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Calculating individualized glycaemic targets using an algorithm based on expert worldwide diabetologists: Implications in real-life clinical practice

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Abstract

Background: The aim of this study was to assess the clinical implications of calculating an individualized HbA_{1c} target using a recently published algorithm in a real-life clinical setting.

Methods: General practitioners (GPs) from the Spanish Society of Family Medicine Diabetes Expert Group were invited to participate in the study. Each GP selected a random sample of patients with diabetes from his or her practice and submitted their demographic and clinical data for analysis. Individualized glycaemic targets were calculated according to the algorithm. Predictors of good glycaemic control were studied. The rate of patients attaining their individualized glycaemic target or the uniform target of $HbA_{1c} < 7.0\%$ was calculated.

Results: Forty GPs included 408 patients in the study. Of the 8 parameters included in the algorithm, "comorbidities," "risk of hypoglycaemia from treatment," and "diabetes duration" had the greatest impact on determining the individualized glycaemic target. Number of glucose-lowering agents and adherence were independently associated with glycaemic control. Overall, 60.5% of patients had good glycaemic control per individualized target, and 56.1% were well controlled per the uniform target of $HbA_{1c} < 7.0\%$ ($P = .20$). However, 12.8% (23 of 246) of the patients with $HbA_{1c} \geq 7.0\%$ were adequately controlled per individualized target, and 2.6% (6 of 162) of the patients with $HbA_{1c} < 7.0\%$ were uncontrolled since their individualized target was lower.

Conclusions: In a real-life clinical setting, applying individualized targets did not change the overall rate of patients with good glycaemic control yet led to reclassification of 7.1% (29 of 408) of the patients. More studies are needed to validate these results in different populations.

KEYWORDS

community care, glycaemic control, HbA_{1c} target, type 2 diabetes, survey research

1 | INTRODUCTION

Clinical guidelines and expert committees on the management of type 2 diabetes have recommended individualization of glycaemic targets.[1-5] The American Diabetes Association and European Association for the Study of Diabetes[5] recommend a more lenient target ($HbA_{1c} < 8\%$; <69 mmol/mol) for patients with multiple co-morbidities, reduced life expectancy, history of hypoglycaemia, or advanced

diabetes complications and a more stringent target such as $HbA_{1c} < 6.5\%$ (48 mmol/mol) for younger patients without co-morbid conditions and no significant adverse effects of glucose-lowering agents. Nevertheless, it is difficult for clinicians to establish an individualized target for a specific patient as there is no algorithm for quantitative calculation, so qualitative approaches are taken.

Recently, Cahn et al[6] published an algorithm on the basis of the expert opinions of leading worldwide diabetologists to calculate an individualized

glycaemic target for each patient. The target is to be calculated using 8 parameters (listed below). For each parameter, a score is given to the individual patient according to 3 levels of risk: low, moderate, or high.

The algorithm was built using data from 2 surveys. In an initial survey, the experts were requested to rank the clinical parameters according to their relative importance. Additionally, the experts were presented with 6 clinical cases covering a wide spectrum of patients with diabetes and treatments and were requested to propose the glycaemic target that they consider most appropriate for the patients described. The algorithm was constructed based upon their responses. For assessment of repeatability of the results, 30 months after the initial survey, all those who responded to the survey were invited to propose a glycaemic target for 3 of the original 6 cases. Finally, 3 new cases were presented to 57 additional international expert diabetologists—who offered glycaemic targets to the patients described. Their responses overlapped those proposed by the algorithm. To date, no clinical data have been published showing the implications of this algorithm in clinical practice, and there is no information regarding the proportion of patients with type 2 diabetes included in each of the 3 levels of risk for each of the 8 parameters.

Publications regarding type 2 diabetes usually use the target of $HbA_{1c} \geq 7\%$ (53 mmol/mol) to identify patients who are poorly controlled. In this study, we ascertained whether according to the individualized targets calculated using the new algorithm, the proportion of poorly controlled patients would be different.

2 | MATERIAL AND METHODS

2.1 | Study conduct

This project was conducted by the Spanish Society of Family Medicine Diabetes Expert Group. All members of the diabetes working group were contacted by mail and invited to participate in the study. In the Spanish health system, every general practitioner (GP) is in charge of about 1500 patients with approximately 150 patients with type 2 diabetes listed. A random sample of patients was selected from the patient list of each participating GP.

Each physician reviewed the medical record of the patients with diabetes and collected relevant clinical and demographic data. The results were sent to the scientific committee who, according to the 8 parameters, calculated the individualized glycaemic target for each patient and analysed the results. Variables obtained from the patient files included the following: age, sex, duration of diabetes, co-morbidities, diabetes complications, glucose-lowering agents used, and last measured HbA_{1c}. Therapeutic adherence was registered according to physician opinion. Copayment for drugs was noted as well. In Spain, there are different formulas of copayment for subsidization of medications by the public health system according to the level of income of the patient and if he or she is working or retired. Copayment ranges from no payment for retired and low-income patients to 60% for working patients with high incomes. Finally, the characteristics of the participating physicians (age, years in practice, and number of patients in his or her list) were registered.

The project was approved by the Ethics Committee from *Hospital Universitario San Juan de Alicante* (Spain) on February 2016.

2.1.1 | Calculating the individualized glycaemic targets

According to Cahn et al,[6] 8 parameters are required to calculate the individualized target HbA_{1c}: risk of hypoglycaemia from treatment, life expectancy, important co-morbidities, macrovascular and advanced microvascular complications, cognitive function, adherence and motivation, disease duration, and resources and support system. For each parameter, a score was given to each individual patient according to the level of risk: 1 for low risk, 2 for moderate risk, and 3 for high risk. On the basis of these simple and easy to obtain parameters, we used the algorithm published by Cahn et al[6] to calculate the suggested HbA_{1c} target for each patient. The formula for the Individualized Glycaemic Target = 6.5 + (sum of products – 100)/100 was used according to the authors. The coefficients for each parameter, respectively, for low, moderate, and high risk, were as follows: risk of hypoglycaemia from treatment (22.5, 45, and 67.5), life expectancy (20.5, 41, and 61.5), important co-morbidities (13.3, 26.6, and 39.9), macrovascular and advanced microvascular complications (11.9, 23.8, and 35.7), cognitive function (10.3, 20.6, and 30.9), adherence and motivation (7.9, 15.8, and 23.7), disease duration (7.6, 15.2, and 22.8), and resources and support system (5.9, 11.8, and 17.7).

2.1.2 | Statistical analyses

Characteristics of patients with good control vs poor control per individualized glycaemic targets were compared. For continuous variables, the P values were based on t-student test or analysis of variance. For categorical variables, distributions of baseline characteristics were compared by chi-squared test. For multivariate analysis, multiple logistic regression model was used to identify patient and physician-related factors predicting poor glycaemic control. The agreement between the 2 criteria for good HbA_{1c} control (uniform vs individualized target) was calculated using the Kappa index.

The statistical software package SAS (version 9.4, SAS Institute, Cary, North Carolina) was used for all analyses, with a 2-sided P value < .05 taken to indicate statistical significance.

3 | RESULTS

Forty GPs from the Spanish Society of Family Medicine Diabetes Expert Group included patients from their practices in this study (80% from urban areas).

A total of 408 patients were included from all regions of Spain. Their clinical and demographic characteristics are listed in Table 1. The mean ± SD age was 68.9 ± 11.3 years, 48.6% were females and the mean HbA_{1c} was 6.97 ± 1.2% (53 mmol/mol), 14.9% of the patient had an HbA_{1c} > 8% (64 mmol/mol), 24.5% had diabetes duration of less than 5 years, and 64.0% had no evidence of any macrovascular or microvascular complications. The proportion of patients suffering from 12 different co-morbidities were as follows: dyslipidaemia (70.8%), hypertension (69.1%), artrosis (44.6%), anxiety (28.4%), depression (18.1%), dyspepsia (22.5%), chronic obstructive pulmonary disease (12.5%), thyroid dysfunction (11.0%), hepatopathy (10.2%), cancer (7.8%), atrial fibrillation (7.4%), and heart failure (6.9%). Regarding diabetes treatment, approximately 10% of patients were only on medical nutrition therapy without glucose-lowering agents, nearly

TABLE 1 Characteristics of patients associated with good vs poor glycaemic control as determined by individualized HbA$_{1c}$ targets

	All Patients	Good Control (n = 247)	Poor Control (n = 161)	P
Patients				
Age, y; mean ± SD	68.9 ± 11.3	69.5 ± 11.8	67.5 ± 10.8	.10
HbA$_{1c}$, %; mean ± SD	6.9 ± 1.2	6.2 ± 0.5	8.1 ± 1.2	<.01
Gender (female), %	46.8	49.5	44.1	.31
Number of glucose-lowering agents; mean ± SD	1.6 ± 0.9	1.3 ± 0.8	2.1 ± 0.8	<.01
Number of co-morbidities; mean ± SD	3.6 ± 3.1	3.9 ± 3.2	3.3 ± 2.8	.06
Duration of diabetes, y				
<5	24.5%	29.3%	16.6%	.02
5-20	64.6%	59.9%	71.7%	
>20	10.9%	10.8%	11.7%	
Cognitive impairment, %	11.3	12.9	9.7	.52
Macrovascular complications, %	22.5	26.6	19.3	.26
Microvascular complications, %	22.7	22.1	24.8	.79
Glucose-lowering agents, %				
(n)				
Metformin	77.0	71.6	86.9	.00
Sulfonylureas	13.7	12.6	15.9	.37
Glinides	5.1	4.1	7.6	.14
Pioglitazone	0.7	0.5	1.4	.33
DPP4 inhibitors	31.1	23.0	46.2	.00
SGLT2 inhibitors	6.1	3.6	9.7	.01
GLP1-Ra	2.2	1.4	4.1	.09
Insulin	23.8	18.5	34.5	.00
Poor therapeutic adherence, %	30.5	21.6	44.1	<.01
Physicians				
Age, y; mean ± SD	49.5 ± 8.7	49.2 ± 8.8	49.8 ± 8.6	.55
Gender (female), %	47.3	47.7	44.8	.58
Years in practice; mean ± SD	13.1 ± 9.3	12.5 ± 8.8	13.6 ± 10.1	.26
Number of patients in the list; mean ± SD	1538.4 ± 206.5	1534 ± 215.0	1532 ± 195.1	.94

Abbreviation: SD, Standard deviation.

40% were treated with only 1 glucose-lowering agent, 33% were treated with 2, and 17% were treated with 3 or more drugs. Metformin was used by nearly 80% of the patients. The characteristics of the participating physicians are listed in Table 1. Their mean age was 49.5 ± 8.7 years, 47.3% female, with an average of 13.1 ± 9.3 years in the practice, and a list of approximately 1500 (1538.4 ± 206.5) patients in their practice.

The proportion of patients included in each risk category is shown in Figure 1. The variables that had the greatest impact on calculating the individualized glycaemic target were as follows: "comorbidities" (present in 71% of patients), "risk of hypoglycaemia from treatment" (high in 24% of the patients), and "diabetes duration" (>20 y in 11%).

Despite individualized target calculation,[6] the recommended HbA$_{1c}$ target remained <7% (53 mmol/mol) in 53.9% of patients;
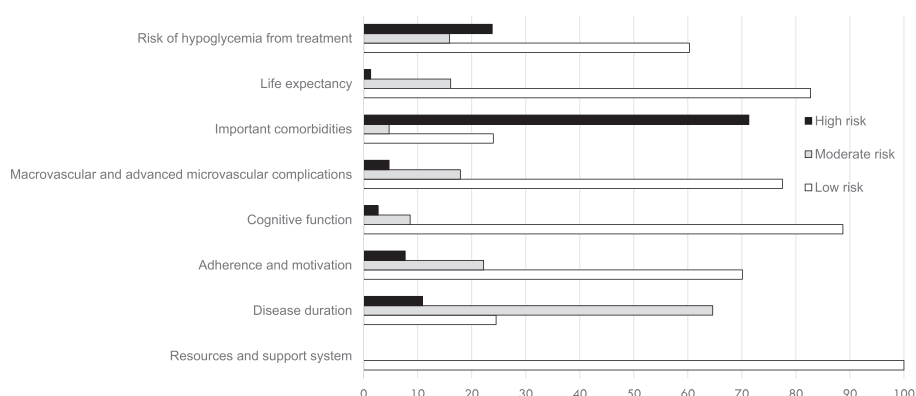
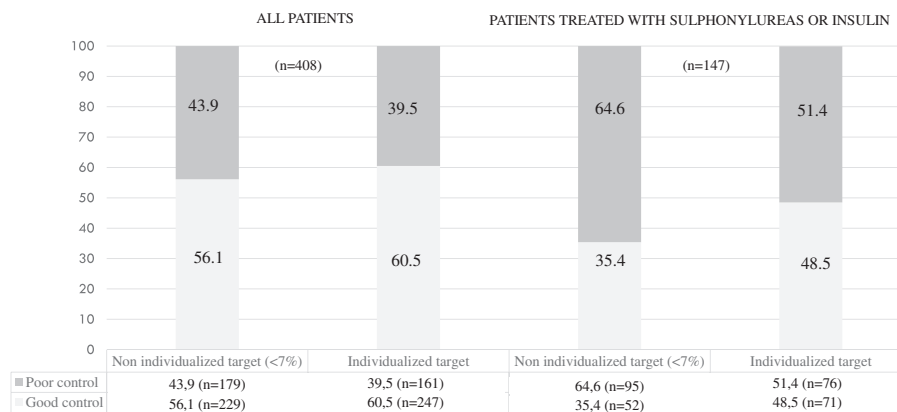**FIGURE 1** Distribution of patients with type 2 diabetes by risk category

FIGURE 2 Proportion of patients with type 2 diabetes with good control according to nonindividualized target (HbA$_{1c}$ < 7.0%) vs individualized target

65.6% of them presented good control. In 39.5% of patients, the individualized target was established between 7% and 7.5% (53-58 mmol/mol); 61.7% of them presented good control. In 6.1% of patients, the individualized target was between 7.5% and 8% (58-64 mmol/mol); 68.2% of them presented good control. And only 0.6% of patients had an individualized target of 8% or higher, and all of them presented good control (Figure S1). The scale does not dictate a target of lower than 6.5% (48 mmol/mol) for any patient. No differences were found regarding gender or ethnicity.

Overall, 60.5% of patients had good glycaemic control, and 39.5% had poor control, according to the individualized calculation of HbA$_{1c}$ targets (Figure 2). The characteristics of the patients and the participant physicians associated with poor glycaemic control based on individualized HbA$_{1c}$ targets are shown in Table 1. In multiple logistic regression analysis, the higher number of antidiabetic drugs and poor adherence to the treatment were significant predictors of poor glycaemic control. Additional antidiabetic drugs increased—odds ratio, 2.3 (95% confidence interval [CI], 1.7-3.2)—the probability of poor glycaemic control, with similar effect of poor adherence to treatment—odds ratio, 2.3 (95% CI, 1.5-3.5) (Table 3).

Assessing the patients' glycaemic control per nonindividualized target (<7%) showed that 229 (56.1%) patients were well controlled. A similar proportion of patients were at target when individualized targets were calculated (247, 60.5%), P = .20 (Figure 2). From those 229 patients with good control (<7%), 97.4% of them also had good control based on individualized target calculation, and from those with poor control (≥7%), 87.2% also had poor control based on individualized target calculation. The Kappa index was 0.86 (95% CI, 0.82-0.90).

Among patients with good control defined as HbA$_{1c}$ < 7% (53 mmol/mol), 2.6% were insufficiently controlled according to

individualized targets as their target was calculated to be lower. On the other hand, among patients with poor control defined as HbA$_{1c}$ ≥ 7% (53 mmol/mol), 12.8% were well controlled according to individualized targets as tight glycaemic control was not indicated in their case and a glycaemic target of ≥7% (53 mmol/mol) appeared to be appropriate. Overall, the use of individualized glycaemic targets led to reclassification of 29 of 408 (7.1%) patients.

Since the algorithm carries the greatest significance in those treated with glucose-lowering agents potentially causing hypoglycaemia, we analysed the subgroup of patients using sulfo-nylureas and/or insulin (N = 147). Per the uniform target of HbA$_{1c}$ < 7% (53 mmol/mol), 52 of 147 (35.4%) patients were considered well controlled; however, assessing glycaemic control per the individualized target revealed that 71 of 147 (48.5%) patients were considered well controlled (P < .01) (Table 2). Among the patients considered poorly controlled per the uniform target of HbA$_{1c}$ < 7% (53 mmol/mol), 20% were considered well controlled per the individualized target. In total, 19 of 147 (13.1%) patients were reclassified when assessing their level of glycaemic control per the individualized targets (Table 3). Prospective studies are needed to find out whether individualized treatment algorithms will result in lower cardiovascular morbidity and mortality in patients with type 2 diabetes.

4 | DISCUSSION

This is the first study applying the recently published HbA$_{1c}$ algorithm for calculation of an individualized glycaemic target in a real-life clinical setting in a random sample of patients. Applying individualized vs nonindividualized targets resulted in a similar proportion of patients

TABLE 2 Concordance of good vs poor glycaemic control as assessed by a HbA$_{1c}$ target of <7.0% vs individualized target in patients using sulfonylureas and/or insulin

	Good Control (Individualized HbA$_{1c}$ Target)	Poor Control (Individualized HbA$_{1c}$ Target)	Total
Good control (HbA$_{1c}$ < 7%)	52 (100.0%)	0 (0.0%)	52 (100.0)
Poor control (HbA$_{1c}$ ≥ 7%)	19 (20.2%)	76 (79.7%)	95 (100.0)
Total	71	76	147

Kappa = 0.733 (95% confidence interval, 0.623-0.842).

TABLE 3 Multiple logistic regression analysis: predictors of poor glycaemic control based on individualized HbA$_{1c}$

	B	Standard Error	Wald	Sig	Odds Ratio	95% CI	
						Low	High
PT age	0.018	0.014	1.781	0.182	1.018	0.992	1.046
PT gender (female)	0.249	0.257	.939	0.333	1.283	0.775	2.125
PT copayment	0.614	0.327	3.526	0.060	1.848	0.974	3.508
PT number of glucose-lowering agents	0.847	0.162	27.415	<0.001	2.332	1.699	3.202
PT therapeutic adherence	0.829	0.211	15.418	<0.001	2.292	1.515	3.467
PT DM duration	0.070	0.246	.082	0.775	1.073	0.662	1.739
PT on insulin	0.071	0.317	.050	0.823	1.073	0.576	1.999
PH age	−0.004	0.021	.040	0.842	.996	0.955	1.038
PH gender (female)	−0.189	0.262	.519	0.471	.828	0.495	1.385
PH years in practice	0.032	0.019	2.853	0.091	1.033	0.995	1.072
PH number of patients	−0.001	0.001	.999	0.318	.999	0.998	1.001
Constant	−4.34	1.890	5.279	0.022	0.013		

Abbreviations: *B*, coefficient; CI, confidence interval; DM, diabetes mellitus; Sig, statistical significance; PH, physician; PT, patient.

with good glycaemic control, yet 12.8% of the patients considered poorly controlled, due to an HbA$_{1c}$ ≥ 7%, were sufficiently well controlled per individualized target, and 2.6% of the patients considered well controlled, due to HbA$_{1c}$ < 7.0, were poorly controlled per the individualized target. Focusing on the subgroup of insulin and/or sulfonylurea users yielded a significantly higher proportion of well-controlled patients when using individualized vs uniform glycaemic targets.

It is important to note that not all variables have the same impact on modification of the target in clinical practice. The results show that 2 of 8 parameters included in the algorithm "comorbidities" and "risk of hypoglycaemia from treatment" are the most frequent issues that modify the HbA$_{1c}$ target when individualized targets are calculated. On the other hand, "life expectancy" and "cognitive function" are characteristics that have less influence on individualized targets in this relatively healthy type 2 diabetic population. Only 1.3% of the patients were categorized by the GPs as high risk with respect to life expectancy, and only 2.7% of patients were categorized as high risk with respect to cognitive impairment, so these variables had less of an impact in our population on the modification of the HbA$_{1c}$ targets.

We assessed the extent to which individualized targets modified the proportion of patients with good glycaemic control. In our study, the proportion of patients with good glycaemic control was similar when uniform vs individualized targets were applied (56.1% vs 60.5%; P = .20). This may be attributed to the relatively good glycaemic control in our population, only 14.9% with an HbA$_{1c}$ > 8% (64 mmol/mol). Comparably, in a recent study conducted in Spain by Mata-Cases et al,[7] which included approximately 300 000 patients, the proportion of patients with HbA$_{1c}$ ≤ 7% (53 mmol/mol) was quite similar to ours and ranged between 52.2% and 55.6% over the years, yet the proportion of patients with HbA$_{1c}$ > 8% was higher (20.4-22.4% over the years). Similarly, in a recent survey in Israel, 13% of diabetic patients[8] had HbA$_{1c}$ > 9%. Probably, repeating this evaluation in a population with poorer control may yield a larger difference in the proportion of well-controlled patients per individualized vs universal glycaemic targets. The GPs were selected from the Spanish Society of Family Medicine Diabetes Expert Group, and perhaps this was a bias

of better practice than usual. It is also possible that in Spain, primary care doctors are individualizing their patients' glycaemic targets in their usual practice.

Although the agreement between both criteria (individualized vs uniform targets) for glycaemic control was quite good, 7.1% of patients were misclassified once individualized targets vs a uniform target of <7% (53 mmol/mol) were applied.

In the subgroup of patients treated with sulfonylureas and/or insulin, calculation of individualized targets led to reclassification of 13.1% patients, highlighting the greater significance of the algorithm in this population.

Poor glycaemic control is often attributed to therapeutic inertia,[9] defined as the tendency to maintain current treatment strategies despite results demanding escalation.[10] Individualized glycaemic targets are often used as an explanation for lack of treatment intensification—claiming the prevailing HbA$_{1c}$ is high because of the frailty of the particular patient population and not because of clinical inertia. Nevertheless, even when using individualized glycaemic targets, it is clear that clinical therapeutic inertia is still present in diabetes treatment with a similar proportion of patients attaining their individualized or uniform target (Figure 2); yet as discussed this may be slightly different if calculated in populations with higher rates of poorly controlled patients.

In our study, poor glycaemic control was associated with longer duration of diabetes, use of more glucose-lowering agents, treatment with insulin, higher copayment, and poor therapeutic adherence. The characteristics of the participating physicians were not associated with poor HbA$_{1c}$ control. In multivariate analysis (Table 3), only a higher number of glucose-lowering agents and poor adherence according to the physician's opinion were associated with poor glycaemic control. The association of high number of drugs with poor glycaemic control may be explained by the tendency for clinical inertia, as drugs are often added late when the HbA$_{1c}$ level is high and the intensification of treatment may not have been done properly in terms of dosing and timing. A study conducted in Spain[11] showed that in patients on metformin and poor glycaemic control, treatment intensification was decided upon after an average of 2 years of failure to meet target

and the average HbA_{1c} at the time of intensification was 8.01% (64 mmol/mol). It is also possible that multiple drug use reflects a more advanced disease with lower beta-cell reserves, which tends to be more difficult to control. Furthermore, the association of poor therapeutic adherence and inadequate glycaemic control is well documented in the literature,[12,13] although reverse causality is possible—with physicians describing their poorly controlled patients as nonadherent.

This study demonstrates the clinical benefits of calculating individualized glycaemic targets in clinical care. The algorithm is currently available in a free mobile app (HbA_{1c} calculator), yet it requires manual input of the data. It would be of interest to develop within the electronic clinical software a simple automatic algorithm, as proposed by Cahn et al[6] to calculate an individualized HbA_{1c} target for each patient in clinical practice as is now available for assessing cardiovascular risk.

Several limitations to our analysis should be noted. The physicians participating in this clinical exercise are those who have a particular interest in diabetes, and therefore, glycaemic control in this population is somewhat better than in the overall diabetic population as previously discussed. Furthermore, approximately half of the population is treated with no drug therapy or metformin alone—questioning the necessity of defining glycaemic targets in a population who is not of significant risk from therapy. As observed in the subgroup of insulin/sulfonylurea users, the algorithm indeed carries greater significance in this population. Finally, as mentioned in the article by Cahn et al,[6] the purpose of the algorithm is as a decision support tool for the physician, and the final glycaemic target is to be determined by the treating physician on an individual basis. Ascertainment of the glycaemic target per the algorithm alone might not be fully concordant with the physicians' clinical intuition as supported by the algorithm.

In conclusion, co-morbidities and risk of hypoglycaemia from treatment are the most frequent issues that modify the HbA_{1c} target when individualized targets are calculated. In our study population, there was relative concordance of the individualized targets and uniform target of $HbA_{1c} < 7.0\%$, yet 1 of 9 patients considered poorly controlled per $HbA_{1c} < 7.0\%$ is adequately controlled per individualized target. More studies are needed to validate these results in different populations.

AUTHOR CONTRIBUTIONS

F.A.G. researched the data, designed the study, reviewed the article, coordinated the group of investigators, and approved the final version of the article submitted; A.M.C.C., X.C., M.R., and J.M.M. researched the data, designed the study, reviewed the article, and approved the final version of the article submitted; A.C. and I.R. contributed to the discussion, reviewed the article, and approved the final version of the article submitted; D.O.B. designed the study, coordinated the group of investigators, conducted statistical analysis, wrote the draft, reviewed the article, and approved the final version of the article submitted.

F.A.G. and D.O.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

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