement of therapy with greater chronological alacrity.

Treatment advancement typically relies upon measurement of HbA_{1c}. Although long-term management is appropriately directed by HbA_{1c}, initial management, rapid advancement of pharmacotherapy requires monitoring of fasting glucose status, which can reflect day-to-day changes in control, versus the 90-120-day control window provided by A_{1c} monitoring. As discussed below, most currently available agents achieve as much as 80% or more of their potential to lower fasting glucose within 4 weeks of initiation. Waiting to advance therapy beyond that interval suggests lack of awareness of the time course of action of therapy.

Additionally, Monnier et al.¹⁵ (Figure 1) have shown that in most newly diagnosed patients with DM2 (particularly when HbA_{1c}

Figure 1. Relative contributions of postprandial and fasting hyperglycemia (%) to the overall diurnal hyperglycemia over quintiles of glycated hemoglobin A_{1c} (HbA_{1c}).¹⁵ Adapted with permission from *Diabetes Care* 2003;26:881-885. Reproduced with permission from the *American Diabetes Association*. a=Significant difference was observed between fasting and postprandial plasma glucose (paired t test). b=Significantly different from all other quintiles (analysis of variance [ANOVA]). c=Significantly different from quintile 5 (ANOVA).



is >7.3%), it is the fasting glucose component of dysglycemia that is the primary contributor to elevated HbA_{1c}. Hence, we believe in a “fix the fasting first” philosophy when addressing most individuals with hyperglycemia. Although there is a linear relationship between HbA_{1c} and adverse outcomes, recent literature (notably from the Action to Control Cardiovascular Risk in Diabetes¹⁶ [ACCORD] study) has challenged the concept that lower is always better. In ACCORD, patients randomized to tight control (HbA_{1c} <6.0%) had worse cardiovascular outcomes than those randomized to “traditional” therapy.¹⁶ The ADA 2011 position statement reiterates that HbA_{1c} goals must be individualized.¹⁷ Considerations for individualization include age, health status, comorbidities, regimen complexity, body habitus, economic issues, duration of diabetes, presence of known cardiovascular disease, microvascular complications, hypoglycemia awareness, and personal health preferences.¹⁷

Indeed, there are some circumstances where prudence would argue against tight control. For instance, persons with a history of severe hypoglycemia may be at risk for further recurrences. If a patient has hypoglycemia unawareness, glucose levels may progress to precariously low levels before characteristic symptoms emerge to stimulate correction, placing the patient at substantial risk. Similarly, medications that mask or blunt physiological responses to hypoglycemia (eg, beta-blockers and alpha-beta-blockers) may augment risk. In any of these circumstances, clinicians would be wise to avoid overly tight control.

BENEFITS OF GLYCEMIC CONTROL

In the UK Prospective Diabetes Study (UKPDS),³³ the composite endpoint of “any diabetes-related endpoint” was reduced by 12% for an

achieved HbA_{1c} of 7.0% (intensive treatment group) versus 7.9% (conventional treatment group), microvascular endpoints (retinopathy, nephropathy, neuropathy) were reduced by 25%, and there was also a decrease in need for laser treatments and cataract surgery.¹⁸ These beneficial effects were seen without distinction as to which category of pharmacotherapy was used; that is, no demonstrable difference in endpoint reduction among sulfonylurea, insulin, or metformin was noted in the overall population studied. In addition to microvascular treatment benefits seen in UKPDS, long-term observation of the cohort showed what has been termed the “legacy effect”: favorable effects years after conclusion of the trial. After 10 years of post-trial monitoring, the group that had received intensive treatment originally showed reductions in any diabetes-related endpoint, microvascular disease, myocardial infarction, and all-cause mortality; these favorable results were found despite the fact that by the end of this observation period, HbA_{1c} levels in the group originally assigned to intensive treatment were essentially the same as the group originally assigned to conventional treatment.¹⁹ Another important trial that showed benefits of glucose control in DM2 was the Kumamoto study.²⁰ In a population of 110 Japanese DM2 patients, retinopathy was reduced by 69% and nephropathy by 70% after 6 years of intensive glucose control to an HbA_{1c} level of 7.1%.²⁰

One of the often neglected benefits of good glucose control is the effect upon quality of life. Although motivation for patients to adhere to medication regimens may spring from a desire to avoid microvascular and macrovascular consequences, patients who feel better are directly rewarded for their efforts. In a randomized, double-blind study of DM2 patients (*n*=569), subjects were assigned to active treatment (sulfonylurea) or placebo for

12 weeks, at which point numerous quality of life endpoints were compared.²¹ Symptom distress, general perceived health, cognitive functioning, and overall visual analog scale improved in the treatment group, but worsened in the placebo group. Active treatment also had an impact on the number of work days missed. In their zeal to prevent “hard” endpoints, clinicians should not lose sight of the benefits on quality of life that may be achieved through good glucose control.

RELEVANT PATHOPHYSIOLOGY

DM2 is a progressive disorder; it appears that once beta-cell loss begins, the process continues indefinitely.²² We know of no therapy that has been shown to meaningfully attenuate this progressive loss in humans. The progressive nature of diabetes necessitates that clinicians become familiar with complementary therapies that are necessary as the disease progresses.

DM2 is considered an “ecogenic” disorder, meaning that both genetic and lifestyle factors are involved. Pathogenic defects involved in glucose dysregulation include the pancreas (alpha and beta cells), the gastrointestinal tract, liver, skeletal muscle, and adipose tissue. Stressors, such as infection or injury, that activate counter-regulatory hormones (cortisone and epinephrine) may also contribute to glucose dysregulation (see ADA Position Statement²³).

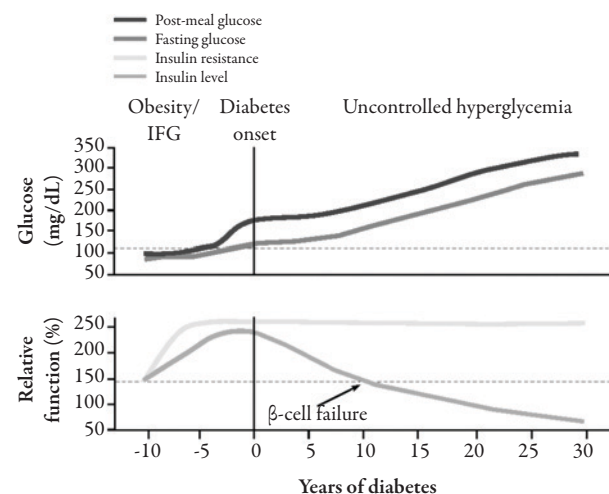
Multiple pathologies are associated with diabetes, foremost of which (at least initially), appears to be insulin resistance.²⁴ As much as a decade before fasting or postprandial glucose becomes elevated (Figure 2), insulin resistance may be present. As long as increased beta-cell activity compensates for this insulin resistance, no derangement of fasting or postprandial glucose is evident.

It has been reported that by the time a diagnosis of DM2 has been made, 50% of

beta-cell function has been lost.²⁶ At this point, insufficient insulin is available to counteract insulin resistance, and suprathreshold glucose levels (postprandial and/or fasting) emerge. It is obvious that diabetic dysfunction occurs well before we make the clinical diagnosis, because as many as 50% of DM2 patients already have one or more diabetic complications the day the diagnosis is made.²⁷

Insulin resistance occurs in multiple tissue compartments: the skeletal muscle, liver, and adipose compartment all exhibit insulin resistance leading to both hyperglycemia and dyslipidemia. It is not surprising, therefore, that multiple therapies will be needed to address multiple pathophysiological defects. For instance, the gastrointestinal tract is increasingly recognized as a critical organ in glucose metabolism. The incretin class of agents, currently comprising the glucagon-like peptide-1 (GLP-1) receptor agonists, such as exenatide and liraglutide, and dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin,

Figure 2. Natural history of type 2 diabetes. Upper panel: the dotted line represents the threshold for diagnosing impaired fasting glucose (IFG; 110 mg/dL). Lower panel: the dotted line represents a reduction in relative function by about 50%.²⁵ *Figure adapted with permission from Natural History of Type 2 Diabetes© 2010 International Diabetes Center, Minneapolis, MN, USA.*



saxagliptin, and linagliptin, harnesses the capacity of GLP-1 to modulate glucose. Indeed, it has been suggested that more than 50% of meal-stimulated insulin production is attributable to intestinal incretins.²⁸

Another gastrointestinal-related phenomenon in diabetes is the absence of first-phase insulin secretion.²⁹ In healthy individuals, a dietary glucose load is met with an almost immediate insulin response known as first-phase insulin release; this prompt response by preformed insulin keeps pace with rapidly rising glycemia. Due to the absence of first-phase insulin release (typical of DM2), rapidly rising glucose levels are unmet and result in inappropriate tissue exposure to elevated glucose. Alpha-glucosidase inhibitors help to address this pathophysiological defect by slowing glucose absorption, incretins do so by delaying gastric emptying, and a low glycemic index diet addresses this defect by selecting foods that produce a less rapid rise in glucose levels.

Pancreatic alpha-cell dysfunction compounds the problems of hyperglycemia. Supranormal glucose levels in healthy individuals suppress glucagon production by alpha cells, yet diabetic patients demonstrate continued

glucagon production, even in the presence of hyperglycemia. In response to hyperglycemia, rising insulin levels should shut down hepatic glycogenolysis. However, since the liver is also insulin resistant, it does not respond appropriately to insulin levels, and continues to produce glucose despite hyperglycemia. Incretins suppress excess glucagon production. Although insulin resistance is the pathological defect with which clinicians are most familiar, it should be clear from the discussion above that incretin pathways, particularly as related to glucagon dysregulation, also offer an opportunity for modulation of a fundamental pathophysiological defect in DM2.

PHARMACOLOGICAL CATEGORIES

Many therapeutic choices exist, which allows individualized intervention by selecting medications that work in a complementary fashion to address the various pathophysiological defects of DM2. Currently available antidiabetic medications are broadly classified into four mechanistic groups: insulin enhancers, insulin sensitizers, hepatic modulators, and intestinal

Table 1. Mechanisms of action of commonly used antidiabetic medications.¹⁴

Drugs	Increased insulin	Insulin resistance	Hepatic glucose metabolism	Intestinal glucose absorption/regulation
Alpha-glucosidase inhibitors				X
Metformin		X	X	
Sulfonylureas	X			
Glinides	X			
Thiazolidinediones		X	X	
GLP-1 R analogs	X		X	X
DPP-4 inhibitors	X		X	X

DPP-4=dipeptidyl peptidase-4; GLP-1 R=glucagon-like peptide-4 receptor.

regulators (Table 1). Combination therapies should employ agents with complementary mechanisms. There is no suggestion that using two agents with similar mechanisms (eg, sulfonylurea plus a glinide) will be beneficial.

Tolerability

Any choice of therapy should, of course, include considerations of tolerability. The most common factors that limit acceptability are weight gain and hypoglycemia. To ensure adherence and success in goal attainment, clinicians should routinely advance therapy in a method that minimizes risk of hypoglycemia, as well as providing clear advice about management of hypoglycemia, should it occur. Finally, consistent enquiry about medication-induced adverse effects that might limit compliance should be routine.

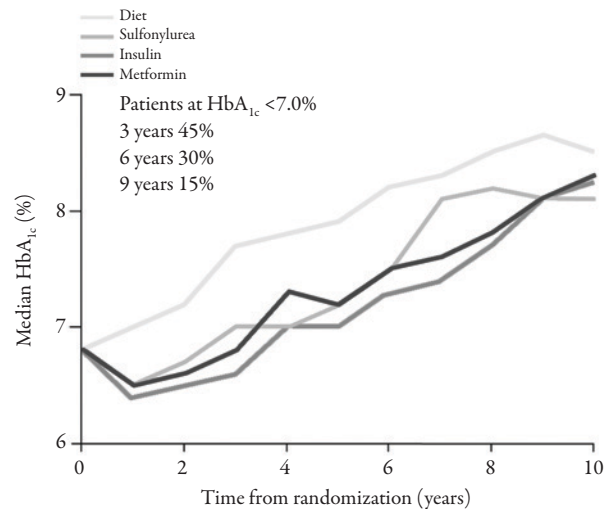
MANAGEMENT OF DIABETES

Pharmacotherapy for dysglycemia is only one limb of the treatment approach. All persons with DM2 will require lifestyle changes, periodic monitoring of cardiovascular risk factors (lipids, glucose, and blood pressure), attention to target-organ damage (renal-function, ophthalmological-function, and nerve-function monitoring), and a long-term relationship with healthcare professionals; therefore, we do not wish to oversimplify care of diabetes to just glucose control. That being said, skillful control of glucose is a cornerstone of comprehensive therapy. Unfortunately, monotherapy has distinct limitations for most patients.

Limitations of Current Monotherapies

Monotherapy is unlikely to maintain adequate control in DM2 over the long term. This does

Figure 3. Median glycated hemoglobin A_{1c} (HbA_{1c}) levels in cohorts of patients followed up to 10 years by assigned treatment in the UK Prospective Diabetes Study (UKPDS) 34.³⁰ Figure adapted with permission from DeFronzo et al., *Annals of Internal Medicine*; 1999. Table inset from Turner et al.³¹



not necessarily reflect inadequacy of the pharmacotherapy, but instead may reflect several other factors. First, DM2 is a progressive disease and no treatment has been convincingly shown to retard this loss of function. As can be seen in Figure 3, all four treatment choices in the UKPDS (diet, metformin, sulfonylurea, and insulin) were associated with progressive loss of HbA_{1c} control despite titration.³² After 3 years on treatment, only 45% of patients remained at target HbA_{1c}, and by 6 years, only 30% of those receiving monotherapy were at goal.³¹ Hence, clinicians must become aware of the essential inevitability of polypharmacy for glucose control in patients with DM2. Second, many persons become more sedentary as they age because of the combined effects of social phenomena, comorbidities such as osteoarthritis, and some diabetes-induced disabilities (eg, diabetic peripheral neuropathic pain). Third, common comorbidities, such as hypertension, may be treated with medications that worsen glucose control (eg, diuretics and beta-blockers). Finally, patient “fatigue” (less

enthusiasm over long periods of time) may foster poor adherence.

There are limited data to inform clinicians about durability of monotherapy. The A Diabetes Outcome Progression Trial⁹ (ADOPT) compared long-term monotherapy with rosiglitazone, metformin, or glyburide in recently diagnosed DM2 patients ($n=4360$) with reference to their ability to maintain a fasting glucose <180 mg/dL. At 5 years, the rosiglitazone group failure rate (15%) was lower than the sulfonylurea (34%) and metformin (21%) treatment groups. This is the only long-term treatment trial of its type, but lends credence, along with the UKPDS, to the concept that monotherapy is not sustainable in the majority of patients over the long term.

One of the inherent limitations of any monotherapy (except insulin) is that there is a ceiling, or maximum, potential effect on HbA_{1c}. Mean reductions in HbA_{1c} with any monotherapy are rarely greater than 2.0%

(0.5% to 1.5%), depending upon the agent and initial HbA_{1c} level (Table 2).³³ Hence, monotherapy for a patient who is newly diagnosed with DM2 and presents with an HbA_{1c} >9.0% is unlikely to attain an HbA_{1c} goal <7.0%; as the presenting HbA_{1c} increases further, HbA_{1c} goal attainment becomes progressively less likely.

Combination Therapy

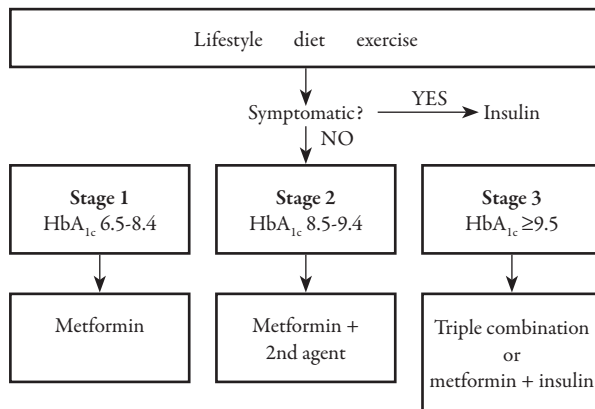
At the current time, an agent of any one of the classes of pharmacotherapy may be rationally combined with any other. Exceptions include combining glinides (nateglinide, repaglinide) with sulfonylureas, which both work by essentially identical methods, so their combination would not be rational (no greater effect would be anticipated). Similarly, use of two agents from the incretin class (GLP-1 receptor analogs and DPP-4 inhibitors) would not be complementary, and would not be

Table 2. Comparison of clinical profiles of common antidiabetic medications.

Drug	Mean HbA _{1c} reduction	Time to achieve maximum therapeutic benefit, weeks		Limitations	Common adverse events
		>80%	100%		
Metformin	1.0% to 2.0%	4	<9	Renal failure, CHF	GI side effects
Sulfonylurea (eg, glipizide GITS)	1.0% to 2.0%	Approximately 6	Approximately 8	Renal, hepatic	Hypoglycemia
Glinide (eg, nateglinide)	1.0% to 2.0%	Approximately 3	4	Three or four times a day dosing	Hypoglycemia
Alpha-glucosidase inhibitor	0.5% to 0.8%	-	-	None	GI side effects
Thiazolidinedione (eg, pioglitazone)	0.5% to 1.0%	6	14	Severe CHF, weight gain	Weight gain
DPP-4 inhibitors	0.5% to 0.8%	3	6	Renal disease	
Exenatide	1.0% to 2.0%	3	4	Renal disease	Nausea
Liraglutide	0.5% to 1.1%	2	4	-	

CHF=chronic heart failure; DPP-4=dipeptidyl peptidase-4; GI=gastrointestinal; GITS=gastrointestinal therapeutic system. Based on Kuritzky et al.³³

Figure 4. Suggested treatment algorithm for patients with type 2 diabetes mellitus, according to glycated hemoglobin A_{1c} (HbA_{1c}) level at presentation. Treatment should be adjusted every 4 weeks (6–8 weeks for thiazolidinediones [TZDs]) based upon degree of fasting blood glucose (FBG) attained.¹⁴ Adjust dosage q4w* based upon degree of FBG reduction attained.
*q6-8w for TZDs.



expected to have an enhanced effect. Although disputed by some, the preponderance of expert opinion suggests that the combination of any insulin secretagogue with insulin is not rational polypharmacy.¹⁴ With those exceptions, agents from any other classes may be successfully combined. Choice of therapeutic agent should be influenced by the level of HbA_{1c} elevation. For simplification purposes pertinent to the majority of patients seen in the primary care setting, we stratify diabetic control by HbA_{1c} level: stage 1 (HbA_{1c} 6.5% to 8.4%), stage 2 (HbA_{1c} 8.5% to 9.4%), and stage 3 (HbA_{1c} >9.5%) (Figure 4). This approach is based on the concepts explored by Nathan et al. in the ADA/EASD consensus statement.¹⁴

Lifestyle is at the foundation of all treatment regimens and may alone reduce HbA_{1c} as much as 2.9%. This potential efficacy notwithstanding, the majority of patients with lifestyle modification will still require

adjunctive monotherapy to control HbA_{1c} even at stage 1; unless a specific contraindication exists, metformin should be a therapeutic component at all steps of treatment. At stage 2, we believe it is unlikely that HbA_{1c} will be sufficiently controlled with monotherapy (metformin), so combination therapy should be considered routinely. With metformin as the foundation, a second agent (at lowest dose) may be initiated concomitantly, titrating the dose as often as every 4 weeks. As Table 2 shows, 80% or more of drug efficacy is measurable within that interval (with the exception of thiazolidinediones, which may require 6-8 weeks to attain a similar magnitude of efficacy).^{35,36} In a meta-analysis of randomized controlled trials of at least 3 months duration evaluating the addition of non-insulin antidiabetic drugs to maximal stable metformin therapy, all classes of agent were associated with similar significant reductions in HbA_{1c} versus placebo and were significantly more likely to achieve HbA_{1c} goal than placebo (Table 3).³⁷

We disagree with the most recent American Association of Clinical Endocrinologists (AACE) guideline that suggests combination therapy as the initial step for persons with HbA_{1c} 7.0% to 8.0%,³⁸ noting that a substantial component of this population (especially those at the lower end of this range) will be able to attain goal with one of the more potent agents; a similar approach (initial monotherapy with metformin, for instance) is supported in the most recent ADA/EASD position paper.¹⁴ Utilization of polypharmacy prior to maximizing glycemic control with well chosen monotherapy seems, to us, overtreatment at stage 1 and exposes the patient to unnecessary expense, potential adverse effect profile, complexity, and risk for hypoglycemia.

Stage 2 HbA_{1c} levels can occasionally be controlled with monotherapy, but most

Table 3. Results of a meta-analysis of randomized controlled trials comparing the efficacy of noninsulin antidiabetic drugs when added to metformin therapy in patients with type 2 diabetes not controlled by metformin alone. *Adapted with permission from Phung et al. JAMA 2010;303:1410-1418.³⁷ Copyright © 2010 American Medical Association. All rights reserved.*

Group vs. placebo	Percentage change in HbA _{1c}		HbA _{1c} goal achieved	
	No. of trials	WMD (95% CI)	No. of trials	RR (95% CI)
All drugs	20	-0.79 (-0.90, -0.68)*	10	2.56 (1.99, 3.28)†
Sulfonylureas	3	-0.79 (-1.15, -0.43)*	1	3.38 (2.02, 5.83)
Glinides	2	-0.71 (-1.24, -0.18)	1	3.20 (1.47, 7.58)
Thiazolidinediones	3	-1.00 (-1.62, -0.38)†	1	1.69 (1.24, 2.33)
AGIs	2	-0.65 (-1.11, -0.19)	0	NA
DPP-4 inhibitors	8	-0.79 (-0.94, -0.63)†	6	2.44 (1.78, 3.33)†
GLP-1 analogs	2	-0.99 (-1.19, -0.78)	1	3.96 (2.37, 6.79)

* $I^2 \geq 75\%$

† $I^2 = 50\%$ to 75%

AGIs= α -glucosidase inhibitors; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; HbA_{1c}=hemoglobin A_{1c}; NA=not applicable; RR=relative risk; WMD=weighted mean difference.

individuals at stage 2, and essentially all persons at stage 3, merit initiation of combination therapy at the outset, since no monotherapy (insulin excepted) has a significant likelihood of attaining its goal.^{39,40} Indeed, at stage 3 it is likely that triple therapy will be necessary, although occasionally, metformin combined with fully titrated insulin may achieve its goal.⁴¹ For symptomatic patients at any stage of diabetes or during acute metabolic stress (eg, infection or surgery), consideration of insulin to correct the typical large excursions of glucose is appropriate. Often, after a period of stabilization in these patients, a return to oral therapy may be more convenient. As mentioned above, patient preferences should also ultimately shape the therapeutic plan.

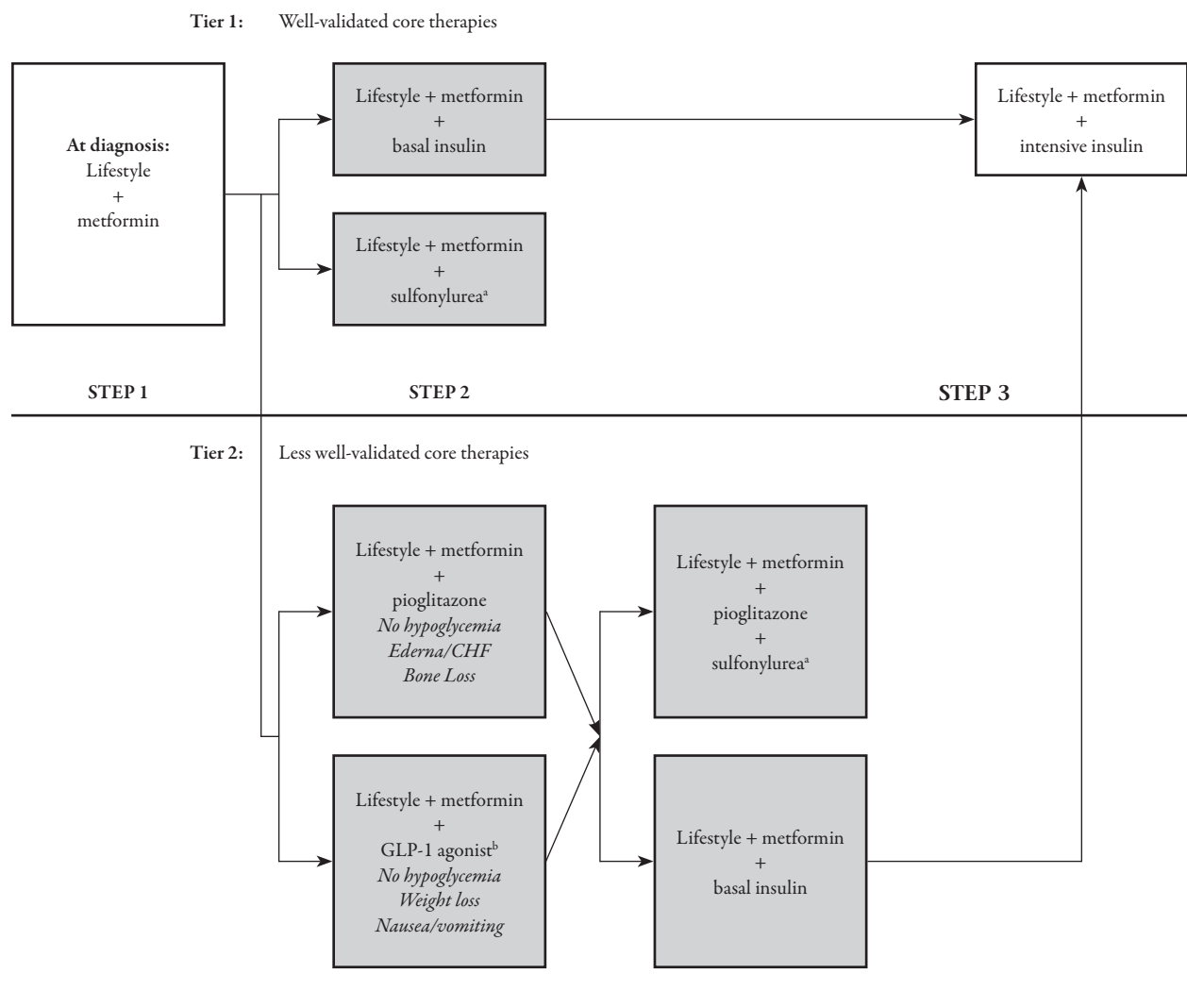
The ADA/EASD algorithm for the metabolic management of DM2 (Figure 5) supports initial treatment of DM2 with metformin, in the absence of contraindications.¹⁴ All other classes of pharmacotherapy are complementary to

metformin. Choice of the next agent will largely depend upon the above-mentioned factors, because there is a paucity of well controlled clinical trials that directly compare different diabetes treatment regimens.¹⁴ As mentioned earlier, a recent meta-analysis of antidiabetic agents combined with metformin demonstrated similar HbA_{1c} reductions with all classes of agents, but differences in their associations with weight gain and risk of hypoglycemia.³⁷ The combination with which clinicians have the most familiarity is probably metformin plus a sulfonylurea. The use of this combination is reflected in a 29-week study⁴² comparing monotherapy with glyburide or metformin versus glyburide plus metformin. The results showed the combination provided near maximal reduction in fasting glucose within 5 weeks, amounting to an 80-mg/dL greater reduction than either monotherapy.⁴² A longer-term study, the PRESERVE-Beta trial,⁴³ assessed the effects of glyburide or nateglinide plus metformin

in 428 treatment-naïve patients with DM2 over 2 years. In patients treated with glyburide/metformin, HbA_{1c} was reduced from 8.3% to 6.9% after 104 weeks, whereas nateglinide/metformin treatment reduced HbA_{1c} from 8.4% to 6.9% ($P < 0.0001$ vs. baseline for both groups), demonstrating that good glycemic control can be maintained for 2 years with either treatment regimen.⁴³

In a 6-month study of DM2 patients ($n=701$) whose baseline HbA_{1c} was 8.0% while on metformin (ie, the preferred initial oral monotherapy in DM2 as per the 2009 ADA/EASD algorithm¹⁴), subjects were randomized to placebo or sitagliptin 100 mg once daily.⁴⁴ By the end of the trial, mean HbA_{1c} was 7.26% in the DPP-4 inhibitor group versus 7.95% in the placebo group. Another study evaluating

Figure 5. American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) consensus algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle interventions at every visit and check glycated hemoglobin A_{1c} (HbA_{1c}) every 3 months until HbA_{1c} is $<7\%$ and then at least every 6 months. The interventions should be changed if HbA_{1c} is $\geq 7\%$.¹⁴ ^aSulfonylureas other than glibenclamide (glyburide) or chlorpropamide. ^bInsufficient clinical use to be confident regarding safety. CHF=congestive heart failure; GLP-1=glucagon-like peptide-1. Copyright 2009 American Diabetes Association. From *Diabetes Care* 2009;32:193-203. Reproduced with permission from the American Diabetes Association.



a combination of metformin plus a DPP-4 inhibitor assessed sitagliptin (100 mg once daily or 50 mg twice daily) and metformin (500 or 1000 mg twice daily) alone and in combination in 1091 DM2 patients with mean baseline HbA_{1c} 8.8%.⁴⁵ Adding sitagliptin 50 mg twice daily to metformin 500 mg twice daily provided another 0.6% HbA_{1c} reduction compared with metformin alone. Similarly, adding sitagliptin 50 mg twice daily to metformin 1000 mg twice daily provided an additional 0.8% HbA_{1c} reduction compared with metformin alone. Two 52-week studies assessed the efficacy and safety of two other DPP-4 inhibitors, vildagliptin⁴⁶ and saxagliptin,⁴⁷ in patients with DM2 inadequately controlled with metformin. Results of these trials demonstrated that addition of a DPP-4 inhibitor to a metformin regimen resulted in HbA_{1c} reductions comparable to those with glicazide plus metformin⁴⁶ or glipizide plus metformin,⁴⁷ with the added advantage of fewer hypoglycemic events, and either weight loss or no weight gain. Thus, the currently available DPP-4 inhibitors have more in common with each other than dissimilarities between them. Efficacy of HbA_{1c} reduction, safety, and tolerability appear comparable for the three currently available DPP-4 inhibitors. A Canadian trial conducted in 16 clinics assembled 200 DM2 patients with HbA_{1c} ≥8.5% despite being on maximally tolerated doses of metformin and a sulfonylurea (mean baseline HbA_{1c} was 9.7%).⁴¹ The ADA/EASD 2009 algorithm identifies metformin plus a sulfonylurea as a well validated step-two combination.¹⁴ It is not uncommon for clinicians to choose oral triple-therapy combinations, despite the lack of support that a third oral agent could bring patients from so high an HbA_{1c} (9.7%) down to goal (<7.0%). Indeed, at the end of the trial, only 14% of subjects who had a thiazolidinedione

(troglitazone) added to their existing sulfonylurea/metformin regimen achieved an HbA_{1c} <7.0%.⁴¹

This communication has focused primarily upon skillful combinations of non-insulin tools. Nonetheless, sometimes, insulin is a preferred choice, especially when combination therapy is likely to consist of three or more agents or when patients are symptomatic. Rather than trying to achieve control with three oral agents, earlier addition of basal insulin (ie, neutral protamine hagedorn [NPH], detemir, or glargine) or incretin mimetic (exenatide, liraglutide) is much more likely to attain an HbA_{1c} goal <7.0%. The Treat-to-Target Trial⁴⁸ compared insulin glargine and NPH administered once nightly in 756 DM2 subjects with an HbA_{1c} >7.5% who were receiving one or two oral agents. After 18 weeks, the mean HbA_{1c} in both groups had dropped to 7.0%. The frequency of hypoglycemia was significantly greater in the group that received NPH, but both agents were equally successful in reaching the HbA_{1c} goal (<7.0%).

The DURATION-2 trial,⁴⁹ a 26-week double-blind randomized study, assessed the efficacy and safety of exenatide once weekly ($n=170$) versus sitagliptin ($n=172$) or pioglitazone ($n=172$) in metformin-treated patients. At the end of the study, HbA_{1c} levels were reduced significantly more by exenatide (7.2%) than with sitagliptin (7.7%) or pioglitazone (7.4%); treatment differences were -0.6 for exenatide versus sitagliptin ($P<0.0001$) and -0.3 for exenatide versus pioglitazone ($P=0.0165$). Also, in a double-blind, placebo-controlled study in 733 patients treated with metformin and a sulfonylurea, exenatide-treated patients were more likely to achieve HbA_{1c} levels ≤7% than placebo-treated subjects (exenatide 10 μg, 34% and 5 μg, 27%, placebo, 9%; both doses of exenatide $P<0.0001$).⁵⁰ Liraglutide, the latest GLP-1 agonist to come to the US

market, was evaluated in a series of phase 3 trials (Liraglutide Effect and Action in Diabetes [LEAD]);⁵¹⁻⁵⁴ liraglutide therapy resulted in an average HbA_{1c} level reduction of 1.18% across all trials.

CONCLUSIONS

Skillful management of DM2 requires attention to multiple paths of dysfunction, with particular regard for lifestyle modulation, glucose control, cardiovascular risk factor reduction, and respect for the complexity such a diverse disorder places before our patients. Microvascular toxicity (retinopathy, nephropathy, and neuropathy) is reduced by good glucose control; hence, prompt glycemic goal attainment should be a compelling agenda. Combination therapy is an appropriate tool to maximize success in glucose control. Historically, sluggishness to advance treatment in a timely fashion despite inadequate goal attainment (commonly called “clinical inertia”), contributed to by both clinicians and patients alike, has been commonplace in DM2 patients. The plentiful and diverse tools available for good glucose control allow rational combinations to promptly gain control of dysglycemia. Lack of awareness of the timecourse of action of therapeutic agents may have limited the briskness with which clinicians titrate dosage. We hope that the instructive tables and diagrams depicting the typical timecourse of efficacy for available agents will be instrumental in addressing previous obstacles to prompt goal attainment. Consistent goal attainment can be enhanced by awareness of the pertinent physiological derangements attendant to DM2. Skillful combination of pharmacotherapies is intended to reduce risk for target organ damage and improve the quality of our patients’ lives.

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