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CLINICAL APPLICATIONS

Treat-to-Target Insulin Titration Algorithms When Initiating Long or Intermediate Acting Insulin in Type 2 Diabetes

Poul Strange, M.D., Ph.D.

Abstract

Background:
Until recently, titration of insulin in type 2 diabetes clinical trials was typically left up to the investigator's discretion with a simple statement of the target ranges for glucose. In type 2 diabetes trials the average glycemic control achieved was usually less than desirable. Since then a number of trials have been conducted and reported utilizing various algorithms under various conditions. The objective of this article is to provide a review of the evidence to date.

Methods:
In addition to studies already identified through work in the area, the literature was searched using PubMed with the search words "insulin and titration" and subsequently "insulin and algorithm" from which studies starting insulin therapy using insulin titration algorithms in type 2 diabetes were selected.

Results:
The different algorithms and achieved results for glycemic control and hypoglycemia, as well as factors appearing to impact the results, are reviewed.

Conclusion:
The recent introduction of rigorously implemented insulin titration algorithms when adding on basal insulin to oral drugs in inadequately treated type 2 diabetes patients has led to better average glycemic control with little risk of severe hypoglycemia, as long as the morning fasting plasma glucose target is not lower than 100 mg/dl. Insulin titration algorithms have undergone and continue evolution in the direction of increased patient control.

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Author Affiliation: Poul Strange Consulting LLC, Princeton Junction, New Jersey

Abbreviations: (FPG) fasting plasma glucose, (GOT) Glycemia Optimization Trial, (HbA1c) hemoglobin A1c, (L-TTT) Levemir Treat-to-Target, (NPH) neutral protamine Hagedorn, (TTT) Treat-to-Target

Keywords: algorithm, basal, detemir, fasting glucose, FPG, glargine, insulin, NPH, severe hypoglycemia, titration

Corresponding Author: Poul Strange, M.D., Ph.D., Poul Strange Consulting LLC, 34 Berkshire Drive, Princeton Junction, NJ 08550; email address pstrange@verizon.net

Introduction

Despite the long history of insulin therapy, adjusting insulin doses is largely left to the art of the individual health care provider. United States insulin and insulin analogue labels' "Dosage and Administration" sections emphasize individualized dosing with little further direction.[1–3] Until the last 5 years, studies generally reported specified target glucose ranges as being left to the investigator's discretion to achieve. Average glycemic control reported from multicenter trials of type 2 diabetes starting insulin therapy typically did not achieve the targets stated in protocols for glucose ranges and reported hemoglobin A1c (HbA1c) values above 8%[4,5] or closer to 8% than 7%.[6,7]

During the last decade uniform insulin titration algorithms have been applied in several trials initiating long or intermediate acting insulin in type 2 diabetes patients often referred to as Treat-to-target. Several of the trials were designed for other primary purposes than algorithm development and have therefore used one specific algorithm. Interpretation of algorithm merit in those cases is somewhat difficult and has to rely on cross trial comparisons. Various factors in addition to the numbers in the algorithm apparently affect the achieved results. Those factors include the rigor with which the algorithm is enforced in the study, whether titrations are health care provider or patient directed, and the frequency of dose adjustments. Additionally, characteristics of the patients, including how advanced their disease is and what oral drugs are concomitant and/or discontinued at the start of insulin therapy, are important.

The purpose of this article is to review the experience from implementation of algorithms of starting basal insulin as an add on to oral drugs in type 2 diabetes trials. Because the focus is on broad implementation, this article is limited to multicenter trials. This review is not completely exhaustive, but contains the trials giving the key observations likely to drive future change.

Algorithms When Starting Long or Intermediate Acting Basal Insulin

The algorithms for basal insulin titration and their implementation have evolved steadily further away from complete real time health care provider control over every dose decision. The first step was the acceptance of one algorithm for all patients, which at the time was considered radical by most investigators. The second step became acceptance algorithm enforcement. As benign experience was building, investigators subsequently felt comfortable with patient-directed algorithms.

An overview of individual treatment arms in the trials described in this article is shown in **Table 1**. The glucose values reported in the literature are either blood or plasma referenced. In this article, blood referenced values are converted to plasma values using the multiplier of 1.11 as recommended by the International Federation of Clinical Chemistry.[8]

Glucose Targets, Ranges, and Insulin Adjustment Steps

Common to all algorithms is that dose changes are based on averages of a varying number of days' morning fasting self-monitored glucose. From this general theme there are many variations.

The starting dose has been 10 U, 20 U, or based on the morning fasting plasma glucose (FPG) using the formula of Holman and Turner,[9] which is (FPG (mg/dl) – 50)/10, typically yielding just short of 20 U. Within these options there does not appear to be any difference in achieved glycemic control and hypoglycemia rate, which will not be dealt with further.

An overview of the morning FPG ranges driving basal insulin adjustments is given in **Figure 1**. The different algorithms are displayed from left to right roughly in the temporal sequence of trial implementation. This illustrates the development from many step clinic-driven algorithms through similar patient-driven algorithms to algorithms with fewer steps titrated with increasing frequency by the patient. The two are not independent of each other. When a clinic has to titrate the insulin dose for the individual patient, there is a very natural limitation on the possible frequency. Consequently, the clinic has to be able to make substantial dose increments at high average glucose so the patient is not left for too long a time in poor glycemic control. However, the patient can easily titrate often, for which there is a long tradition for those with type 1 diabetes. With more frequent titration there is no longer a need for large steps at high glucoses and the algorithms can be simplified in terms of number of steps. At the extreme is INSIGHT,[10] which has only one step of one unit titrated every morning by the patient.

The glucose targets of the algorithms in the sense of where no more dose increments would be done are somewhat

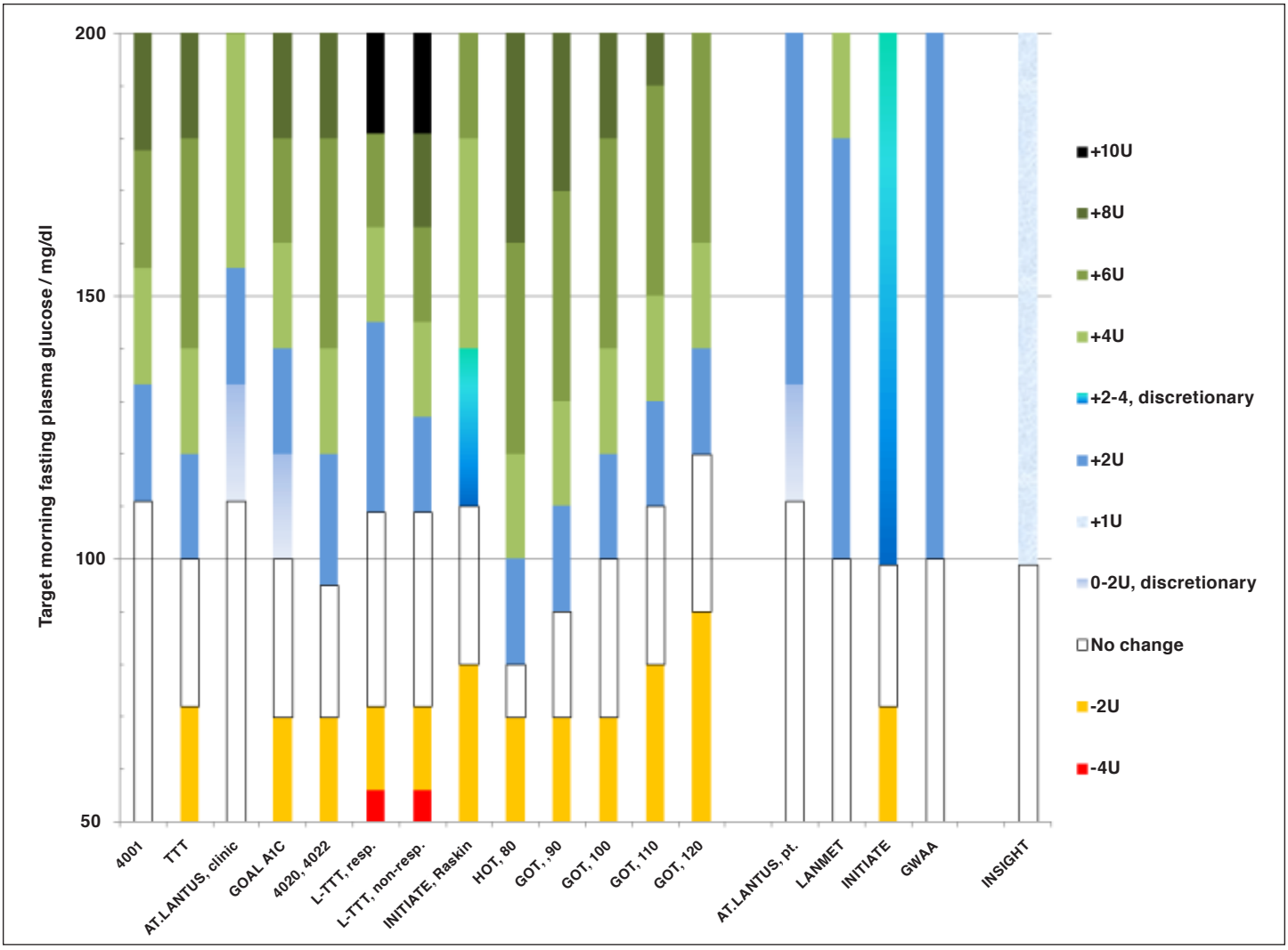

Figure 1. Insulin titration steps given average self-monitored morning FPGs in key studies. The left were designed for weekly titration minimally in the beginning of the studies, the next group for titration every 2 to 3 days, and the final on the right for daily titration. The studies are displayed from left to right roughly in the temporal sequence of trial implementation consistent with the algorithm evolution with the one notable exception of the AT.LANTUS trial patient algorithm that is placed further to the right with the every 2–3 days.

elusive, as some algorithms prescribe discretionary dose increments in the lowest range. Interpreted as the lower boundary of the range where a dose increment is mandated or suggested, the tested targets range from 80 to 120 mg/dl (**Figure 1**). However, there is a difference between a mandated dose increment and a discretionary one. Safety-conscientious health care providers with little algorithm experience may consider a discretionary increment no change. Interpreted as the lower boundaries of mandated dose increments, targets are as high as 130 mg/dl in AT.LANTUS[11] (**Figure 1**).

There is much debate about what the morning fasting target should be and typically people look strictly at achieved dose and HbA1c. The achieved end average doses, FPGs, and HbA1cs of the trials reviewed here are displayed as a function of the morning FPG target in **Figure 2**. While there is a clear relationship between the average dose and the glucose target at the trial level (**Figure 2a**), a relationship is less clear for FPG that, with two exceptions in Yki-Järvinen's LANMET[12] and INITIATE[13] trials, has remained stubbornly above 115 mg/dl irrespective of the target (**Figure 2b**); and there is clearly not a simple relation for the achieved HbA1c (**Figure 2c**). **Figure 2** contains a mixture of insulin neutral protamine Hagedorn (NPH), insulin glargine, and insulin detemir, and while the insulin may have an impact on the dose with higher doses achieved in the mentioned order (**Table 1**), the Treat-to-Target (TTT)[14] and Levemir Treat-to-Target (L-TTT)[15] trials show a minimal difference between the achieved HbA1c results between intermediate and long acting insulins when titrated using this methodology. Other factors must therefore be important for the achieved glycemic results.

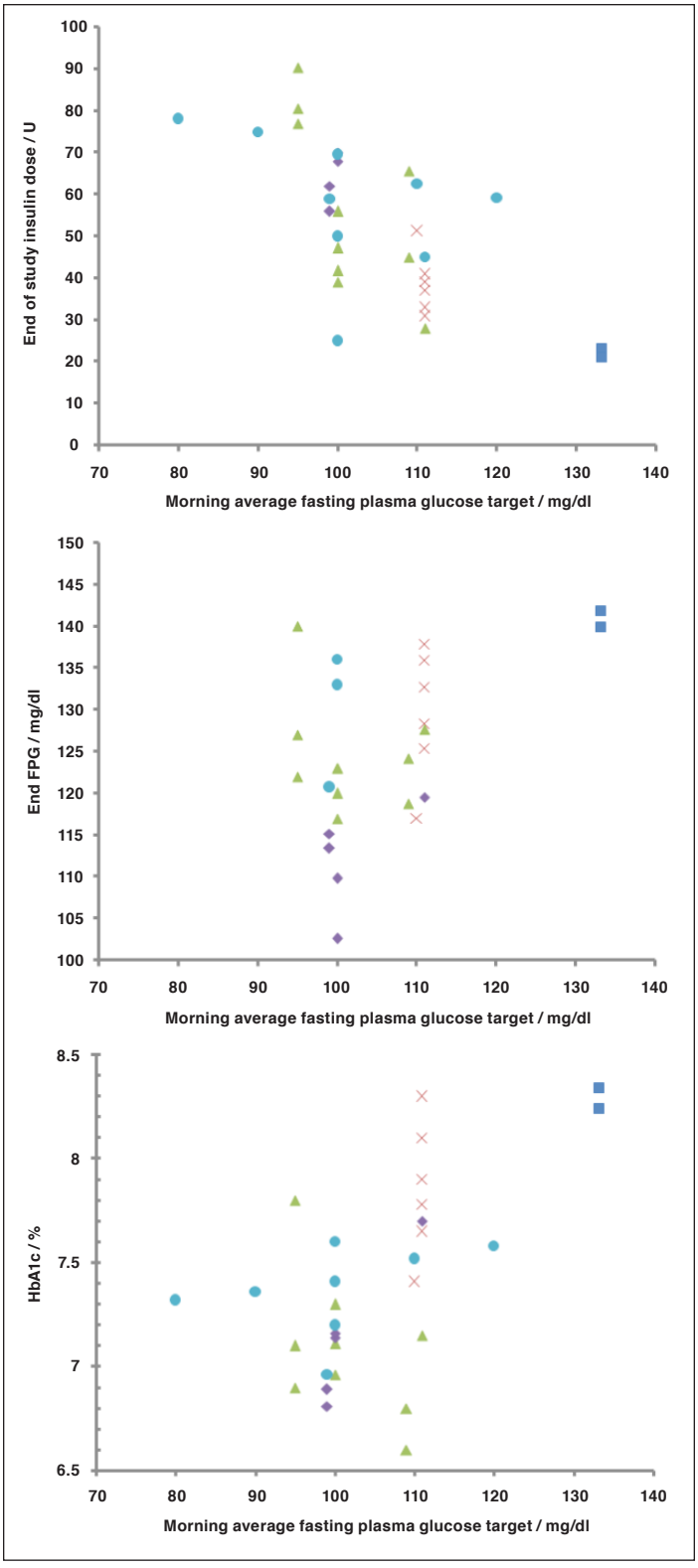

Figure 2. Insulin dose (a), FPG (b), and HbA1c (c) achieved as a function of morning FPG target. Squares: studies with a target range, but no specific prescribed insulin dose adjustments. X: studies with insulin dose algorithms, but left to the investigator's discretion to follow. Triangles: studies with insulin dose algorithms and centralized oversight over adherence. Diamonds: studies with insulin dose algorithms adjusted by the patient, but under tight clinic supervision. Circles: studies with insulin dose algorithms adjusted by the patient with minimal clinic supervision.

Considering strictly the morning FPG target, the question has been more or less definitively answered with the Glycemia Optimization Trial (GOT),[16] which randomized patients to five different targets ranging from 80 to 120 mg/dl (**Figure 1**) while everything else in the trial was held constant. Despite a substantial dose difference of 20 U between the extreme targets and the relatively high doses achieved, the HbA1c difference was limited to 0.25%. It is thus fair to conclude that the absolute morning FPG target as an isolated factor has little impact on achieved glycemic results within the 80- to 120-mg/dl range. GOT compared the rate of severe hypoglycemia events between the treatment groups and whereas the rates were similar with targets from 100 to 120 mg/dl, the rate doubled from the target of 100 to 90 mg/dl and increased further to 80 mg/dl (**Table 1**). The increased incidence of severe hypoglycemia at targets lower than 100 mg/dl has been confirmed in the 4020[17] and 4022[18] trials, which both had a target of 95 mg/dl and showed severe hypoglycemia incidences of 5 and 9.3%, respectively (**Table 1**). Given the lack of incremental effect combined with the increased incidence of severe hypoglycemia, most health care providers would probably agree that the morning target FPG should not be less than 100 mg/dl.

Implementation and Adherence

The trials reviewed in this article generally achieved better glycemic control than in trials of the past, indicating that a specific algorithm in the protocol offers a glycemic control advantage over simply stating a guideline goal range and leaving titration up to the investigator's discretion (**Figure 2c**). The implementation methodology appears to be of major importance for adherence to the protocol algorithm. Broadly, the implementation can be characterized as investigator discretion with no specific enforcement measures put in place centrally, investigator directed but centrally monitored and enforced, patient directed with close clinic oversight, and patient directed. Simply providing the algorithm is not enough, but each of the three latter approaches has proven successful (**Figure 2**).

Investigator Discretion versus Centralized Enforcement

4001[19] and TTT[14] offer good illustrations of centralized enforcement impact. Both studies were sponsored by the same company and were started at about the same time. Both studies utilized an algorithm for insulin titration that, except for the higher starting dose in 4001 using the Holman and Turner algorithm,[9] were similar given a stated leniency in the range 100–120 mg/dl in TTT (**Figure 1**). The major difference between the trials was the investigator discretion in 4001 versus the centralized

oversight of algorithm adherence in TTT. The average end doses for NPH and Lantus were 37 and 39 U in 4001 and 42U and 47 U in TTT, resulting in end HbA1c values of 8.3, 8.1, 7.0, and 7.0%, respectively. The consistent differences in dose and HbA1c are too large to be explained by other factors than the lack of enforcement in 4001 at a time when people were not comfortable pushing the basal dose. Since TTT, similar results have been observed in L-TTT using similar centralized oversight methodology.[15] In contrast, the 4013[20] trial, using essentially the same algorithm as TTT, but without the centralized oversight, again yielded somewhat disappointing HbA1c values of around 7.7%. The ability of centralized algorithm adherence oversight to achieve the best possible HbA1c thus seems clear.

GOAL_A1c[21] directly compared investigator discretion versus investigator-directed and -enforced titration. The incremental benefit in HbA1c lowering was limited to 0.2% in the enforced or "active" groups in contrast with the larger difference seen earlier. A critical difference from 4001 was that patients in all groups received a compact disc size pamphlet containing the algorithm and direction for its use. The effect of the enforcement was therefore confounded by the effect of patient direction discussed later. A good indication that this is the case comes from the insulin dose of 50 U and end HbA1c of 7.6% in the "usual titration" group. The GOAL_A1C study used a very broad range of investigators and a patient population that, if anything, should have fared worse given the discontinuance of the thiazolidinedione in 25% of the patients (see later).

The centralized enforcement methodology is useful to answer questions about the best possible achievable efficacy with specific drugs, but it is very resource intensive and not realistic in clinical practice. Patient direction is considerably easier to implement in clinical practice and is therefore extremely relevant from effectiveness rather than the narrow efficacy perspective.

Patient Direction with Clinic Oversight

Several trials offer insight into the effect of letting patients themselves titrate insulin based on algorithms. AT.LANTUS[11] compared a four-step algorithm with weekly adjustments directed by the clinic versus a two-step algorithm with adjustments every 3 days directed by the patient (**Figure 1**). The impact of patient direction is thus confounded by the differences in the algorithm. More seriously from the perspective of addressing the comparative question, patient direction was not completely free of clinic impact because the subjects' dose adjustments were reviewed by the investigator at clinic visits or over the telephone with a frequency of every other week. Clinic-directed titration and patient-directed groups had end doses of 41 and 45 U, HbA1c changes from a baseline of -1.1 and -1.2% ($p < 0.001$), and achieved HbA1c values of 7.9 and 7.7%, respectively. The primary end point in AT.LANTUS was the incidence of severe hypoglycemia with no difference found between the two treatment groups. It can therefore be concluded that the patient-directed approach is safe and, in terms of glycemic control, appears to be at least as good as the clinic-directed weekly titration.

Yki-Järvinen took patient-directed insulin titration with clinic oversight further using self-monitored FPGs uploaded via a telephone modem to assist the clinic in guiding patient-directed insulin titration in LANMET.[12] Contact with the patient with either a physical visit or a telephone call occurred every other week similar to AT.LANTUS. There is thus a mix of patient direction and clinic oversight, but no centralized monitoring of clinics' ability to adhere, which is the real costly procedure. Patients treated inadequately with either metformin alone or metformin in combination with a sulfonylurea were randomized to continue metformin, discontinue the sulfonylurea, and add either insulin NPH or insulin glargine. The end doses were 70 and 68 U, and end HbA1c values were 7.2 and 7.1%, respectively. This result is impressive and also indirectly validates the conclusion of the centralized clinic adherence oversight described earlier, because the results included centers with average HbA1c values of 7.8 and 7.6%, which is not likely to have happened with centralized oversight. Yki-Järvinen subsequently followed this up with INITIATE[13] comparing individual versus group education in type 2 diabetes patients initiating insulin glargine as add-on therapy in a setup similar to LANMET with clinic contact every other week until week 16 and every 4 weeks thereafter. The end doses were 62 and 56 U with end HbA1c values of 6.9 and 6.8% for the individual and group education groups, respectively. While not mentioned, it may be suspected that the marginally better results are because of better implementation in the centers with less than stellar results in LANMET. Importantly, the great results of the group education may lower the cost of the clinic.

Patient Direction with Minimal Clinic Change of Practice

Gerstein implemented a more radical patient directed approach in INSIGHT.[10] Clinic contact initially occurred every other week, but after 4 weeks the clinic contact went to every 4 weeks and after 12 weeks to 6-week

intervals. Clinic oversight was thus minimally if at all intensified compared to standard clinical practice. Patients were taught to "start with an initial dose of 10 units, and advised to increase this by 1 unit each day until achieving a FPG (FPG) ≤5.5 mmol/liter (99 mg/dl)." The end insulin dose was 38 U and HbA1c 7.0%. From an effectiveness point of view, this is an outstanding result.

Oral Drugs

The trials vary greatly in treatment of oral drugs when initiating insulin.

All trials, with the exception of a subset of patients in GOAL_A1C, who turned out to have exclusionary serum creatinine for metformin therapy by package insert,[21,22] retained the metformin when adding insulin. Some of the best glycemic control results have been achieved in trials using only metformin as the oral drug (LANMET[12] and 4022[18]), and the subset of patients GOAL_A1C, who discontinued the metformin, had higher HbA1c values at the end point. While the evidence is not conclusive in a strict scientific sense, it all points in the direction of retaining metformin if possible, which is also consistent with studies comparing insulin to insulin with metformin in type 2 diabetes.[23]

To date there appears to be no published data directly describing adding insulin to thiazolidinedione oral therapy. The trials in this review that recruited patients in thiazolidinedione treatment 4022, GOAL_A1C, and GOT[16] all discontinued the thiazolidinedione when introducing insulin. This particular patient population ended with higher HbA1c values in the GOAL_A1C trial, and previous evidence adding thiazolidinediones to insulin indicates good results in combination therapy for glycemic control.[24,25] While not proven, it therefore appears that retaining the thiazolidinedione from a strict glycemic control perspective is beneficial.

The evidence is more muddled for sulfonylureas. Most trials included in this article retained sulfonylureas, and some of the best results have been achieved in trials where the majority of patients were treated with sulfonylureas. However, under the conditions of discontinuing thiazolidinediones, adding insulin glargine in the 4022[18] trial resulted in lower HbA1c values when combined with metformin (7.1%) than sulfonylurea (7.8%) likely caused by a high rate of hypoglycemia in the sulfonylurea stratum (**Table 1**). This result is consistent with retrospective database analysis from a large managed-care database where the insulin sulfonylurea combination did poorly in terms of achieving the target of glycemic control.[26] The evidence for sulfonylureas is thus contradictory enough to require specifically designed trials to resolve the issue.

Too Much of a Good Thing?

To this point, this review has largely ignored the issues of time, dose, and weight. In trials with rigorous titration implementation there is a striking cross trial consistency in the time plots of FPG and HbA1c values over time. FPG typically reaches the lowest value in 12 weeks and HbA1c values trail this by about 6 weeks. It would therefore appear that the maximally achievable effect of basal insulin alone as an add on to orals has been achieved by 12 weeks. Despite this, it is very clear from trials where the dose development over time is published that the doses keep increasing. As examples the insulin glargine dose in TTT increased from 37 to 47 U or 27% from weeks 8 to 24[27] and the insulin detemir dose in L-TTT increased from 0.66 to 0.77 U/kg or 17% from weeks 12 through 24[15] both with little or no effect on FPG or HbA1c values. It thus appears that patients after 12 weeks of continued titration of basal insulin become insulin resistant. This apparent basal insulin-induced insulin resistance is not a new idea and the evidence supporting it is reviewed by Shanik and colleagues.[28] It is also consistent with the results of GOT that a 20 U dose difference between the extreme groups resulted in only 0.25% difference in HbA1c.[16] For purposes of this review it therefore seems appropriate to question whether the relentless up-titration of basal insulin alone in the face of diminishing returns is really the best therapeutic approach. Knowledge about physiology may indicate that patients might be better served by the introduction of prandial insulin after 12 weeks.

Conclusion

The recent introduction of rigorously implemented insulin titration algorithms when adding on basal insulin to oral drug in inadequately treated type 2 diabetes patients has led to better average glycemic control with little risk of severe hypoglycemia as long as the morning FPG target is not lower than 100 mg/dl. Insulin titration algorithms have undergone and continue evolution in the direction of increased patient control.

While the evidence indicates that retaining metformin and thiazolidinediones leads to the best glycemic results, the evidence for sulfonylureas is ambiguous.

The increasing average insulin doses after 12 weeks in the face of diminishing incremental returns for glycemic

Table 1.
Overview of Individual Treatment Groups Using Bedtime Intermediate or Long Acting Insulin as Add-On Therapy to Oral Drugs in Trials of Type 2 Diabetes Patients Treated Inadequately with Oral Drugs Alonea

First Author	Trial Name	n	BMI kg/m^2	Treatment		A1C %		FPG ml/dl			Titration	Insulin Dose		Hypoglycemic events			
														All or <70		Severe	
				Insulin	Oral	Start	End	Start	End	Target		U	~U/kg	% pts.	/pt. y	% pts.	/pt. y
Yki-Järvinen	3002	214	29	Lantus	SU and/or met, some acarbose	9.1	8.3	204	140	133	No algorithm	23	0.27	33			
Yki-Järvinen	3002	208	29	NPH	SU and/or met, some acarbose	8.9	8.2	208	142	133	No algorithm	21	0.25	42			
Fritsche	4001	229	29	Lantus	Glimepiride	9.1	8.1	240	136	111	A., Investigator discretion	39	0.48	43			0.04
Fritsche	4001	234	29	NPH	Glimepiride	9.1	8.3	244	138	111	A., Investigator discretion	37	0.46	58			0.12
Riddle	Treat-To-Target	367	33	Lantus	91% two, rest one	8.6	7.0	198	117	100	A., Central oversight	47	0.48		9.2	2.5	
Riddle	Treat-To-Target	389	32	NPH	91% two, rest one	8.6	7.0	194	120	100	A., Central oversight	42	0.42		12.9	1.8	
Janka		177	30	Lantus	met and SU	8.9	7.2	191	128	111	A., Central oversight	28	0.33	61	2.6		0.00
Raskin	INITIATE	116	31	Lantus	met and TZD	9.8	7.4	243	117	110	A., Investigator discretion	51	0.55	16	0.7		
Davies	AT.LANTUS, clinic	2315	29	Lantus		8.9	7.9	188	125	111	A., Investigator discretion	41	0.51	26		0.9	1.87
Davies	ATLANTUS, patient	2273	29	Lantus		8.9	7.7	188	120	111	A., Patient, clinic assisted	45	0.55	30		1.1	2.36
Heine	GWAA	260	31	Lantus	met and SU	8.3	7.2	187	136	100	A., Patient directed	25	0.28		6.3	1.5	
Kennedy	GOALA1C	3953	34	Lantus	met and/or SU, DC TZD	8.9	7.6	211	133	100	A., Patient directed	50			3.7		0.09
Kennedy	GOALA1C	3940	34	Lantus	met and/or SU, DC TZD	8.9	7.3	211	123	100	A., Central oversight	56			6.0		0.14
Eliaschewitz	4013	250	27	NPH	Glimepiride	9.2	7.8	215	133	111	A., Investigator discretion	31		63			4.40
Eliaschewitz	4013	132	27	Lantus	Glimepiride	9.1	7.7	224	128	111	A., Investigator discretion	33		53			2.60
Rosenstock	4013	103	35	Lantus	met+SU	8.8	7.1	188	123	100	A., Central oversight	39	0.40	55	7.7	2.9	
Yki-Järvinen	LANMET	61	32	Lantus	met	9.1	7.1	234	110	100	A., Patient, clinic assisted	68	0.69	54	5.0		0.00
Yki-Järvinen	LANMET	49	31	NPH	met	9.3	7.2	232	103	100	A., Patient, clinic assisted	70	0.66	57	7.7		0.00
Hermansen	Levemir Treat-To-Target	227	29	Levemir	One or two 65% Oral	8.6	6.8	200	124	109	A., Central oversight	66	0.77	64	8.6		0.01
Hermansen	Levemir Treat-To-Target	225	29	NPH	One or two 65% Oral	8.5	6.6	194	119	109	A., Central oversight	45	0.54	80	16.0		0.08
Gerstein	INSIGHT	206	31	Lantus	0, met and/or SU	8.6	7.0	191	121	99	A., Patient directed	38	0.41	49			
Yki-Järvinen	INITIATE	63	32	Lantus	met and/or SU, individual edu	8.7	6.9		113	99	A., Patient, clinic assisted	62	0.64	44	3.5	0.0	
Yki-Järvinen	INITIATE	58	31	Lantus	met and/or SU, group edu	8.8	6.8		115	99	A., Patient, clinic assisted	56	0.60	40	3.1	0.0	
Meneghini	4020	129	34	Lantus	met or SU	9.4	6.9	225	122	95	A., Central oversight	77		49		5.0	
Hollander	4022	72	35	Lantus	met	9.0	7.1	197	127	95	A., Central oversight	81			2.1	9.3	0.20
Hollander	4022	40	35	Lantus	SU	9.0	7.8	197	140	95	A., Central oversight	90			3.9	9.3	0.10
Tanenberg	GOT	927	35	Lantus	met and/or SU, DC TZD	9.3	7.3			80	A., Patient directed	78					0.19
Tanenberg	GOT	910	35	Lantus	met and/or SU, DC TZD	9.2	7.4			90	A., Patient directed	75					0.12
Tanenberg	GOT	927	35	Lantus	met and/or SU, DC TZD	9.3	7.4			100	A., Patient directed	70					0.05
Tanenberg	GOT	948	35	Lantus	met and/or SU, DC TZD	9.2	7.5			110	A., Patient directed	63					0.08
Tanenberg	GOT	915	35	Lantus	met and/or SU, DC TZD	9.3	7.6			120	A., Patient directed	59					0.02

[a] In keeping with evolution, references are listed as they appeared in the literature. Empty spaces indicate that data are not available in the publications. Papers not mentioned in the text are Janka,[29] Raskin's INITIATE,[30] Heine's GWAA,[31] and Rosenstock's 4014.[32] Abbreviations: BMI, body mass index; A1C, hemoglobin A1c; FPG, fasting plasma glucose; U, unit; % pts., percent of patients; /pt. year, per patient year; SU, sulfonylurea; met, metformin; TZD, thiazolidinedione; DC, discontinue; edu, education; A., algorithm.

control suggests that introduction of meal insulin after 12 weeks for patients, who are still not in adequate glycemic control, may be a better approach than continued up-titration of the basal insulin.

Disclosures:

Poul Strange is founder of Poul Strange Consulting LLC. Among the clients two could possibly be perceived as constituting a conflict of interest—sanofi aventis, and Valeritas—in which Poul Strange holds the title of Chief Scientific Officer.

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