



# Clinical Assessment of Individualized Glycemic Goals in Patients With Type 2 Diabetes: Formulation of an Algorithm Based on a Survey Among Leading Worldwide Diabetologists

*Diabetes Care* 2015;38:2293–2300 | DOI: 10.2337/dc15-0187

Avivit Cahn,<sup>1</sup> Itamar Raz,<sup>1</sup>  
Yosef Kleinman,<sup>2†</sup> Ran Balicer,<sup>3</sup>  
Moshe Hoshen,<sup>3</sup> Nicky Lieberman,<sup>3</sup>  
Naomi Brenig,<sup>4</sup> Stefano Del Prato,<sup>5</sup> and  
William T. Cefalu<sup>6</sup>

## OBJECTIVE

Observations over the past few years have demonstrated the need to adjust glycemic targets based on parameters pertaining to individual patient characteristics and comorbidities. However, the weight and value given to each parameter will clearly vary depending on the experience of the provider, the characteristics of the patient, and the specific clinical situation.

## RESEARCH DESIGN AND METHODS

To determine if there is current consensus on a global level with regard to identifying these parameters and their relative importance, we conducted a survey among 244 key worldwide opinion-leading diabetologists. Initially, the physicians were to rank the factors they take into consideration when setting their patients' glycemic target according to their relative importance. Subsequently, six clinical vignettes were presented, and the experts were requested to suggest an appropriate glycemic target. The survey results were used to formulate an algorithm according to which an estimate of the patient's glycemic target based on individualized parameters can be computed. Three additional clinical cases were submitted to a new set of experts for validation of the algorithm.

## RESULTS

A total of 151 (61.9%) experts responded to the survey. The parameters "life expectancy" and "risk of hypoglycemia from treatment" were considered to be the most important. "Resources" and "disease duration" ranked the lowest. An algorithm was constructed based on survey results. It was validated by presenting three new cases to 57 leading diabetologists who suggested glycemic targets that were similar to those calculated by the algorithm.

## CONCLUSIONS

The resultant suggested algorithm is an additional decision-making tool offered to the clinician to supplement clinical decision making when considering a glycemic target for the individual patient with diabetes.

<sup>1</sup>Diabetes Research Center, Hadassah Hebrew University Medical Center, Jerusalem, Israel

<sup>2</sup>Diabetes Unit, Shaare Zedek Medical Center, Bikur Cholim Campus, Jerusalem, Israel

<sup>3</sup>Clalit Institute for Research, Tel Aviv, Israel

<sup>4</sup>Department of Computer Science Education, Michlala Jerusalem College, Jerusalem, Israel

<sup>5</sup>Department of Clinical and Experimental Medicine, University of Pisa School of Medicine, Pisa, Italy

<sup>6</sup>Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA

Corresponding author: Itamar Raz, ntv502@netvision.net.il.

Received 26 January 2015 and accepted 4 September 2015.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0187/-/DC1>.

†Deceased.

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

The recent American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) Position Statement acknowledges the complexity of glycemic control and emphasizes the importance of individualization of care (1). Tight glucose control in type 2 diabetes has been shown to reduce the prevalence of microvascular complications in randomized prospective trials (2,3). Nevertheless, the accumulated results from the type 2 diabetes cardiovascular trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation [ADVANCE] trial, and the Veterans Affairs Diabetes Trial [VADT]) suggest that not everyone benefits from aggressive glucose management (4–6); therefore, the glycemic target and the means to attain it should be tailored for each patient. Striving for near normoglycemia (i.e., HbA<sub>1c</sub> of 6%) may be recommended for select patients with short disease duration, long life expectancy, and no cardiovascular complications. Less stringent HbA<sub>1c</sub> goals, i.e., 7.5–8.0% or even slightly higher, may be considered appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, and extensive comorbid conditions (e.g., frail adults) and those in whom the target is difficult to attain (7,8). The Position Statement elaborates the complexity in the clinical arena and identifies the important decision elements to be considered while setting a glycemic target for the individual patient and stresses the importance of involving the patient in defining a realistic goal that is both feasible and acceptable (1).

Shifting the weight from a rigid and uniform HbA<sub>1c</sub> target to individualized goals certainly has its downside and in the clinical setting is not always an easy decision. This goal is further complicated by different practices, availability of resources, and medications and differences in disease presentation in various regions of the world. In this regard, striving for “individualized” goals could potentially mean a different approach as guided by the rationale prevalent for that geographic region. This leads us to a “gray zone” in which there are no simple answers or clear-cut numbers; there is no “gold standard” upon which one can rely. An additional problem posed by personalized medicine on a

global level is the difficulty of maintaining quality control by health administrations. Since there is no fixed number, which can be universally defined as an acceptable target, how can one determine whether adequate diabetes care is being provided to the community? Would it be fair for a provider to be judged on his/her patients not achieving a goal <7% if the majority of them have severe cardiovascular disease and the associated comorbidities that would argue against tight control? Is it appropriate to judge all providers around the world with one standard, given the constraints in resource-poor areas? Under these circumstances, treatment decisions must combine current medical knowledge with clinical judgment and patient preference.

To obtain a real-life assessment of thoughts on personalized diabetes care and to determine whether there was consensus on approach, we sought the opinion of expert diabetologists throughout the world. Initially, we evaluated what parameters the target HbA<sub>1c</sub> should be based on. The recent guidelines suggested basing the recommended HbA<sub>1c</sub> on seven parameters: 1) patient attitude and treatment efforts, 2) risks potentially associated with hypoglycemia, 3) disease duration, 4) life expectancy, 5) important comorbidities, 6) established vascular complications, and 7) resources and support system (1). We constructed a survey to assess whether there are additional parameters that should be considered when setting the patient’s individual target HbA<sub>1c</sub>. We also deliberated as to whether the decision elements were of equal importance or whether some were more important than others. Finally, we requested an opinion on what the international diabetes opinion leaders thought of their patients’ target HbA<sub>1c</sub> and how tight or lenient they thought the HbA<sub>1c</sub> should be in real-life conditions.

## RESEARCH DESIGN AND METHODS

### Selection of Key Opinion Leaders

Key opinion leaders in diabetology were selected from various regions of the world and were chosen based on several factors: 1) recognition regionally/internationally for their contribution to the field, 2) position as leader of diabetes health policy in their country, 3) principal investigators

of clinical studies, 4) international consultants on scientific advisory boards, 5) productivity in publications in international leading medical journals, and 6) actively involved in formulating clinical practice recommendations. The list of experts was composed with the assistance of those authors who are physicians and additional colleagues. I.R., Y.K., and A.C. finalized the list, which included all experts proposed by the authors. The expert diabetologists across the world were approached via e-mail with an invitation to participate in our survey.

The most commonly cited international guidelines are from the ADA and American Association of Clinical Endocrinologists, representing North American experts, and the EASD, representing mostly Western European diabetologists (1). Thus, we determined that approximately half of the experts included in the survey should practice in one of these two regions. Aiming to encompass worldwide opinion leaders as well, the following regions were also included: the Far East, the Middle East, Eastern Europe, and Latin America, each region constituting ~10% of the surveyed population.

### Construction of an Online Survey

An online survey composed of two sections was developed. In the first section, 11 parameters affecting the patient’s recommended HbA<sub>1c</sub> target were listed. These were taken from the ADA/EASD guidelines and expanded by four additional parameters (Table 1). Two of the original parameters were divided: the parameter “patient attitude and expected treatments efforts” was separated into “functional attitude” (motivation) and “adherence to therapy.” Additionally, the parameter “established vascular complications” was divided into “macrovascular” and “microvascular” complications. Furthermore, two additional parameters were included: “cognitive function” and “risk of hypoglycemia from treatment”; the latter reflects the risk stemming from the treatment itself (i.e., insulin poses a greater risk than metformin). The physician was invited to rate these parameters according to their relative importance (1 ranked the most important from a clinical perspective and 11 the least important clinical factor). The parameters were scrambled

**Table 1—Original decision elements (ref. 1), their modification in the survey, and the calculation of an algorithm based on eight parameters and five parameters**

Parameters in the guidelines	Parameters in the survey	Eight parameters	Relative weight in eight-parameter algorithm (%)	Five objective parameters	Relative weight in five-parameter algorithm (%)
	Risk of hypoglycemia from treatment	Risk of hypoglycemia from treatment	22.5	Risk of hypoglycemia from treatment	29.7
Life expectancy	Life expectancy	Life expectancy	20.5	Life expectancy	27.0
Risk potentially associated with hypoglycemia	Risk potentially associated with hypoglycemia				
Important comorbidities	Important comorbidities	Important comorbidities	13.3	Important comorbidities	17.5
Macrovascular and advanced microvascular complications	Established macrovascular complications	Macrovascular and advanced microvascular complications	11.9	Macrovascular and advanced microvascular complications	15.7
	Established microvascular complications				
	Cognitive function	Cognitive function	10.3		
Functional attitude and adherence	Adherence to therapy Functional attitude	Adherence and motivation	7.9		
Disease duration	Disease duration	Disease duration	7.6	Disease duration	10.0
Resources and support system	Resources and support system	Resources and support system	5.9		

and presented in a different order to each participant to avoid bias.

In the next section of the survey, six clinical cases were composed, covering a wide spectrum of patients with diabetes and treatments. These ranged from the newly diagnosed patient with diabetes and no evidence of complications to the frail, elderly patient with multiple complications and/or comorbidities. (A full record of the cases is available in the Supplementary Data.) The physician was requested to input the target HbA<sub>1c</sub> he/she would then recommend for each patient. The cases were presented in random order to each participant.

For assessment of repeatability of results, 30 months after the initial survey, all those who responded to the survey were invited to propose a glycemic target for three of the original six cases.

#### Calculation of an Algorithm for Assessing Glycemic Target

An algorithm was computed based on the relative ranking of the parameters, excluding parameters with similar scores and related context. The average ranking of each parameter (designated  $x$ ) (1 as most important, 11 the least) was then inverted ( $1/x$ ) so that the most important parameter was the largest number and the least important the smallest one. The product was then squared in order

to increase the gap between the different parameters to better reflect the expert's opinion. The relative weight of each parameter was calculated as the ratio of that parameter's product ( $1/x^2$ ) to the sum of all parameters' products.

#### Validation of the Algorithm

Three new clinical cases were constructed ranging from the young healthy patient to the one with long-standing diabetes and multiple comorbidities. We approached a new set of key opinion leaders requesting that they propose an HbA<sub>1c</sub> target for these virtual patients. Diabetologists selected were those who did not respond to the initial survey, and in addition we included national lead investigators (endocrinologists) from recent cardiovascular outcome studies—SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus), TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), and DECLARE (Dapagliflozin Effect on Cardiovascular Events)—if they had not previously been included. I.R., A.C., S.D.P., and W.T.C. approved the choice of experts, and A.C. finalized the list.

## RESULTS

### Response to the Survey

A total of 151 experts responded to the survey (61.9%): 142 physicians answered

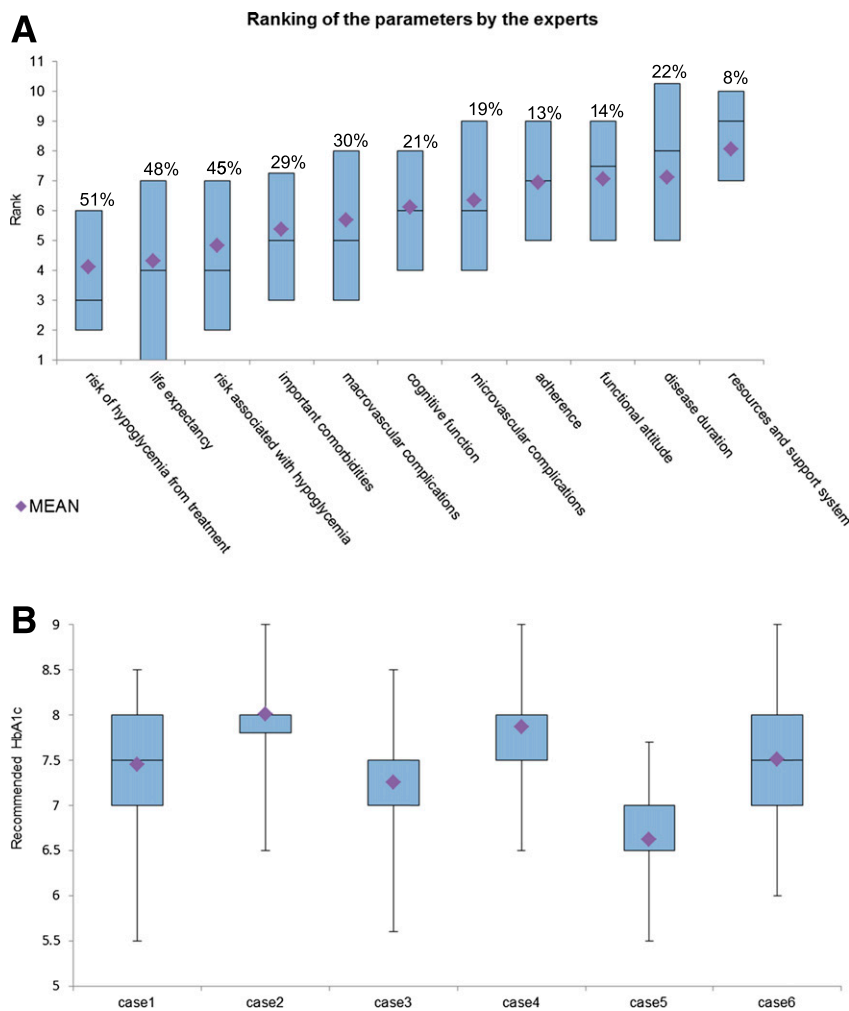
both sections of the survey; 2 completed just the first section of the survey, regarding the relative importance of the parameters; and 7 answered the second section of the survey only—designating a target HbA<sub>1c</sub> to each clinical vignette. An average of 3.3 min was spent on parameter sorting and 59 s on each case.

### Ranking of the Parameters

Based on survey results, and as one may expect, the rankings of the parameters by the global experts in the area of clinical importance were significantly different (Fig. 1A). "Risk of hypoglycemia from treatment" ranked the highest with >50% of the physicians counting it among the top three. "Life expectancy" was ranked among the top three by 48% of the physicians with 30% of the responders considering it to be the most important. "Disease duration" ranked low with a median rank of 8. "Resources and support system" was considered by most to be one of the least important parameters with >50% ranking it among the lowest three.

### Glycemic Targets Proposed

The range of the target HbA<sub>1c</sub> suggested for each case (median and interquartile range [IQR]) is shown in Fig. 1B. As evidence to support the complexity of an individualized goal, the SD suggested for



**Figure 1**—Survey results. *A*: Box plot showing the mean, median, and IQR of the ranking of the parameters by the experts. The percentages above the columns indicate the % of experts who counted the parameter among the top 3. *B*: The glycemic targets recommended by the experts for each individual case. Case 1, ACCORD-type patient with severe micro- and macrovascular disease; case 2, nursing home resident with dementia; case 3, elderly patient with new-onset diabetes and long-standing coronary artery disease; case 4, elderly patient with mild dementia and long-standing diabetes treated with basal-bolus insulin regimen; case 5, middle-aged patient with new-onset diabetes; case 6, patient with schizophrenia, noncompliance, and microvascular complications.

each level was large. For example, in cases 1 (severe micro- and macrovascular disease) and 6 (mental health issue and noncompliance) opinions varied extensively so that in case 6 approximately a third of the experts proposed the target to be 7.0%, a third proposed 7.5%, and a third proposed 8.0%. Cases 2 (nursing home resident with dementia) and 4 (elderly with mild dementia) showed a near-normal distribution with a median of 8%. In case 3 (elderly, new-onset type 2 diabetes, and coronary artery disease), most physicians supported a target of 7–7.5%, and in case 5 (middle-aged with new-onset disease) most suggested 6.5–7%.

The survey noted an important observation in that the responses were similar between different regions; however, we recognize that there are insufficient representatives from each region to conclusively discuss the various observed disparities.

For assessment of repeatability of the experts' decision, three of the original vignettes have resubmitted to the same experts who did provide suggestion in the first run. One hundred of 151 responded to the request to repeat the survey. The results are available in Table 3 (right column) showing an almost complete overlap of the recent to the original HbA<sub>1c</sub> target value.

### Computing an Algorithm

On the basis of the relative ranking of the parameters as suggested by the experts, we then constructed an algorithm to compute an individualized HbA<sub>1c</sub> target according to the severity score of each parameter. When striving toward this goal, we felt three parameters received similar scoring and appeared redundant and were therefore omitted from further calculations: 1) “advanced microvascular complications” was combined with “macrovascular complications,” 2) “motivation” was combined with “adherence,” and 3) the “risk potentially associated with hypoglycemia” was omitted. The latter was considered an important parameter by most experts, yet its ranking did not significantly differ from “life expectancy,” “important comorbidities,” or “macrovascular complications.” We made the assumption that a patient’s potential risk from hypoglycemia stems from age, comorbidities, macrovascular complications, and treatment regimen. This parameter is difficult to objectively quantitate, and therefore we opted not to consider it in an independent manner.

After the above assumptions, we were left with eight parameters for consideration. Six parameters were those originally proposed by the ADA guidelines, and if anything, our exercise confirmed the clinical validity and importance of those parameters. However, two additional parameters were added: “cognitive function” and “risk of hypoglycemia from treatment,” which reflects the extent to which current antidiabetes treatment regimen poses a risk of development of hypoglycemia. The relative weights of the parameters in the final algorithm were calculated as described and are shown in Table 1.

The HbA<sub>1c</sub> target to be proposed by the algorithm was restricted to the range of 6.5–8.5%. We set this range because it encompassed 95.1% of the recommended HbA<sub>1c</sub> goals proposed by the experts in all cases included in our survey, which represented a wide spectrum of patients. Furthermore, this range of glycemic targets falls in line with that suggested by Ismail-Beigi et al. (9) and later endorsed by the Diabetes Care Expert Forum (8) and may be the consensus range given the diverse cases presented.

Based on the above calculations, we propose that the glycemic target may be calculated as follows. For each parameter, a score should be given to each individual patient: 1 for low risk, 2 for moderate, and 3 for high risk (according to Table 2). The weight of each parameter, as appears in Table 1, is multiplied by 1, 2, or 3 (Table 2), and the products are summed. For example, if the patient has a low risk of hypoglycemia from treatment, the product would be  $22.5 * 1 = 22.5$ ; if the patient has limited life expectancy, the product would be  $20.5 * 3 = 61.5$ . The formula is further calculated as follows:

Glycemic target

$$= 6.5 + (\text{sum of products} - 100)/100$$

Three of the eight parameters comprising the algorithm may be considered “subjective”: “cognitive function,” “adherence to therapy,” and “resources and support system.” The combined weight of these three parameters is nearly 25%; they may shift the target HbA<sub>1c</sub> by up to 0.5% (a quarter of the predefined range of possible glycemic targets). An alternative minimalistic model, including only the five objective parameters, may be calculated as well. The relative weights of the parameters in this model are shown in Table 1. The calculation of the glycemic target is based on the same formula.

Both models may be then be merged to generate a model, which is easier for use in clinical practice. The physician, the patient, or, alternatively, a computer based on the electronic medical database can calculate five objective parameters for each individual and suggest a glycemic goal. Subsequently, the computer will fit the patient’s five parameters into the eight-parameter formula to calculate a “worst case” and “best case” scenario for the remaining three objective parameters. The product of these calculations will

generate an HbA<sub>1c</sub> target with 0.5% tolerance and a value (not necessarily in the mid-range) that is the recommended target based solely upon the objective factors.

Table 3 illustrates the implementation of the algorithm in the clinical vignettes, which yielded relative agreement between the experts and the glycemic target automatically generated.

#### Validation of the Algorithm

The algorithm was used to generate the HbA<sub>1c</sub> target value for three virtual patients. The same cases have been presented to 57 international expert diabetologists to identify an HbA<sub>1c</sub> target value based on their clinical assessment. Results are shown in Table 3, where it can be appreciated how the algorithm-generated values are almost completely superimposable to those indicated by the diabetes experts.

#### CONCLUSIONS

The clinical data accumulated in the recent decade have triggered a shift from the pursuit of a universal target HbA<sub>1c</sub> to a more flexible one, dependent upon individual patient characteristics (1). However, the downside of individualized targets is the lack of a “gold standard” and the paucity of truly objective data from which a clinician can base a decision. This puts the provider in a position from which a decision needs to be made based on personal experience and current knowledge of the evidence supporting the goals. We do recognize that this is the “art of medicine,” but it also could potentially result in heterogeneous delivery of diabetes care.

Given this background, what guidance can we give providers on how to approach selecting glycemic targets? Who are the physicians who will outline the particularities of diabetes care in this era of individualized care? How many physicians are needed to capture all the

accumulated international experience and data? The aforementioned Position Statement was written by 10 authors and 25 additional collaborators (1) but, as we are aware, was vetted extensively with experts from around the world. In our exercise for “real-world” targets, the strength of the approach came from opinions and direction provided by >140 expert diabetologists and from different regions around the world. Thus, we feel this assessment does encompass the entire spectrum of worldwide opinion leaders. Our purpose was to generate a “global” picture on prevailing clinical practice and expertise. Altogether, our survey suggests a certain degree, as expected, of variability in the weight the expert attributes to the clinical variables to be considered in the identification of individualized glycemic targets, which translate to a dispersion of the HbA<sub>1c</sub> values identified in the different clinical conditions represented in the six vignettes. In some circumstances, such as cases 1 and 6, opinions greatly diverged, thus demonstrating that in some cases—i.e., case 6, a schizophrenic individual suffering from diabetes complications—it is nearly impossible to reach consensus.

Nonetheless, the survey provides a powerful starting point in the attempt to build up a computer-based aid or smart phone app to support clinical decision of the physician. Part of the strength of the information comes from a high degree of repeatability of the clinical decision, as shown by resubmitting the same cases to two-thirds of the experts who initially contributed to the survey.

The algorithm was based on five objective parameters, all of which are easily extrapolated from electronic medical records. 1) Risk of hypoglycemia from treatment: This parameter basically is represented by the antihyperglycemic medications in use. It was considered

**Table 2—Calculating the relative weight of the parameters**

Risk of hypoglycemia from treatment	Low risk	Moderate risk	High risk
Life expectancy	Long	Decreased	Short
Important comorbidities	None	One	Two or more
Macrovascular and advanced microvascular complications	None	One	Two or more
Cognitive function	Excellent	Some decline	Severe decline
Adherence and motivation	Excellent	Moderate	Reduced
Disease duration	Short (<5 years)	Moderate (5–20 years)	Long (>20 years)
Resources and support system	Readily available	Available with effort	Limited



**Table 3—Implementation of the algorithm**

	Risk of hypoglycemia from treatment	Life expectancy	Comorbidities	Macrovascular complications	Disease duration	Recommended glycemic target by algorithm	Expert's opinion, median (IQR)	Results of repeat survey, median (IQR)
<b>Original cases</b>								
#2: A 70-year-old nursing home resident. Has moderate dementia and is currently treated with basal insulin.	3	2	3	3	2	8.1 (7.7–8.2)	8.0 (7.8–8.0)	8.0 (8.0–8.5)
#3: An 80-year-old lawyer recently diagnosed with diabetes. Suffers from ischemic heart disease but does not have congestive heart failure. Is not taking any antidiabetes drugs at the moment and is eager to treat his condition. No evidence of microvascular complications.	1	2	2	2	1	7.1 (7.0–7.4)	7.0 (7.0–7.5)	7.5 (7.0–7.5)
#4: An 87-year-old man has long-standing diabetes, mild dementia, and micro- and macrovascular complications. Is moderately compliant with current basal-bolus insulin regimen.	3	3	3	3	3	8.5 (8.0–8.5)	8 (7.5–8.0)	
#5: A 45-year-old teacher has just been diagnosed with diabetes. No complications and not taking any antidiabetes medication. Has resources and is willing to take care of herself.	1	1	1	1	1	6.5 (6.5–7.0)	6.5 (6.5–7.0)	6.5 (6.5–7)
<b>New cases</b>								
#1: A 47-year-old diagnosed with type 2 diabetes 4 years ago. Not suffering from any diabetes complications. BMI 32.5 kg/m <sup>2</sup> . Currently treated with metformin and a DPP-4 inhibitor and moderately compliant.	1	1	1	1	1	6.6 (6.5–7.0)	6.5 (6.5–6.8)	
#2: A 75-year-old was diagnosed with diabetes 10 years ago. Has stable IHD; PTCA 10 years ago and has well-controlled hypertension and hyperlipidemia. No evidence of microvascular complications. Antidiabetes medications include metformin and glimepiride (4 mg b.i.d.).	2	2	2	2	2	7.4 (7.3–7.7)	7.5 (7.0–7.5)	
#3: A 67-year-old man diagnosed with diabetes >20 years ago. Is an active smoker and suffers from IHD and CHF NYHA IV, S/P CABG 12 years ago, and 2 PTCAs in the last 3 years. Microvascular complications include diabetic foot and macroalbuminuria. Has severe CRF. Antidiabetes medications include DPP-4 inhibitor, bedtime insulin, and injection of short-acting insulin for lunch. Noncompliant.	3	3	3	3	3	8.3 (8.0–8.5)	8.0 (7.5–8.0)	

Implementation of the algorithm in the clinical cases. The algorithm's output is calculated according to the eight-parameter algorithm, and the range is calculated using five parameters as described in the text. CABG, coronary artery bypass graft; CHF, congestive heart failure; CRF, chronic renal failure; DPP-4, dipeptidyl peptidase-4; IHD, ischemic heart disease; NYHA IV, New York Heart Association stage 4; PTCA, percutaneous transluminal coronary angioplasty.

to be the most important with >50% of physicians rating it among the top three. The association of severe hypoglycemia with morbidity and mortality has been extensively discussed in recent literature, possibly accounting for the emphasis the experts placed upon this parameter (10,11). 2) Life expectancy: In our algorithm, we followed current recommendations considering life expectancy, as proposed by the guidelines (1) and not age, attempting to capture the biological rather than chronological age. There are several validated models used for approximating this variable from clinical databases such as the Charlson score or more advanced tools based on comorbidity scores such as the Johns Hopkins Adjusted Clinical Groups (ACG) risk score (12). 3) Important comorbidities: This parameter may be extracted from a medical database according to predefined ICD-9 codes or based on comorbidity scores. It differs from life expectancy, as it does not take into account the age of the patient. 4) Macrovascular and advanced microvascular complications: This parameter may also be extracted automatically from the database. Advanced microvascular complications include proteinuria and/or estimated glomerular filtration rate <50 mL/min, proliferative retinopathy and/or retinopathy requiring local treatment, and diabetic foot ulcer. Autonomic neuropathy and advanced diabetic cardiomyopathy diagnoses that are seldom recorded and will therefore not be included—posing a limitation of this model. 5) Disease duration: This is a parameter that appears in most large databases but is also the least accurate due to the intrinsic difficulties in identifying the true time of development of diagnostic hyperglycemia. In line with this concern, in our algorithm disease duration has the minimal weight the experts considered it should be given.

On the basis of these simple and easy-to-obtain parameters, we have used the algorithm to calculate the suggested HbA<sub>1c</sub> target value in the four cases with the smallest variability among the experts opinion showing quite a strong overlap. The validity of the algorithm was further corroborated by a similar high degree of overlap when it was used to calculate target HbA<sub>1c</sub> in three new patients' cases and by comparing the results with the values identified

by a new set of international diabetes experts.

It must be, however, emphasized that this computer-based algorithm and our attempt to “quantify” the importance of clinical factors based on expert opinion are not intended to replace clinical judgment. Nonetheless, given the difficulty in agreeing upon an individualized target, the goal is to supplement clinical decision making with a guiding target estimate based on scientific consensus in a realm of multiple cooperating vectors. Yet, even with the aid of a proposed algorithm, the final glycemic goal is to be decided by the physician and the patient, while taking into consideration the computed goal in the context in which it was provided as an aid based on consensus when considering the factors involved in arriving at an appropriate glycemic target.

Our algorithm and its formulation have several limitations. The selection of the experts was not based on a systematic scoring system, and it is probable that many worldwide experts have not been included. Additionally, we did not collect data regarding age, years in practice, clinical setting, etc., from the survey responders. However, we did aim to include individuals who were nationally and/or internationally recognized for their contribution to the field including national lead investigators from some of the recent large diabetes trials. Additionally, the opinions collected were those of physicians alone; diabetes nurses or educators were not included in the survey.

In summary, the call for individualization of care has been widely received with physicians appropriately aiming for diverse goals in different patients. Yet, there is no uniformity in the way individualization is undertaken, and the glycemic target aimed for in a specific patient may vary extensively depending upon the individual physician consulted and the region of practice. The algorithm we propose, based on a survey of >140 worldwide experts and validated by >50, is an attempt to “quantify” clinical factors and clinical disparities using the combination of a mathematical model and clinical intuition in an attempt to standardize individualized care. The aid of a validated algorithm would have great clinical importance and would enhance our ability

to deliver better diabetes care for our patients while avoiding the hazards associated with both over- and under-treatment. It could become an additional tool in the hands of health care administrations allowing a more balanced assessment of the quality of care. Finally, delivery of care may become more standardized and easier to communicate to the medical personnel caring for patients with diabetes. Obviously any proposed algorithm needs further study and validation. From our experience with the survey it is evident that attempting to reach an individualized goal for patients is clearly not an easy task or one that has general consensus . . . yes, providers will still have to rely on the true “art of medicine” . . .

### In Memoriam



*Dr. Yosef Kleinman (1948–2013) was a renowned diabetologist in Israel. During his career as head of the Internal Medicine Section in a Jerusalem Hospital, he established and administrated a diabetic foot clinic for many years and devoted his life to the care of his patients. Personalization of care was one of his mottoes. He was the enthusiastic and passionate promoter of our survey and subsequent development of the algorithm. Unfortunately he did not live to see his work's culmination. This article is dedicated to his memory.*

**Acknowledgments.** The authors thank those who contributed time and effort in the completion of the survey (full list is available in Supplementary Data).

**Funding.** W.T.C. is supported in part by National Institutes of Health (NIH) grant 1U54-GM-104940,

which funds the Louisiana Clinical and Translational Science Center, and NIH grant P50-AT-002776.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** A.C., I.R., and Y.K. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. R.B., M.H., and N.B. researched data, contributed to discussion, and reviewed and edited the manuscript. N.L., S.D.P., and W.T.C. contributed to discussion and reviewed and edited the manuscript. A.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** Parts of this study were presented at the 2nd China Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), Shanghai, China, 9–11 May 2013.

## References

- Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–1379
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865
- 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
- Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559
- Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
- Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
- American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care* 2015;38(Suppl. 1):S1–S89
- Raz I, Riddle MC, Rosenstock J, et al. Personalized management of hyperglycemia in type 2 diabetes: reflections from a Diabetes Care Editors' Expert Forum. *Diabetes Care* 2013;36:1779–1788
- Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann Intern Med* 2011;154:554–559
- Seaquist ER, Miller ME, Bonds DE, et al.; ACCORD Investigators. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. *Diabetes Care* 2012;35:409–414
- McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;35:1897–1901
- Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–682