Clinical Considerations for Use of Initial Combination Therapy in Type 2 Diabetes

Avivit Cahn[1] and William T. Cefalu[2]

Diabetes Care 2016;39(Suppl. 2):S137–S145 | DOI: 10.2337/dcS15-3007

Type 2 diabetes is a progressive disorder characterized by increasing hyperglycemia and the need to gradually intensify therapy in order to achieve and maintain glycemic control. Early initiation of combination therapy has been proposed as an approach to achieve glycemic goals earlier and delay the deterioration of glycemic control and with possible better preservation of β-cell function. We discuss in this article the pros and cons of this approach, focusing on individuals with HbA_{1c} at diagnosis of 7.5–9.0%, where difference of opinion still exists on management. Initial combination therapy is proposed to lead to better and faster achievement of glycemic targets versus monotherapy and to impede clinical inertia and may possibly slow the deterioration of β-cell function. However, treating patients with sequential therapy is proposed to allow one to fully assess the efficacy and risk-to-benefit ratio of each drug as it is added. Furthermore, there is no evidence to support that rapid addition and titration of medications according to the glycemic profile achieved are inferior to initial combination therapy if glycemic targets are attained in a timely manner. Initial combination therapy is argued to postpone clinical inertia to the next decision point but does not eliminate it. Additionally, it may have been the agents chosen and not the timing of their initiation that led to improved β-cell function in the studies of initial combination therapy, and there are no data currently comparing use of the same drugs initiated simultaneously or sequentially. Heightened awareness of providers, individualization of therapy and setting, and reaching glycemic targets remain the mainstays of care.

Type 2 diabetes affected 415 million people worldwide in 2015, with a predicted rise to nearly 642 million by 2040 (1). Tight glycemic control has been shown to reduce the risk of complications, yet this is not easily achieved or maintained (2). The disease is a progressive disorder characterized by ongoing deterioration of glycemic control and worsening pancreatic function with the need to gradually intensify therapy in order to maintain appropriate glycemic targets (3). In the UK Prospective Diabetes Study (UKPDS), after 9 years of monotherapy with diet, insulin, or sulfonylurea, only 9, 28, and 24% of subjects, respectively, maintained an HbA_{1c} level of $<$7% (53 mmol/mol), and in the subset of obese patients randomized to metformin only 13% attained an HbA_{1c} of $<$7% (53 mmol/mol) after 9 years (4).

Early initiation of combination therapy has been proposed as an approach to delay the deterioration of glycemic control with possible better preservation of β-cell function early on in the disease (5,6). Yet, there are advantages and disadvantages from each perspective with regard to cost, side effect profile, and complexity. Thus, the pros and cons of this approach will be explored in this article in addition to discussion of the mechanism of action, efficacy, and safety of different combination therapies.

[1]*Diabetes Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel*
[2]*Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA*

Corresponding author: Avivit Cahn, avivit@hadassah.org.il.

This publication is based on the presentations at the 5th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca.

PRO

Achieving Glycemic Targets

Hyperglycemia is the major risk factor for microvascular complications, and HbA_{1c} reduction is a well-established means of reducing development of complications (2). However, glycemic control is still not achieved in a large number of patients. According to the U.S. NHANES (National Health and Nutrition Examination Survey), during the years 2007–2010 only 52.5% of individuals with self-reported diabetes had achieved the goal of HbA_{1c} <7% (<53 mmol/mol) (7). Similarly, in a study conducted in nine European countries 37.4% had an HbA_{1c} ≥7% (≥53 mmol/mol) (range 25.9% in the Netherlands to 52.0% in Turkey) (8). In Israel, 64.3% of patients with diabetes attained their glycemic targets in year 2013: targets defined as HbA_{1c} <7% (<53 mmol/mol) for patients aged 18–75 years and HbA_{1c} <8.0% (<64 mmol/mol) for patients aged >75 years or with diabetes duration >10 years (9). Poor control was observed in 12.2% of patients with diabetes, with an HbA_{1c} >9.0% (>75 mmol/mol) (9).

Attainment of glycemic targets is of utmost importance, and the initial use of combination therapy leads to greater HbA_{1c} reduction, enabling more individuals to achieve their glycemic goals (see further discussion of the individual combinations). Initiating therapy with a single drug, as is suggested by many algorithms, may not suffice, as the pathogenesis of type 2 diabetes is complex and stems from multiple metabolic defects (10). Thus, addressing multiple metabolic pathways simultaneously leads to an increased hypoglycemic effect.

Avoiding Clinical Inertia

It has long been recognized that the extent of time spent in a state of hyperglycemia increases the risk of complications (11). Hyperglycemia can leave an early imprint in cells of the vasculature and of target organs, creating a negative "metabolic memory," favoring the future development of complications. However, in spite of the importance of achieving appropriate glycemic targets there still exists a gap between the goals set and those attained. Clinical inertia is defined as failure to initiate or intensify treatment in a timely manner in individuals whose health is likely to improve with this intensification (12). In a retrospective cohort study of >80,000 people with type 2 diabetes in the U.K., between years 2004 and 2006 with follow-up until April 2011, significant delays in treatment intensification were noted. Median time to treatment intensification in people with an HbA_{1c} ≥8.0 (≥64 mmol/mol) taking one oral antidiabetes drug was 1.6 years and for those taking two oral antidiabetes drugs was >6.9 years (13). Fu et al. (14) analyzed a large U.S. electronic medical record database between the years 1997–2008 and noted median time to treatment intensification of 14 months after persistent HbA_{1c} ≥7.0% (≥53 mmol/mol) for 6 months on metformin alone. Insufficient adherence to "goal setting" and lack of adequate patient-physician communication were proposed to be contributors to clinical inertia according to results of an online patient-physician survey. Though physicians well appreciated the risks associated with poor diabetes control, only 25% of patients reported they were worried about developing diabetes complications, whereas the rest were unconcerned or believed the risk was remote (12).

A proactive approach to treatment intensification was proposed >10 years ago attempting to minimize time spent in a state of hyperglycemia (15). Current American Diabetes Association/European Association for the Study of Diabetes/American Association of Clinical Endocrinologists treatment guidelines support initiation of metformin therapy at diagnosis parallel to lifestyle modification (16,17). Initial combination therapy is to be considered in individuals with an HbA_{1c} >7.5% (>58.5 mmol/mol) (16) or >9.0% (>75 mmol/mol) (17). Thus, the debate really centers on the need for combination therapy at levels of HbA_{1c} for which controversy exists (i.e., HbA_{1c} 7.5–9.0%) and whether at these levels initiating combination therapy based on pathophysiology is preferred over adding stepwise therapy based on glycemic goals.

β-Cell Preservation

Failure of the β-cell to compensate for increasing insulin resistance has been recognized as the hallmark of type 2 diabetes, and the rate of deterioration of glycemic control parallels that of deterioration of β-cell function and/or decline in mass (18–20).

Attempts at β-cell preservation are best undertaken as early in the disease stage as possible, as later attempts may yield lesser results. There is insufficient evidence as of yet to identify the optimal means for β-cell preservation. Striving for normoglycemia early, at disease onset, by intensive insulin therapy has been shown to induce a remission that has been demonstrated to last for as long as 2 years (21). A shorter time interval between diagnosis and intensive insulin therapy predicts a higher chance for remission (22).

Several drug classes have demonstrated a possible effect on β-cell preservation. The thiazolidinedione rosiglitazone has demonstrated glycemic durability superior to metformin and glyburide in A Diabetes Outcome Progression Trial (ADOPT) (3). Furthermore, improvement in β-cell function has been demonstrated to be the predominant underlying pathophysiological mechanism in inducing glycemic remission from impaired glucose tolerance to normal glucose tolerance with pioglitazone in the Actos Now for the prevention of diabetes (ACT NOW) study, further underpinning the benefit of this drug or class in the preservation of β-cell function (23).

Incretin-based therapies have demonstrated the ability to preserve β-cell function in animal models, though the clinical implication of these data in human studies is not fully understood (24,25). Administration of exenatide for 172 weeks resulted in superior β-cell function compared with glargine, an effect that was partially maintained even after drug cessation (26). Additionally, in a 52-week study of liraglutide versus placebo, after 4 weeks of intensive insulin therapy patients receiving liraglutide demonstrated improved β-cell function versus placebo, though this effect was not maintained after drug washout (27).

Dipeptidyl peptidase (DPP)-4 inhibitors have shown a positive effect on β-cell function in clinical studies as well. Treatment with saxagliptin versus placebo resulted in lesser reduction in HOMA of β-cell function—an effect that was most prominent in patients not taking any baseline medication or taking metformin alone (28). An analysis of all phase III studies of linagliptin has demonstrated a superior effect of linagliptin on HOMA of β-cell function

versus comparators (29). Administration of vildagliptin versus placebo resulted in improved β-cell function as well, yet the effect was not sustained after a 4-week washout period (30).

The most successful methods for β-cell preservation early in disease onset are yet unclear. It appears that alleviation of hyperglycemia, regardless of the means, is the most important contributor to β-cell preservation. Possibly, striving for normoglycemia early at disease onset, or even at the prediabetes stage, and maintaining normoglycemia safely by combination therapy as required may change the natural history of disease (6). Whether the use of a particular drug or class carries benefit beyond that of others is still unresolved. A dedicated trial assessing the benefit of metformin, glucagon-like peptide 1 receptor agonists, or bariatric surgery on β-cell function in early diabetes is underway and will hopefully shed some light on the benefit these approaches may have (31).

CON

The Need for Individualization of Care

Diabetes, defined by hyperglycemia, is not a single disorder, and the heterogeneity of disease is becoming more evident with our better understanding of the multiple pathophysiological defects underlying the disease (32,33). Most individuals with diabetes are classified as having type 2 diabetes, which reflects a combination of insulin resistance and impaired insulin secretion; however, the relative contribution of each of these two elements varies in different patients.

Diabetes is not a disease of "one size fits all," and individualization of care with careful selection of medications is becoming realized as one of the mainstays of care. Whereas it is known and generally accepted that metformin is the initial therapy after diagnosis, a number of factors must be considered prior to consideration of the added therapy regarding whether it is given sequentially or added initially with metformin. What we can agree on, as outlined above, is that there appear to be given levels of HbA_{1c} where there is general agreement on when to consider initial combination therapy. As stated, treatment guidelines support initiation of metformin therapy at diagnosis parallel to lifestyle modification in individuals with an HbA_{1c} >7.5% (>58.5 mmol/mol) (16) or >9.0% (>75 mmol/mol) (17). What is not so clear is whether initial combination therapy carries greater benefit than sequential addition of therapy in subjects with much lower HbA_{1c} levels and who otherwise may be asymptomatic. Given this dilemma, what factors need to be discussed in order to choose initial combination versus sequential therapy? It may be also best to agree on what we do or do not know and to determine whether timing of therapy may play a difference. What is generally accepted as known is follows:

1) Tight glycemic control reduces complications
2) Type 2 diabetes is a progressive disease
3) There remain unmet clinical needs: weight gain, hypoglycemia, etc.
4) Adherence and compliance remain issues
5) Most therapies fail to adequately control postprandial hyperglycemia
6) Most therapies fail to maintain long-term glycemic control
7) Clinical inertia is a factor in failure to intensify therapy

To have a better understanding of whether early initiation of combination therapy has advantages over sequential titration of individual agents, we propose a discussion of the two strategies with regard to key clinical questions as outlined in Table 1.

Would Clinical Inertia Be Reduced?

We recognize that diabetes is a progressive disease and requires intensification of therapy over time in order to maintain adequate glycemic control (4). Nevertheless, the rate of progression of diabetes varies between individuals and cannot be accurately predicted at diagnosis. The Diabetes Research on Patient Stratification (DIRECT) study identified multiple clinical, laboratory, and genetic markers associated with faster progression of diabetes after diagnosis, yet the study could not account for additional behavioral patterns affecting compliance with dietary and exercise regimens, which are predictors for diabetes progression as well (34). Yet, we do know that "clinical inertia," defined as "failure to initiate or intensify therapy despite an inadequate treatment response," exists and appears to have increased over more recent years (35). Thus, would the earlier timing of therapy for initial combination result in reduction of inertia? One would argue it would not if sequential therapy is added as recommended. For example, Abdul-Ghani et al. (36) evaluated initial combination therapy with metformin, pioglitazone, and exenatide compared with add-on therapy to metformin with a sulfonylurea and then insulin. In this study, as opposed to the triple initial therapy, the conventional approach began with metformin at 1,000 mg/day, and at 1 month, if fasting plasma glucose (FPG) concentration was >6.1 mmol/L (110 mg/dL), metformin was increased to 2,000 mg and glipizide started at 5 mg/day. If, at 2 months, FPG was >6.1 mmol/L (110 mg/dL) or HbA_{1c} was >6.5%, glipizide was increased to 10 mg and then to 20 mg. If, at 3 months, FPG was >6.1 mmol/L (110 mg/dL) or HbA_{1c} >6.5%, glargine insulin was started at 10 units before breakfast and escalated weekly by 1–5 units (based on FPG and HbA_{1c} levels) to 60 units/day to maintain FPG at <6.1 mmol/L (110 mg/dL). In this case, sequential therapy was used aggressively

Table 1—Factors to consider in choosing early initial combination therapy or sequential titration of individual agents

• Would clinical inertia be reduced?
• Would there be a delay in deterioration of glycemic control? Better durability? Better β-cell function over time? Does the approach address pathophysiology better?
• Does it allow for assessing individual response?
• Are the costs appropriate? Would this approach result in cost savings and reduction in complications over time?
• Is the risk-to-benefit ratio acceptable?
• Would it improve unmet clinical needs, such as weight gain, hypoglycemia, etc.?
• Would adherence/compliance remain issues?

and appropriately. When looking at the time-related change in HbA_{1c}, it appears the sequential therapy worked just as well as the initial triple therapy in reducing the HbA_{1c} levels during the first 6 months (Fig. 1). Clearly, over time there was better HbA_{1c} control with the initial triple therapy, but that is argued to be a function of the agents used and the different mechanism of action—not the timing of addition of the agents. So, in this case, sequential titration of therapy when done aggressively can achieve the target goals in a timely manner. Starting initial combination therapy may not necessarily resolve the issue of clinical inertia but, rather, just postpone it to the next stage of required treatment intensification. For reduction of clinical inertia, it is not the suggested regimen; it is the heightened awareness of the providers.

Would There Be a Delay in Deterioration of Glycemic Control? Better Durability? Better β-Cell Function Over Time? Does the Approach Address Pathophysiology Better?

As outlined above in the triple therapy data (36) and as well described in studies such as ADOPT (3) and others, durability may be a function of the agent used and mechanism of action and not simply due to timing of the agents as initial therapy as opposed to sequential titration. We know of no other study that has tested durability of the same agents as a function of use as either initial combination therapy or sequential titration. All of the studies to date have reported on differences based on specific agent used—not the timing.

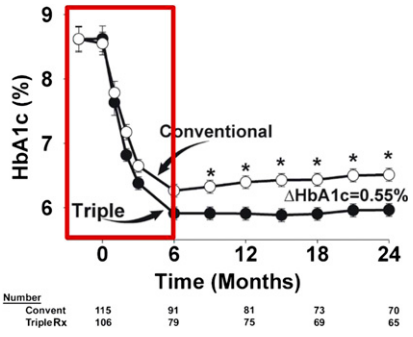

Figure 1—Time-related change in HbA_{1c}. HbA_{1c} in participants receiving conventional (Conventional) and initial combination (Triple) therapy during the 24-month follow-up period (*$P < 0.01$). Reprinted with permission from Abdul-Ghani et al. (36).

Does it Allow for Assessing Individual Response?

Our understanding of the genetic basis of type 2 diabetes is expanding with nearly 80 susceptibility loci identified, and attempts have been made to correlate phenotype of glucose disposition with particular genotypes (33,37). Accordingly, the individual response to medications differs from one patient to another. Clinical variables such as disease duration, age, baseline HbA_{1c}, and BMI have been found to predict clinical responses to metformin, sulfonylureas, basal insulin, or incretin-based therapies, whereby the variables affected clinical responses differently in each medication (38–40). It is also known that any single agent may have a defined effect on HbA_{1c} levels so that in individuals with poorly controlled HbA_{1c}, i.e., $HbA_{1c} > 9\%$, there may be general consensus on the need for initial combination therapy, as a single therapy is unlikely to achieve glycemic target. In addition, the field of pharmacogenomics in diabetes is expanding with identification of "susceptibility loci" to individual drug classes (37,41).

The clinical response of one individual to a particular medication can differ from the response of another individual. Therefore, it is of paramount importance to assess the benefit of antidiabetes medications on a one-to-one basis by sequentially adding each medication, or not, after failure of the mono/dual therapy. In this way, the full efficacy of the added-on medication can be fully realized.

Are the Costs Appropriate? Would This Approach Result in Cost Savings and Reduction in Complications Over Time?

There are several studies estimating the cost-effectiveness of the new, more costly antidiabetes agents, yet many of these are subject to multiple confounders. The comparator of the new drug greatly affects the outcome of the analysis, and it is difficult to quantify the cost-effectiveness of softer outcomes such as fewer hypoglycemic events or improved quality of life (42). Moreover, many of these studies are industry funded, adding further bias to the analyses.

Initial combination therapy, as discussed below, may include in addition to metformin a new and costly antidiabetes agent for which cost-effectiveness must be individually assessed. The cost of these novel agents remains a significant barrier to their use in many regions of the world, and evidence for long-term efficacy and safety is often required by the local medical insurance agents for individual reimbursement in countries with better economic situations. Initial combination therapy may minimize the time spent in hyperglycemia secondary to clinical inertia or progressive β-cell failure, yet it stands to be proven in validated economic models that the excess time spent in hyperglycemia is more costly than the initial combination of two drugs, one of which is usually relatively expensive. But if sequential therapy was used appropriately and agents were added in a timely manner to minimize the time spent in a hyperglycemia state as guidelines suggest, this argument for initial combination therapy would also be lessened.

The particular drugs and combinations assessed need to be studied comparatively evaluating their short-term effectiveness in HbA_{1c} reduction as well as their long-term benefits on β-cell function, durability, and reduction of complications in order to provide better assessment of their cost-effectiveness (43).

Is the Risk-to-Benefit Ratio Acceptable?

Prescribing medications that may not be mandatory may result in exposing many individuals to unduly harm, as the long-term safety of antidiabetes medications has yet to be determined.

Metformin has shown reasonable safety in clinical trials and epidemiological studies and is therefore a reasonable first-line therapy (16,17). The pancreative and overall safety of incretin-based therapies, a commonly proposed second-line therapy, has yet to be established (44–47). Thiazolidinedione use has become restricted because of safety issues as well (48). Sodium–glucose cotransporter (SGLT) 2 inhibitors, a novel drug class, have only recently become registered in many regions. The first long-term cardiovascular safety trial of this class of drugs was recently reported (49). Reports of ketoacidosis in patients with type 2 diabetes using the drug warrant further study and better delineation of the population who may be at risk (50). However,

knowledge of this side effect and pathogenesis will allow the provider to manage this issue. Use of sulfonylureas has been declining due to hypoglycemia and unresolved cardiovascular safety issues (51).

Overall, patients with diabetes are a vulnerable population, at high cardiovascular risk and suffering from multiple comorbidities, and the risk-to-benefit ratio of each drug must be carefully weighed. Initial combination therapy entails prescription of multiple drug classes with their accordant known and unknown risks.

There is no question that every agent added will result in additional side effects for some patients. It is also well-known that side effects are greater with two-drug combinations as opposed to monotherapy (52). Thus, sequential titration of therapy will allow the provider to judge the side effect profile of each agent and address it appropriately, whereas if side effects occur in initial combination therapy, one may not be sure which of the compounds in the combination caused the side effects. Sequential therapy may minimize complexity of the regimen and potentially can improve compliance. Initial combination therapy may mask an excellent response to one element of the combination, or a poor response to another, possibly condemning the patients to years of use of a drug that carries minimal benefit to them.

Unselective use of initial combination therapy ignores the spectrum of disease observed with diabetes and may result in overtreatment of individuals who may have maintained adequate glycemic control with monotherapy or even just by lifestyle modification for a prolonged period of time.

Would it Improve Unmet Clinical Needs, Such as Weight Gain, Hypoglycemia, Etc.?

There is no evidence to date that a change of timing of the same agents as early combination as opposed to sequential titration of therapy will have any favorable benefits on weight. Clearly, one could argue that addition of sulfonylurea earlier in the course may increase weight gain earlier, but if aggressive titration is achieved over a few months, this may be minimal. With use of the same agents, hypoglycemia would be an issue regardless of timing.

Would Adherence/Compliance Remain Issues?

No evidence exists that would suggest that earlier combination of therapy as opposed to sequential titration would result in greater adherence or compliance of patients.

SUGGESTED INITIAL COMBINATION THERAPIES

Although nearly all antidiabetes drug classes may be used in combination, there are particular combinations that have been extensively studied, particularly for those available as single pill combinations, thereby enhancing patient compliance. Combination pills comprised 6.7% of the prescriptions fills in the U.S. retail pharmacies in 2012 (53). The most commonly used combinations were those of DPP-4 inhibitors and metformin; however, combination therapy of metformin-sulfonylureas and metformin-pioglitazone were commonly used as well (53).

Metformin is now the most widely accepted first-line therapy for type 2 diabetes (16,17); therefore, most initial combination therapies proposed include metformin. A recent meta-analysis assessed the benefit of early combination therapies that included metformin versus metformin alone and demonstrated superior results of the combination therapy with better HbA_{1c} reduction (weighted mean difference −0.43% [95% CI −0.56, −0.30]) and increased odds of attaining the goal of HbA_{1c} <7% (<53 mmol/mol) (relative risk 1.40 [95% CI 1.33–1.48]) (54). With exclusion of initial combinations that included sulfonylureas or glinides (13 comparisons analyzed) there was no increased risk of hypoglycemia in the combination group compared with the metformin group (relative risk 1.20 [0.91–1.56]) (54).

Approximately 5–10% of individuals cannot tolerate metformin therapy (55), and therefore alternative combinations excluding metformin are studied as well, though their use as first-line therapy is quite limited.

Table 2 shows selected studies assessing initial combination therapies versus the individual monotherapies. The combination of metformin and DPP-4 inhibitors is widely used and is available as a combination pill, thus enhancing patient compliance (56–59). A meta-analysis including five studies comparing initial combination therapy versus metformin monotherapy demonstrated superior HbA_{1c} reduction (mean difference −0.49% [−0.57, −0.40]) and better FPG reduction (mean difference −0.80 mmol/L [−0.87, −0.74]) but lower weight loss (0.44 kg gained [0.22, 0.67]). Initial combination therapy did not pose an increased risk of hypoglycemia or prolong the risk of gastrointestinal side effects (60).

Combination of metformin with thiazolidinediones has been studied in multiple trials. Though the results of these trials are positive, demonstrating better HbA_{1c} reduction with these fixed-dose combinations (61,62), safety issues surrounding the drug class (48) have significantly restricted its use. On the other hand, pioglitazone has recently become generically available, thus reducing its cost and possibly increasing its use in the near future.

The combination of pioglitazone and DPP-4 inhibitors has been studied as well (63–66). Better HbA_{1c} reduction was perceived with the combination, yet weight gain was greater with the combination versus with pioglitazone alone in some of the trials. The utility of this combination as first-line therapy is limited and restricted to those who cannot tolerate metformin or have a contraindication to its use.

SGLT2 inhibitors are a novel class of antidiabetes medications exerting their effect by inhibiting renal glucose reabsorption and producing glucosuria. Initial combination therapy of dapagliflozin and metformin has been shown to be more effective in HbA_{1c} reduction versus dapagliflozin monotherapy or metformin monotherapy (67).

The SGLT2 inhibitors are becoming available as single pill combination therapies with metformin, competing with the metformin–DPP-4 inhibitor combination pills as possible first-line initial combination therapy. Both options have minimal side effects, beyond those of metformin alone, and do not cause hypoglycemia. Whereas significant weight loss is observed with the combination of SGLT2 inhibitors and metformin (67), weight neutrality or minimal weight gain is observed with the combination of DPP-4 inhibitors and metformin (60). The glucosuric effect of SGLT2 inhibitors is accompanied by an increased rate of endogenous glucose

Table 2—Selected trials comparing initial combination therapy with initial monotherapy

Combination	Study design/treatment arms	HbA_{1c} change from baseline (%)	Weight change (kg)	Ref.
Metformin + DPP-4 inhibitors				
Metformin + sitagliptin**	RCT, 104 weeks			56
	Sitagliptin 50 mg + metformin 1,000 mg b.i.d.	−1.7 (−1.8, −1.5)	−1.2 (−2.0, −0.3)	
	Sitagliptin 50 mg + metformin 500 mg b.i.d.	−1.4 (−1.6, −1.2)	0 (−0.8, 0.9)	
	Metformin 1,000 mg b.i.d.	−1.3 (−1.5, −1.2)	−2.4 (−3.3, −1.5)	
	Metformin 500 mg b.i.d.	−1.1 (−1.3, −0.9)	−0.8 (−1.9, 0.3)	
	Sitagliptin 100 mg QD	−1.2 (−1.4, −0.9)	0.5 (−0.7, 1.7)	
Metformin + saxagliptin	RCT, 76 weeks (uptitration of metformin)			57
	Saxagliptin 5 mg + metformin 2,000 mg	−2.31 ± 0.07*	−1.2	
	Saxagliptin 10 mg + metformin 2,000 mg	−2.33 ± 0.07*	−0.7	
	Saxagliptin 10 mg	−1.55 ± 0.08*	−0.3	
	Metformin 2,000 mg	−1.79 ± 0.07*	−1.0	
Metformin + vildagliptin	RCT, 24 weeks			58
	Metformin 1,000 mg + vildagliptin 50 mg b.i.d.	−1.8 ± 0.06*	−1.19 ± 0.22	
	Metformin 500 mg + vildaglitpin 50 mg b.i.d.	−1.6 ± 0.06*	−1.17 ± 0.23	
	Vildagliptin 50 mg b.i.d.	−1.1 ± 0.06*	−1.62 ± 0.22	
	Metformin 1,000 mg b.i.d.	−1.4 ± 0.06*	−0.59 ± 0.22*	
Metformin + linagliptin	RCT, 24 weeks		†	59
	Linagliptin 2.5 mg + metformin 500 mg b.i.d.	−1.2 ± 0.1*		
	Linagliptin 2.5 mg + metformin 1,000 mg b.i.d.	−1.6 ± 0.1*		
	Linagliptin 5 mg QD	−0.5 ± 0.1*		
	Metformin 500 mg b.i.d.	−0.6 ± 0.1*		
	Metformin 1,000 mg b.i.d.	−1.1 ± 0.1*		
	Placebo	0.1 ± 0.1*		
Pioglitazone + DPP-4 inhibitors				
Pioglitazone + alogliptin	RCT, 26 weeks			63
	Pioglitazone 30 mg + alogliptin 25 mg	−1.71 ± 0.081*	3.14 ± 0.295*	
	Pioglitazone 30 mg + alogliptin 12.5 mg	−1.56 ± 0.081*	2.51 ± 0.296	
	Pioglitazone 30 mg	−1.15 ± 0.083*	2.19 ± 0.302*	
	Alogliptin 25 mg	−0.96 ± 0.081*	−0.29 ± 0.291*	
Pioglitazone + linagliptin	RCT, 24 weeks			64
	Pioglitazone 30 mg + linagliptin 5 mg	−1.06 ± 0.07*	2.3*	
	Pioglitazone 30 mg	−0.75 ± 0.11*	1.2*	
Pioglitazone + sitagliptin	RCT with extension, 54 weeks			65
	Pioglitazone 45 mg + sitagliptin 100 mg	−2.4 (−2.5, −2.2)*	4.8 (3.8, 5.8)	
	Pioglitazone 45 mg	−1.9 (−2.0, −1.7)*	4.1 (3.1, 5.2)	
Pioglitazone + vildagliptin	RCT, 24 weeks			66
	Pioglitazone 30 mg + vildagliptin 100 mg QD	−1.9 ± 0.1*	2.1 ± 0.3*	
	Pioglitazone 15 mg + vildagliptin 50 mg QD	−1.7 ± 0.1*	1.4 ± 0.3*	
	Pioglitazone 30 mg QD	−1.4 ± 0.1*	1.5 ± 0.3	
	Vildagliptin 100 mg QD	−1.1 ± 0.1*	0.2 ± 0.3*	
Metformin + SGLT2 inhibitor				
Metformin + dapagliflozin	RCT, 24 weeks			67
	Dapagliflozin 10 mg + metformin XR	−1.98 (−2.13, −1.83)*	−3.33 (−3.80, −2.86)*	
	Dapagliflozin 10 mg	−1.45 (−1.59, −1.31)*	−2.73 (−3.19, −2.27)*	
	Metformin XR	−1.44 (−1.59, −1.29)*	−1.36 (−1.83, −0.89)*	
DPP-4 inhibitor + SGLT2 inhibitor				
Linagliptin + empagliflozin	RCT, 24 weeks (primary end point)			68
	Empagliflozin 25 mg + linagliptin 5 mg	−1.08 ± 0.06*	−2.0*	
	Empagliflozin 10 mg + linagliptin 5 mg	−1.24 ± 0.06*	−2.7*	
	Empagliflozin 25 mg	−0.95 ± 0.06	−2.1	
	Empagliflozin 10 mg	−0.83 ± 0.06*	−2.3	
	Linagliptin 5 mg	−0.67 ± 0.06*	−0.8*	

Data are means ± SE or means (95% CI). QD, once a day; RCT, randomized controlled trial; XR, extended release. *$P < 0.05$ for comparison of combination vs. monotherapy. **Statistical testing was not performed for between-group differences. †No clinically significant changes in body weight were noted.

production, a mechanism that offsets the drugs' glucose-lowering effect by ~50%. DPP-4 inhibitors inhibit glucagon secretion, thus reducing endogenous glucose production, and the combination of the two drug classes appears to be a promising therapeutic modality (68).

Initial combination therapy of empagliflozin/linagliptin has demonstrated superior HbA_{1c} reduction versus linagliptin alone, yet the efficacy of

high-dose empagliflozin was similar to its combination with linagliptin, the cause for that being unclear. It has been hypothesized that the increased glucosuria observed with high-dose SGLT2 inhibitors, particularly when prescribed to individuals with high baseline HbA_{1c}, may cause a reciprocal elevation in endogenous glucose production that is beyond the capacity of DPP-4 inhibitors to overcome (68). Contrary to the partially negative results of the initial combination therapy, use of a combination of empagliflozin and linagliptin as a second-line therapy, after metformin, yielded positive results, demonstrating superiority of the combination over empagliflozin alone (69).

CONCLUSIONS

The dilemma of initial combination therapy or sequential addition of medications as treatment fails is yet unresolved. As outlined above, a patient with poorly controlled diabetes is one in whom most clinicians would likely start combination therapy just based on the fact that any single agent initially may not be effective. The VERIFY trial (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes mellitus) (70), which is expected to continue for 5 years, will compare initial combination therapy of metformin and vildagliptin to sequential addition of vildagliptin after treatment failure with metformin. This trial may shed light on unanswered questions such as the effect of DPP-4 inhibitors on preservation of β-cell function and, possibly, the "price" of clinical inertia on long-term glycemic control.

The answer, for now, lies in individualization of care while bearing in mind the suggestions of recent guidelines. Clinical inertia reflects something we all transgress in as physicians often led by our patients' unwillingness to "add another drug" or by our own thoughts or concerns of the additional pill burden we are imposing upon our patients. The novel agents that have a favorable side effect profile and do not carry a risk of hypoglycemia may lead physicians to be more willing to intensify therapy at lower HbA_{1c} levels and to strive for lower targets in patients who may benefit from them.

There is not a single answer for the dilemma presented in this article, yet the considerations mentioned must be weighed in each individual case. Moreover, the initial path taken is not necessarily a "no return." With a choice to initiate sequential therapy, close follow-up of the patient must be undertaken aiming to intensify treatment within weeks and not months if glucose targets are not met. Alternatively, if the choice to initiate combination therapy yields any untoward effects, stepping back down to monotherapy is an alternative as well.

Appropriate glycemic targets must be set for the individual patient, and only then can one decide upon the path to follow, as the Chesire cat told Alice (71):

> "Would you tell me, please, which way I ought to go from here?"
>
> "That depends a good deal on where you want to get to," said the Cat.
>
> "I don't much care where —" said Alice.
>
> "Then it doesn't matter which way you go," said the Cat.

Funding. W.T.C. is supported in part by National Institutes of Health grants 1U54-GM-104940 and P50-AT-002776.

Duality of Interest. A.C. reports receipt of consulting fees and payment for lectures from the following: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi. W.T.C. has served as the principal investigator of research studies awarded to his institution by AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Lexicon Pharmaceuticals, MannKind Corporation, and Sanofi and has served as a consultant for Sanofi and Intarcia Therapeutics. No other potential conflicts of interest relevant to this article were reported.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. [Internet], 2015. Available from http://www.idf.org/diabetesatlas. Accessed 29 February 2016
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
3. Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
4. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005–2012
5. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36(Suppl. 2):S127–S138
6. Phillips LS, Ratner RE, Buse JB, Kahn SE. We can change the natural history of type 2 diabetes. Diabetes Care 2014;37:2668–2676
7. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. Diabetes Care 2013;36:2271–2279
8. de Pablos-Velasco P, Parhofer KG, Bradley C, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. Clin Endocrinol (Oxf) 2014;80:47–56
9. Ministry of Health. National program for quality indicators in community healthcare in Israel years 2011-2013 [Internet], 2014. Available from http://www.israelhpr.org.il. Accessed 29 February 2016 [in Hebrew]
10. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773–795
11. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
12. Strain WD, Cos X, Hirst M, et al. Time to do more: addressing clinical inertia in the management of type 2 diabetes mellitus. Diabetes Res Clin Pract 2014;105:302–312
13. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–3417
14. Fu AZ, Qiu Y, Davies MJ, Radican L, Engel SS. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. Diabetes Obes Metab 2011;13:765–769
15. Del Prato S, Felton AM, Munro N, Nesto R, Zimmet P, Zinman B; Global Partnership for Effective Diabetes Management. Improving glucose management: ten steps to get more patients with type 2 diabetes to glycaemic goal. Int J Clin Pract 2005;59:1345–1355
16. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology–clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2015 [article online], 2015. Available from https://www.aace.com/files/dm-guidelines-ccp.pdf. Accessed 29 February 2016
17. American Diabetes Association. Approaches to glycemic treatment. Sec. 7. *Standards of Medical Care in Diabetes—2015*. Diabetes Care 2015;38(Suppl.):S41–S48
18. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA; San Antonio Metabolism Study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio Metabolism (SAM) study. Diabetologia 2004;47:31–39
19. Gastaldelli A. Role of beta-cell dysfunction, ectopic fat accumulation and insulin resistance in the pathogenesis of type 2 diabetes mellitus. Diabetes Res Clin Pract 2011;93(Suppl. 1):S60–S65

20. Meier JJ, Bonadonna RC. Role of reduced β-cell mass versus impaired β-cell function in the pathogenesis of type 2 diabetes. Diabetes Care 2013;36(Suppl. 2):S113–S119
21. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2013;1:28–34
22. Xu W, Li YB, Deng WP, Hao YT, Weng JP. Remission of hyperglycemia following intensive insulin therapy in newly diagnosed type 2 diabetic patients: a long-term follow-up study. Chin Med J (Engl) 2009;122:2554–2559
23. Defronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Prevention of diabetes with pioglitazone in ACT NOW: physiologic correlates. Diabetes 2013;62:3920–3926
24. Ahrén B. DPP-4 inhibition and islet function. J Diabetes Investig 2012;3:3–10
25. Drucker DJ. Incretin action in the pancreas: potential promise, possible perils, and pathological pitfalls. Diabetes 2013;62:3316–3323
26. Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care 2011;34:2041–2047
27. Retnakaran R, Kramer CK, Choi H, Swaminathan B, Zinman B. Liraglutide and the preservation of pancreatic β-cell function in early type 2 diabetes: the LIBRA trial. Diabetes Care 2014;37:3270–3278
28. Leibowitz G, Cahn A, Bhatt DL, et al. Impact of treatment with saxagliptin on glycaemic stability and β-cell function in the SAVOR-TIMI 53 study. Diabetes Obes Metab 2015;17:487–494
29. Heise T, Larbig M, Patel S, et al. The dipeptidyl peptidase-4 inhibitor linagliptin lowers postprandial glucose and improves measures of β-cell function in type 2 diabetes. Diabetes Obes Metab 2014;16:1036–1039
30. Foley JE, Bunck MC, Möller-Goede DL, et al. Beta cell function following 1 year vildagliptin or placebo treatment and after 12 week washout in drug-naive patients with type 2 diabetes and mild hyperglycaemia: a randomised controlled trial. Diabetologia 2011;54:1985–1991
31. RISE Consortium. Restoring Insulin Secretion (RISE): design of studies of β-cell preservation in prediabetes and early type 2 diabetes across the life span. Diabetes Care 2014;37:780–788
32. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet 2014;383:1084–1094
33. Kleinberger JW, Pollin TI. Personalized medicine in diabetes mellitus: current opportunities and future prospects. Ann N Y Acad Sci 2015;1346:45–56
34. Zhou K, Donnelly LA, Morris AD, et al. Clinical and genetic determinants of progression of type 2 diabetes: a DIRECT study. Diabetes Care 2014;37:718–724
35. Lin J, Zhou S, Wei W, Pan C, Lingohr-Smith M, Levin P. Does clinical inertia vary by personalized A1c goal? A study of predictors and prevalence of clinical inertia in a U.S. managed-care setting. Endocr Pract 2016;22:151–161
36. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab 2015;17:268–275
37. Dimas AS, Lagou V, Barker A, et al.; MAGIC Investigators. Impact of type 2 diabetes susceptibility variants on quantitative glycemic traits reveals mechanistic heterogeneity. Diabetes 2014;63:2158–2171
38. Martono DP, Lub R, Lambers Heerspink HJ, Hak E, Wilffert B, Denig P. Predictors of response in initial users of metformin and sulphonylurea derivatives: a systematic review. Diabet Med 2015;32:853–864
39. Monami M, Ragghianti B, Zannoni S, Vitale V, Nreu B, Mannucci E. Identification of predictors of response to basal insulin and DPP4 inhibitors in patients with type 2 diabetes failing to other therapies. Acta Diabetol 2016;53:35–40
40. Khan M, Ouyang J, Perkins K, Nair S, Joseph F. Determining predictors of early response to exenatide in patients with type 2 diabetes mellitus. J Diabetes Res 2015;2015:162718
41. Kavvoura FK, Pappa M, Evangelou E, Ntzani EE. The genetic architecture of type 2 diabetes pharmacotherapy: the emerging genomic evidence. Curr Pharm Des 2014;20:3610–3619
42. Khazrai YM, Buzzetti R, Del Prato S, Cahn A, Raz I, Pozzilli P. The addition of E (Empowerment and Economics) to the ABCD algorithm in diabetes care. J Diabetes Complications 2015;29:599–606
43. Nathan DM, Buse JB, Kahn SE, et al.; GRADE Study Research Group. Rationale and design of the Glycemia Reduction Approaches in Diabetes: a Comparative Effectiveness Study (GRADE). Diabetes Care 2013;36:2254–2261
44. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs–FDA and EMA assessment. N Engl J Med 2014;370:794–797
45. Jensen TM, Saha K, Steinberg WM. Is there a link between liraglutide and pancreatitis? A post hoc review of pooled and patient-level data from completed liraglutide type 2 diabetes clinical trials. Diabetes Care 2015;38:1058–1066
46. Thomsen RW, Pedersen L, Møller N, Kahlert J, Beck-Nielsen H, Sørensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. Diabetes Care 2015;38:1089–1098
47. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. BMJ 2014;348:g2366
48. Schernthaner G, Currie CJ, Schernthaner GH. Do we still need pioglitazone for the treatment of type 2 diabetes? A risk-benefit critique in 2013. Diabetes Care 2013;36(Suppl. 2):S155–S161
49. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
50. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–1642
51. Abdelmoneim AS, Eurich DT, Light PE, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. Diabetes Obes Metab 2015;17:523–532
52. Agency for Healthcare Research and Quality (AHRQ). Quality and patient safety. Available from http://www.ahrq.gov/professionals/quality-patient-safety/index.html. Accessed on 29 February 2016
53. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care 2014;37:1367–1374
54. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 2014;16:410–417
55. Bouchoucha M, Uzzan B, Cohen R. Metformin and digestive disorders. Diabetes Metab 2011;37:90–96
56. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab 2010;12:442–451
57. Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab 2011;13:567–576
58. Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. Diabetes Obes Metab 2009;11:506–515
59. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2012;14:565–574
60. Wu D, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Obes Metab 2014;16:30–37
61. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab 2006;8:650–660
62. Perez A, Zhao Z, Jacks R, Spanheimer R. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin 2009;25:2915–2923
63. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. Diabetes Care 2010;33:2406–2408
64. Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination

therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2011; 13:653–661
65. Yoon KH, Steinberg H, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and pioglitazone in patients with type 2 diabetes: a 54-week study. Diabetes Obes Metab 2012;14:745–752
66. Rosenstock J, Kim SW, Baron MA, et al. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:175–185
67. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;66:446–456
68. Lewin A, DeFronzo RA, Patel S, et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care 2015;38:394–402
69. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015;38:384–393
70. Del Prato S, Foley JE, Kothny W, et al. Study to determine the durability of glycaemic control with early treatment with a vildagliptin-metformin combination regimen vs. standard-of-care metformin monotherapy-the VERIFY trial: a randomized double-blind trial. Diabet Med 2014;31:1178–1184
71. Carroll L. *Alice's Adventures in Wonderland*. London, Macmillan and Co., 1865