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BRIEF REPORT

Glycaemic control in the diabetes and Lifestyle Cohort Twente: A cross-sectional assessment of lifestyle and pharmacological management on Hba1c target achievement

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The majority of patients with type 2 diabetes do not reach target levels of glycated haemoglobin (HbA1c < 7%). We investigated the prevalence of HbA1c-target achievement and opportunities afforded by lifestyle and pharmacological treatment to increase target achievement. We performed cross-sectional analyses of baseline data from the Diabetes and Lifestyle Cohort Twente-1 (DIALECT-1). Patients were divided according to (1) HbA1c <53 and ≥53 mmol/mol (<7%) and (2) non-insulin treatment and tertiles of daily insulin use. We found that 161 (36%) patients achieved the target HbA1c level. Patients with HbA1c ≥53 mmol/mol had a longer duration of diabetes (13 [8-20] vs 9 [4-14] years; $P < .001$) and more frequently were insulin-users (76% vs 41%, $P < .001$). Patients in the highest tertile of insulin use had a higher body mass index than those in the lowest tertile (35.8 ± 5.5 vs 29.8 ± 5.5 kg/m^2; $P < .001$). Achievement of target HbA1c is low in this type 2 diabetes population. High resistance to pharmacological treatment, paralleled with high body mass index, illustrates that increasing insulin sensitivity through lifestyle intervention is the best opportunity to improve HbA1c target achievement in this real-life population.

KEYWORDS

clinical diabetes, insulin therapy, nutrition and diet, oral pharmacological agents

1 | INTRODUCTION

Tight glycaemic control in type 2 diabetes mellitus reduces the risk of microvascular complications and, to a lesser extent, of cardiovascular disease also. Each 1% of mean HbA1c reduction has been associated with a 21% reduction in risk of any diabetes-related complication.[1] In general, a target HbA1c level of <53 mmol/mol (<7%) is optimal, according to diabetes guidelines.[2]

However, a recent meta-analysis demonstrated that HbA1c target achievement is low, with a pooled average of 43% worldwide,[3] both in primary and secondary care settings. The reason for this low target achievement, despite the expanding arsenal of glucose-lowering interventions, remains to be elucidated. Although both lifestyle and pharmacological management contribute to glycaemic control, few studies address both aspects of treatment in relation to HbA1c target achievement.

In this study we aim to (1) investigate the prevalence of ideal HbA1c target achievement in a real-life population of type 2 diabetes patients in secondary health care, and (2) identify opportunities for improving ideal HbA1c target achievement, using an integrated assessment of lifestyle factors and pharmacological treatment.

2 | MATERIALS AND METHODS

This was a cross-sectional study using baseline data from the Diabetes and Lifestyle Cohort Twente-1 (DIALECT-1). DIALECT-1 was

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performed in the outpatient clinic of the Ziekenhuisgroep Twente (ZGT) hospital, Almelo and Hengelo, The Netherlands. The study population and study procedures have been described previously.[4] In brief, 450 patients with type 2 diabetes, aged 18+ years were included and exclusion criteria were renal replacement therapy or inability to understand the concept of informed consent. The ZGT hospital is a secondary health care centre for diabetes treatment. In The Netherlands, criteria for referral from primary to secondary health care are inability to achieve adequate glycaemic control with oral antidiabetic drugs or a standard insulin regimen, macroalbuminuria and/or estimated glomerular filtration rate (eGFR) ≤ 60 mL/min or multiple cardiovascular complications. The study has been approved by local institutional review boards (METC-Twente, NL57219.044.16; METC-Groningen, 1009.68020), is registered in The Netherlands Trial Register (NTR trial code 5855) and was performed according to the Guidelines of Good Clinical Practice and the Declaration of Helsinki.

2.1 | Variables

Sociodemographic characteristics and medical history of participants, as well as current medications, were recorded and anthropometric dimensions were measured using standard procedures. Physical activity was assessed using the previously validated Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH).[5] Diet was assessed using a semi-quantitative validated food-frequency questionnaire (FFQ) that was developed and validated at the Wageningen University, inquiring about intake of 177 items during the last month, taking seasonal variations into account.[6] Both questionnaires were self-administered and completed at home, and subsequently checked for completeness by a trained researcher. Dietary data were converted into daily nutrient intake of macronutrients (ie, carbohydrates, protein, fat) using the Dutch Food Composition Table of 2013. Intake of food groups included in the Dutch Healthy Diet guidelines (DHD) was calculated by summing up daily intake across all food items in that category (Table S1).[7] In addition, specific carbohydrate intake from several different carbohydrate-rich food categories was calculated by summing up carbohydrate content across all food items in that category (Table S2).

Blood was drawn from venipuncture in a non-fasting state, for measurement of HbA1c and other variables relevant to diabetes. HbA1c was measured by the Roche Tina-quant 3rd generation immunoturbidimetric method, standardized according to International Federation of Clinical Chemistry and Laboratory Medicine, on a Clinical Chemistry Analyzer and Immunochemistry Analyzer (COBAS 6000, Roche Diagnostics GmbH, Mannheim, Germany). Data on dietary sodium intake were derived from 24-hour urinary sodium excretion.

2.2 | Targets and definitions

Ideal HbA1c was set as <53 mmol/mol (<7%), according to the European guidelines for management in type 2 diabetes mellitus, which have been adopted for use in The Netherlands. Lifestyle recommendations were maintenance of body mass index (BMI) ≤ 25 kg/m^2, smoking cessation and physical activity (30 minutes of moderate-vigorous exercise) at least 5 days per week.[8] Dietary recommendations were derived from the DHD Guidelines 2015, published by the Health Council of The Netherlands.[7] In brief, recommended intakes were: vegetables, ≥200 g/d; fruits, ≥200 g/d; legumes, ≥1 portion/wk; nuts, ≥ 15 g/d; low-fat dairy, 2 to 3 portions/d; fish, ≥1 portion/wk; tea, ≥3 cups/d; red meat, ≤45 g/d; alcohol, ≤10 g/d; sodium, ≤2.3 g/d; and no hard margarines, cooking fats, processed meat, sweetened beverages or fruit juices. Adherence to these lifestyle guidelines was determined as described previously.[9]

2.3 | Statistics

All statistical analyses were performed using SPSS version 23.0 (IBM, Chicago, Illinois). Normality of data was assessed by visual inspection of frequency histograms. Normally distributed variables were presented as mean ± standard deviation, skewed variables as median (interquartile range) and dichotomous variables as numbers (percentage).

Patients were divided according to HbA1c at ideal target (HbA1c-OIT; <53 mmol/mol; <7%) and HbA1c not at ideal target (HbA1c-NOIT; ≥53 mmol/mol; ≥7%). Differences between groups were tested using students *t*-test (normal distribution), Mann-Whitney U (skewed distribution) and Chi-Square (categorical).

As we found that intensity of blood glucose-lowering treatment was higher in patients with HbA1c-NOIT, we aimed to determine which factors were associated with a higher intensity of treatment. We divided patients into four groups; the first group was comprised of non-insulin users (ie, only non-insulin blood glucose-lowering treatment) and the second, third and fourth groups were based on tertiles of insulin units used per day, as currently no cut-off point to grade intensity of insulin treatment exists. Differences among groups were tested using one-way ANOVA (normal distribution), Kruskal-Wallis (skewed distribution) and Chi-Square.

3 | RESULTS

HbA1c data were available for all of the 450 patients included in DIALECT-1. Baseline characteristics are shown in Table 1. Mean age was 63 ± 9 years, and 58% (n = 261) of the patients were men. The median duration of type 2 diabetes was 11 [7-18] years. Type 2 diabetes-related complications were highly prevalent: 296 (67%) patients had microvascular disease and 160 (36%) had macrovascular disease.

Mean HbA1c in our population was 57 ±12 mmol/mol (7.4% ±3.2%). In total, 161 patients (36%) achieved an HbA1c-OIT, of which 33 patients (7% of total population) achieved an HbA1c < 42 mmol/mol (<6%). Patients with HbA1c-NOIT had a longer median duration of type 2 diabetes than those with HbA1c-OIT (13 [8-20] vs 9 [4-14] years, $P < .001$).

Among the total population, 37% of patients were non-insulin users. In this group, patients with HbA1c-NOIT used more non-insulin blood glucose-lowering drugs per day than patients with HbA1c-OIT (45% vs 18% used 3-4 drugs/d; $P < .001$). The remaining 63% of patients used insulin, and insulin use was substantially higher in those with HbA1c-NOIT (76%) than in those with HbA1c-OIT (41%); ($P < .001$) (Table 1). Although there were no differences in insulin regimens between the ideal HbA1c target groups, the amount of total daily units of insulin was significantly higher in those with HbA1c-NOIT than in those with HbA1c-OIT (86 ± 54 vs 70 ± 42 units/d; $P = .02$).

TABLE 1 Patient characteristics of DIALECT-1 by a breakup of ideal HbA1c target achievement

Variable	*n*	Total population	HbA1c-OIT <53 mmol/mol	HbA1c-NOIT ≥ 53 mmol/mol	*P* value
Number of patients, *n* (%)		*n* = 450	*n* = 161 (36)	*n* = 287 (64)	
Age, y	*450*	63 ± 9	63 ± 9	63 ± 9	.63
Men, *n* (%)	*450*	261 (58)	85 (53)	174 (61)	.13
Diabetes duration, y	*450*	11 [7-18]	9 [4-14]	13 [8-20]	<.001
Body mass index, kg/m^2	*448*	32.9 ± 6.2	33.0 ± 6.8	32.8 ± 5.8	.80
Waist/hip ratio, cm/cm	*441*	1.00 ± 0.09	0.99 ± 0.08	1.01 ± 0.09	.09
Systolic blood pressure, mm Hg	*449*	136 ± 16	135 ± 17	137 ± 16	.25
Diastolic blood pressure, mm Hg	*448*	74 ± 10	74 ± 10	75 ± 9	.53
Heart frequency, beats/min	*444*	74 ± 13	74 ± 14	74 ± 12	.98
Blood pressure on target, *n* (%)	*449*	239 (53)	95 (58)	144 (50)	.11
LDL cholesterol ≤2.5 mmol/L, *n* (%)	*428*	334 (78)	127 (80)	207 (77)	.53
Serum HbA1c, mmol/mol	*450*	57 ± 12	46 ± 5	64 ± 10	<.001
Serum HbA1c, %	*450*	7.4 ± 3.2	6.4 ± 2.6	8.0 ± 3.1	<.001
Glycosuria, g/24 h	*361*	0.5 [0.1-5.5]	0.1 [0.0-0.4]	2.0 [0.2-9.0]	<.001
Co-morbidity					
Microvascular disease, *n* (%)	*444*	296 (67)	104 (65)	192 (68)	.46
Nephropathy, *n* (%)	*446*	189 (42)	77 (48)	112 (39)	.08
eGFR <60, *n* (%)	*450*	104 (23)	49 (30)	55 (19)	.008
Albuminuria, *n* (%)	*445*	136 (31)	48 (30)	88 (31)	.85
Retinopathy, *n* (%)	*447*	108 (25)	26 (16)	84 (30)	.002
Neuropathy, *n* (%)	*450*	162 (36)	57 (35)	105 (37)	.73
Macrovascular disease, *n* (%)	*450*	160 (36)	64 (39)	96 (33)	.22
Coronary artery disease, *n* (%)	*450*	100 (22)	37 (23)	63 (22)	.85
Cerebrovascular disease, *n* (%)	*450*	49 (11)	20 (12)	29 (10)	.48
Peripheral artery disease, *n* (%)	*450*	40 (9)	18 (11)	22 (8)	.23
Pharmacological management					
Metformin, *n* (%)	*450*	333 (74)	120 (74)	213 (74)	.89
Sulfonylureas, *n* (%)	*450*	114 (25)	42 (26)	72 (25)	.87
DPP-4 inhibitors, *n* (%)	*450*	19 (4)	8 (5)	11 (4)	.59
GLP-1 analogues, *n* (%)	*450*	45 (10)	17 (10)	28 (10)	.82
SGLT-2 inhibitors, *n* (%)	*450*	4 (1)	0 (0)	4 (1)	.13
Non-insulin users, *n* (%)	*450*	165 (37)	97 (60)	68 (24)	
Number of used non-insulin agents	*165*				<.001
0, *n* (% of non-insulin users)	*165*	19 (12)	17 (18)	2 (3)	
1, *n* (% of non-insulin users)	*165*	57 (35)	40 (41)	17 (25)	
2, *n* (% of non-insulin users)	*165*	41 (25)	22 (23)	19 (28)	
3, *n* (% of non-insulin users)	*165*	18 (11)	6 (6)	12 (18)	
4, *n* (% of non-insulin users)	*165*	30 (18)	12 (12)	18 (27)	
Insulin users, *n* (%)	*450*	285 (63)	66 (41)	219 (76)	<.001
Basal regimen, *n* (% of insulin users)	*285*	36 (13)	9 (14)	27 (12)	.65
Basal bolus/plus regimen, *n* (% of insulin users)	*285*	160 (56)	39 (59)	121 (55)	
Mixed regimen, *n* (% of insulin users)	*285*	60 (21)	14 (21)	46 (21)	
Bolus only regimen, *n* (% of insulin users)	*285*	29 (10)	4 (6)	25 (11)	
Total daily units of insulin, units/d	*285*	82 ± 52	70 ± 42	86 ± 54	.02
Total daily units of insulin per kg body weight, units/kg	*285*	0.83 ± 0.48	0.73 ± 0.39	0.88 ± 0.50	.04
Dietary intake					
Total energy intake, kcal/d	*439*	1910 ± 644	1845 ± 617	1947 ± 658	.12
Intake of fibers, g/d	*439*	21 ± 7	20 ± 7	21 ± 7	.22
Intake of carbohydrates, g/d	*439*	206 ± 71	200 ± 68	209 ± 72	.20

TABLE 1 (Continued)

Variable	*n*	Total population	HbA1c-OIT <53 mmol/mol	HbA1c-NOIT ≥ 53 mmol/mol	*P* value
Carbohydrate intake from food groups					
Bread, g carbohydrates/d	*439*	59 [42-73]	53 [41-72]	61 [43-75]	.19
Snacks, g carbohydrates/d	*439*	24 [12-37]	21 [9-34]	26 [14-37]	.03
Potatoes, g carbohydrates/d	*439*	20 [12-30]	20 [12-31]	20 [12-30]	.93
Dairy, g carbohydrates/d	*439*	19 [12-29]	19 [11-28]	19 [13-29]	.51
Fruit, g carbohydrates/d	*439*	19 [10-29]	16 [9-27]	21 [11-31]	.12
Rice/pasta/dough, g carbohydrates/d	*439*	8 [4-14]	7 [3-12]	8 [4-15]	.09
Lifestyle guideline adherence					
BMI ≤25 kg/m^2, *n* (%)	*448*	24 (5)	8 (5)	16 (6)	.75
Current smokers, *n* (%)	*450*	75 (17)	31 (19)	44 (15)	.29
Physical activity, *n* (%)	*433*	253 (58)	96 (60)	157 (57)	.53
Vegetable intake, *n* (%)	*440*	31 (7)	11 (7)	20 (7)	.92
Fruit intake, *n* (%)	*440*	122 (28)	44 (28)	78 (28)	.94
Legume intake, *n* (%)	*440*	257 (58)	88 (55)	169 (60)	.27
Nuts intake, *n* (%)	*440*	61 (14)	13 (8)	48 (17)	.008
Fish intake, *n* (%)	*440*	161 (37)	56 (35)	105 (38)	.60
Fats and oils intake, *n* (%)	*440*	286 (65)	112 (70)	174 (62)	.10
Dairy intake, *n* (%)	*440*	88 (20)	29 (18)	59 (21)	.46
Red meat intake, *n* (%)	*440*	54 (12)	20 (13)	34 (12)	.91
Processed meat intake, *n* (%)	*440*	8 (2)	3 (2)	5 (2)	.95
Tea intake, *n* (%)	*440*	36 (8)	17 (11)	19 (7)	.16
Sweet beverages intake, *n* (%)	*440*	150 (34)	54 (34)	96 (34)	.91
Alcohol intake, *n* (%)	*438*	310 (71)	113 (71)	197 (71)	.92
Salt intake, *n* (%)	*443*	53 (12)	30 (19)	23 (8)	.001

Abbreviations: DPP4, Dipeptidylpeptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, Glucagon-like peptide-1, SGLT-2, Sodium-glucose co-transporter-2; HbA1c, glycated haemoglobin; NOIT, not on ideal target; OIT, on ideal target.

In general, adherence to DHD guidelines was low, and was similar, for the most part, between groups (Table 1). Patients with HbA1c-NOIT less often adhered to the guideline concerning dietary salt intake than those with HbA1c-OIT (8% vs 19%; $P = .001$).

When considering the factors associated with higher intensity of blood glucose-lowering treatment (Table 2), we found that HbA1c was higher in each group of higher intensity treatment ($P < .001$); thus, ideal HbA1c target achievement was lower per group ($P < .001$). Body mass index was higher in every higher tertile of daily use of insulin: tertile 1, 29.8 ± 5.5 kg/m^2; tertile 2, 31.9 ± 4.8 kg/m^2; tertile 3, 35.8 ± 5.5 kg/m^2 ($P < .001$). Total carbohydrate intake was higher in insulin users as compared to non-insulin users (207 [168-256] vs 189 [149-234] g/d; $P = .03$), while protein and fat intake were not statistically different between the groups ($P = .09$ and $P = .20$, respectively). Regarding dietary source of carbohydrate, carbohydrate intake from bread, potatoes, dairy and fruit was higher in insulin users than in non-insulin users (Figure S1). Adherence to DHD guidelines was similar, for the most part, among all four groups (data not shown).

4 | DISCUSSION

We studied the prevalence of ideal HbA1c target achievement in a real-world setting of treatment for type 2 diabetes mellitus, and aimed to pinpoint opportunities for improving target achievement. In this secondary care setting, the ideal target of <53 mmol/mol (<7%) was not reached in two-thirds of patients (64%), which is somewhat higher than the reported worldwide pooled-average (57%).[3] The latter report, however, also included less complicated type 2 diabetes mellitus populations. In our population, median diabetes duration was 11 years, and those with HbA1c-NOIT had a longer duration of diabetes than those with HbA1c-OIT (median, 13 vs 8 years). Evaluation of pharmacological treatment showed a high degree of treatment resistance, as patients who did not achieve the target more frequently used insulin (76%), using a quite high average daily dose of insulin (86 units/d). Furthermore, higher daily insulin dosage was paralleled by higher BMI. Therefore, the overall picture in those with HbA1c-NOIT is that of a group using high intensity blood glucose-lowering treatment that is caught in a vicious circle of increased insulin resistance, insulin use and obesity.

Along with treatment resistance, other factors could also play a role in low ideal target achievement. Submaximal pharmacological treatment was present in 57% of HbA1c-NOIT patients, as 24% were not currently using insulin treatment, and 12% and 21%, respectively, were using a basal or mixed insulin regimen. The decision to not initiate a basal bolus/plus insulin regimen in some patients may have been under delibarate consideration, and may be based, for example, on patient preference or the inability to self-monitor blood glucose levels. In addition, treatment adherence should be addressed. Reports have

TABLE 2 Patient characteristics by a breakup of blood glucose-lowering treatment intensity

Variables	No insulin	Insulin tertile 1	Insulin tertile 2	Insulin tertile 3	*P* value
Insulin use, IE min-max	—	7-54	56-90	91-328	
Number of patients, *n* (% of total population)	166 (37)	93 (21)	96 (21)	95 (21)	
Total daily units of insulin, units/d	—	38 [28-44]	70 [62-78]	124 [106-163]	<.001
Total daily units of insulin per kg body weight, units/kg	—	0.41 ± 0.15	0.78 ± 0.16	1.31 ± 0.50	<.001
Age, y	62 ± 9	63 ± 9	64 ± 9	63 ± 8	.25
Men, *n* (%)	93 (56)	56 (60)	47 (49)	65 (68)	.05
Diabetes duration, y	7 [3-12]	11 [7-17]	15 [10-23]	15 [11-20]	<.001
Serum HbA1c, mmol/mol	52 ± 10	59 ± 12	60 ± 11	62 ± 11	<.001
Serum HbA1c, %	6.9 ± 3.1	7.5 ± 3.2	7.6 ± 3.2	7.8 ± 3.2	<.001
HbA1c < 53 mmol/mol, *n* (%)	97 (58)	26 (28)	22 (23)	16 (17)	<.001
Microvascular disease, *n* (%)	90 (55)	61 (67)	67 (70)	78 (83)	<.001
Macrovascular disease, *n* (%)	55 (33)	31 (33)	31 (32)	43 (45)	.17
BMI, kg/m^2	33.5 ± 6.8	29.8 ± 5.5	31.9 ± 4.8	35.8 ± 5.5	<.001
Waist/hip ratio	1.00 ± 0.09	0.98 ± 0.09	0.99 ± 0.08	1.04 ± 0.10	<.001
Adherent to guideline physical activity, *n* (%)	91 (57)	58 (63)	48 (63)	46 (50)	.11
Dietary intake					
Total energy intake, kilocalories/d	1762 [1388-2176]	1859 [1476-2293]	1886 [1520-2318]	1969 [1548-2334]	.12
Urinary sodium excretion, mmol/d	178 ± 78	178 ± 75	177 ± 73	218 ± 87	<.001
Urinary potassium excretion, mmol/d	74 ± 24	80 ± 27	77 ± 26	82 ± 25	.07
Sodium-to-potassium ratio, mmol/mmol	2.51 ± 0.99	2.34 ± 0.90	2.39 ± 0.87	2.77 ± 1.14	.01
Intake of protein, g/d	73 [59-89]	76 [67-91]	77 [65-92]	80 [67-97]	.09
Intake of fat, g/d	71 [49-91]	73 [50-90]	73 [59-93]	78 [60-106]	.20
Intake of carbohydrates, g/d	191 [150-234]	206 [155-243]	208 [169-269]	205 [174-260]	.03

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; IE, insulin units.

found adherence rates of 20%-50% for specific blood glucose-lowering drug classes in type 2 diabetes patients, and low adherence has been associated with decreased HbA1c target achievement, along with worse clinical outcomes.[10]

As a probable explanation for therapy resistance, adherence to lifestyle guidelines was rather low in the studied population. Different meta-analyses have demonstrated that adopting a healthy diet and increasing physical activity can significantly reduce HbA1c and fasting glucose and improve insulin sensitivity.[11] Notably, weight loss can lead to remission in type 2 diabetes, and also in patients who are already using insulin.[12]

The main strengths of this study are the real-world data and the integrated analysis of both lifestyle and pharmacological management. A limitation of this study is a possible reverse causality bias as the result of the cross-sectional setting. In addition, the use of the FFQ to assess diet might lead to underestimation of the intake of unhealthy products in this obese population.[13] Nevertheless, there are currently no better methods for registration of dietary habits in a study of this size.

The question of how ideal HbA1c target achievement can be improved in clinical practice arises. In our opinion, given the apparent resistance to insulin treatment, the aim should be to improve insulin sensitivity, ideally by lifestyle intervention. The high degree of obesity, and the low degree of adherence to DHD guidelines signal important opportunities for lifestyle intervention. Intensifying pharmacological therapy may also improve glycaemic control. Once-daily insulin users could expand to a basal bolus/plus regimen: however, increasing insulin use is associated with weight gain and may fuel the vicious circle of insulin resistance. Moreover, increasing the dose of insulin appears to have limited efficacy; 17% of our population did not achieve the ideal HbA1c target despite 91+ units of insulin/d. In our opinion, pharmacological therapy should be applied to support lifestyle intervention and should aim to facilitate increasing insulin sensitivity. As important options, glucagon-like peptide-1 (GLP-1) analogues and sodium-glucose co-transporter-2 (SGLT-2) inhibitors could be valuable, as they lower HbA1c along with a decrease in body weight and in long-term cardiovascular risk without increased risk of hypoglycaemia.[14,15]

In conclusion, ideal HbA1c target achievement was low in this real-life population of type 2 diabetes patients under treatment in secondary care, apparently because of resistance to pharmacological treatment, paralleled by high BMI. Therefore, treatment should be aimed at increasing insulin sensitivity through lifestyle interventions such as reducing weight, increasing physical activity and adopting a healthy diet.

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Conflict of interest

The authors declare no duality of interest.

Author contributions

SB, GN and GL designed the study. AJ, CG and HB included patients. SSM, SB, GN and GL provided materials. AJ and CG performed the analyses and wrote the manuscript. HB, SSM, SB, GN and GL reviewed the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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