Stratified Patient-Centered Care in Type 2 Diabetes

A cluster-randomized, controlled clinical trial of effectiveness and cost-effectiveness

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OBJECTIVE—Diabetes treatment should be effective and cost-effective. HbA1c-associated complications are costly. Would patient-centered care be more (cost-) effective if it was targeted to patients within specific HbA1c ranges?

RESEARCH DESIGN AND METHODS—This prospective, cluster-randomized, controlled trial involved 13 hospitals (clusters) in the Netherlands and 506 patients with type 2 diabetes randomized to patient-centered (n = 237) or usual care (controls) (n = 269). Primary outcomes were change in HbA1c and quality-adjusted life years (QALYs); costs and incremental costs (USD) after 1 year were secondary outcomes. We applied nonparametric bootstrapping and probabilistic modeling over a lifetime using a validated Dutch model. The baseline HbA1c strata were <7.0% (53 mmol/mol), 7.0–8.5%, and >8.5% (69 mmol/mol).

RESULTS—Patient-centered care was most effective and cost-effective in those with baseline HbA1c >8.5% (69 mmol/mol). After 1 year, the HbA1c reduction was 0.83% (95% CI 0.81–0.84%) (6.7 mmol/mol [6.5–6.8]), and the incremental cost-effectiveness ratio (ICER) was 261 USD (235–288) per QALY. Over a lifetime, 0.54 QALYs (0.30–0.78) were gained at a cost of 3,482 USD (2,706–4,258). ICER 6,443 USD/QALY (3,199–9,686). For baseline HbA1c 7.0–8.5% (53–69 mmol/mol), 0.24 QALY (0.07–0.41) was gained at a cost of 4,731 USD (4,259–5,205). ICER 20,086 USD (5,979–34,193). Care was not cost-effective for patients at a baseline HbA1c <7.0% (53 mmol/mol).

CONCLUSIONS—Patient-centered care is more valuable when targeted to patients with HbA1c >8.5% (69 mmol/mol), confirming clinical intuition. The findings support treatment in those with baseline HbA1c 7.0–8.5% (53–69 mmol/mol) and demonstrate little to no benefit among those with HbA1c <7% (53 mmol/mol). Further studies should assess different HbA1c strata and additional risk profiles to account for heterogeneity among patients.

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Type 2 diabetes causes an enormous economic burden in almost every country. Diabetes treatment must be both effective and efficient (1–7). In 2011, diabetes affected at least 366 million people or 5% of the world’s population (8% of adults) and was responsible for 4.6 million deaths (8). The prevalence of diabetes is expected to increase to 552 million in 2030 (8). In 2011, diabetes care consumed at least 465 billion USD, accounting for 11% of health care expenditures in adults 20–79 years of age (8). The main cause of the high-cost burden of diabetes is its acute and chronic complications, leading to a 3–13-fold increase in costs per patient (9–14). The occurrence of complications is related to nonmodifiable risk factors such as age, sex, and socioeconomic status. It is also related to modifiable risk factors, such as BMI and waist circumference, as well as risk factors not directly related to diabetes, such as comorbidities including depression. HbA1c is widely monitored as a measure of the risk of complications and as a target for intervention. HbA1c may also be important in defining a more comprehensive risk-based approach to diabetes management.

We have previously explored patient-centered care as a treatment strategy for type 2 diabetes (15–17). Earlier, we conducted a cluster-randomized, controlled clinical trial that compared patient-centered care versus professional-directed and usual care (control) in 13 hospitals (clusters). Patient-centered care had very acceptable incremental cost-effectiveness ratios (ICERs) as compared with professional-directed and usual care. These findings stimulated additional studies of self-management promotion, which is presently regarded as an essential and potentially very cost-effective approach to diabetes management (18–20).

Unfortunately, most, if not all, studies focus on the average patient, whereas individual characteristics relate to the risk of developing complications (21–23), the effectiveness of treatment (23), and health care costs (24–26). More effective and efficient diabetes care might be achieved by focusing patient-centered strategies on patients with specific risk profiles. Such approaches have infrequently been described (27,28).

Therefore, we analyzed data from our trial using individual patient data to compare patient-centered with usual care. We stratified patients by baseline HbA1c and measured HbA1c and costs at 1 year, and quality-adjusted life years (QALYs) and health care costs over a lifetime. We tested the hypothesis that a policy of patient-centered care, provided to patients...
in higher baseline HbA1c strata, would result in significantly better outcomes and more efficient health care.

**RESEARCH DESIGN AND METHODS**

**Population and intervention (see CONSORT flow diagram online)**

We conducted a prospective cluster-randomized trial, aiming at 18 hospitals. Four did not participate and one dropped out for financial reasons. Eligible hospitals were situated across the Netherlands and met predefined eligibility criteria in terms of numbers of beds and diabetes specialist nurses. The 13 hospitals were representative of the 120 general hospitals in the Netherlands and delivered ambulatory secondary care. There was no systematic contamination due to geographical differences. The characteristics of the 13 hospitals that participated and the 5 that did not did not differ substantially. There was a small difference in mean HbA1c (SD) between participating and nonparticipating hospitals (7.8 [1.2] vs. 8.0 [1.4], respectively) (Table 1). In the 13 participating hospitals, internists recruited the first 150 patients with type 1 and type 2 diabetes who attended a diabetes clinic, excluding patients who were pregnant or had a poor life expectancy due to other diseases. Enrollment took place between November 1999 and March 2000. Exclusion criteria included participation in another study or being an academic hospital as we sought to study real-life day-to-day clinical care using a low-impact observational approach. After several pilot studies and preintervention baseline patient measurements, each hospital was randomized (without restrictions) to one of three intervention arms, allocating patients with type 2 diabetes into patient-centered, professional-directed, and usual care arms (see CONSORT flow diagram in Supplementary Data online). Allocation was performed by a noninvolved person, a so-called third party, outside the research group, and allocation results were concealed from the investigators until the start of the intervention. The allocation ratio was 4:4:5. Internists and patients allocated to the intervention group were aware of the allocated arm. The unit of randomization equaled the unit of analysis and was depicted as a continuous (the percentage of people benefiting) rather than as a dichotomous (success or failure) outcome. For practical reasons, and as the outcome was nonsubjective, the study was not blinded. The study design was clustered since the intervention strategy could only be implemented by a provider team with a group of patients in a single hospital outpatient setting. Without clustering by hospital, serious contamination at the hospital, patient, and provider level would have taken place. Ex ante, we made no modifications to the trial design or protocol in response to changing circumstances or allocation results.

This article compares two trial arms (see CONSORT flow diagram online) of randomly assigned clusters, the patient-centered arm with n = 240 patients (n = 237 with available HbA1c data at baseline) and the usual care arm with 276 patients (n = 269 with available HbA1c data at baseline). Both subgroups are comparable with respect to baseline patient characteristics (Table 1). In the patient-centered care clusters, patients were not only seen by their internal medicine doctors and diabetes team as in usual care but additionally received detailed diabetes passports based on national guidelines that aim to educate and record results of medical examinations in order to promote shared disease management. Educational meetings for patients were organized in all of the hospitals where the diabetes passports were introduced. Physicians, diabetes specialist nurses, and dietitians attended these meetings with an opinion leader and received personal feedback with benchmarks on baseline data, adherence to key guidelines, and the use of the diabetes passports. Barriers and facilitators were discussed. Internists received personal feedback on clinical performance after 6 months as well as on the use of the diabetes passports. Leaflets and waiting room posters were also distributed. Usual care consisted of visits every 3 months to a specialized nurse and/or internist according to national evidence-based guidelines (CBO Banda Heerveen 1998, ISBN 90-6910-217-X). The standard protocol was rechecked, reexplained, re-emphasized, and followed up in the hospitals involved.

Using individual patient data, we stratified all patients into three groups according to baseline HbA1c (=7% [53 mmol/mol], 7–8.5%, >8.5% [69 mmol/mol]) (Table 1) and examined the effectiveness and cost-effectiveness of patient-centered care in each stratum. The analyses described in this article were not part of the original analyses of the cluster randomized control trial and were therefore performed as secondary analyses.

**Health effects (HbA1c), costs, and cost-effectiveness over 1 year**

The end points regarding the impact of stratification over 1 year were the effectiveness of HbA1c reduction, costs, and ICERs. The latter were obtained from nonparametric bootstrapping and estimated mean (95% CI). Each of these simulations used
| Table 1—Baseline characteristics |
|----------------------------------|
|                                | Randomized hospitals | Excluded hospitals | Usual care | Patient-centered care | Total population | Population HbA1c at baseline |
|                                | n = 13 (1,465 patients) | n = 5 (450 patients) | n = 276 patients | n = 240 patients | n = 506 | n = 99 | n = 244 | n = 163 |
| **Women (%)**                  | 53                    | 54                    | 54.1                  | 54.1                  | 55                    | 45                    | 59                    | 55                    |
| **Age ± SD, years**            | 58 ± 16               | 59 ± 16               | 65.4 ± 10.4           | 64.0 ± 11.0           | 65 ± 11               | 65 ± 11               | 66 ± 11               | 64 ± 10               |
| **Mean years since diagnosis ± SD** | 13.4 ± 10.2          | 12.5 ± 9.7            | 14.6 ± 10.3           | 12.6 ± 11.5           |             |             |             |             |
| **Type 1 diabetes, %**         | 31                    | 27                    |             |             |             |             |             |             |
| **Duration of diabetes, median (IQR), years** | 11 (6–17) | 7.5 (3–15) | 11 (6–17) | 12 (8–17) |             |             |             |             |
| **Medication, n (%)**          |                       |                       |                       |                       |             |             |             |             |
| Tablets only                   | 52 (10)               | 17 (17)               | 22 (9)                | 12 (7)                |             |             |             |             |
| Insulin only or in addition to tablets | 432 (84) | 77 (78) | 209 (86) | 138 (85) |             |             |             |             |
| Insulin                        | 361 (70)              | 69 (70)               | 168 (69)              | 119 (73)              |             |             |             |             |
| Tablets and insulin            | 71 (14)               | 8 (8)                 | 41 (17)               | 19 (12)               |             |             |             |             |
| **Mean HbA1c ± SD, % mmol/mol**| 7.8 ± 1.2             | 8.0 ± 1.4             | 7.9 ± 1.1             | 8.1 ± 1.2             | 8.1 ± 1.3 | 6.5 ± 0.4 | 7.7 ± 0.4 | 9.5 ± 0.9 |
| Mean total cholesterol ± SD, mmol/L | 62 (11) | 64 (13) | 63 (10) | 65 (11) | 65 (12) | 48 (2) | 61 (2) | 80 (8) |
| Mean weight ± SD, kg            | 84 ± 24               | 83 ± 16               | 85 ± 20               | 84 ± 15               |             |             |             |             |
| Mean BMI ± SD, kg/m²            | 30.0 ± 5.5            | 30.3 ± 5.0            | 30 ± 5                | 29 ± 5                | 30 ± 6     | 31 ± 5     |             |             |
| Mean systolic blood pressure ± SD, mmHg | 145 ± 22 | 146 ± 23 | 150 ± 21 | 148 ± 23 |             |             |             |             |
| Mean diastolic blood pressure ± SD, mmHg | 80 ± 11 | 80 ± 11 | 80 ± 11 | 81 ± 11 |             |             |             |             |
| **Diabetes control 1 year trial data** |             |             |             |             |             |             |             |             |
| **Effectiveness**              |                       |                       |                       |                       |             |             |             |             |
| HbA1c, %                       | 8.1 ± 1.3             | 7.8 ± 1.2             |                       |                       |             |             |             |             |
| HbA1c, mmol/mol                | 6.5 (12)              | 6.2 (11)              |                       |                       |             |             |             |             |
| Percentage of patients (%)     |                       |                       |                       |                       |             |             |             |             |
| HbA1c<7.0 (33), 7–8.5 (33–69), >8.5 (69) | 16/54/30 | 24/56/20 |             |             |             |             |             |             |
| **Costs**                      |                       |                       |                       |                       |             |             |             |             |
| Percentage of patients taking insulin | 71 | 79 |             |             |             |             |             |             |
| Mean costs of glucose control (USD) | 1,880 | 2,627 |             |             |             |             |             |             |

The first two columns (randomized and excluded hospitals) have been modified after Table 1 published in Dijkstra et al. Patients and nurses determine variation in adherence to guidelines at Dutch hospitals more than internists or settings. Diabetes Med 2004;21:586–591. The second two columns (usual and patient-centered care) have been modified after Table 1 published in Dijkstra et al. Patient-centered and professional-directed implementation strategies for diabetes guidelines: a cluster-randomized trial-based cost-effectiveness analysis. Diabetes Med 2005;23:164–170.
1,000 bootstrap samples drawn from the original dataset containing the individual patient records. Direct costs per patient were estimated and standardized by multiplying each resource use component by the unit cost and summing the results at baseline and after 1 year for the main cost drivers: costs of medication (unit costs: insulin, −497 USD; tablets, −223 USD), costs of glucose monitoring (236 USD for glucose testing once every 6 weeks), and costs of implementation strategies (3.7 USD per patient) (29).

**Health gain, medical costs, and cost-effectiveness over a lifetime**

The primary end points with respect to efficacy over a lifetime were effectiveness, QALYs (assessing the long-term complications and the excess cardiovascular morbidity and mortality associated with diabetes), as well as costs, based on the estimated events and prevalence of complications. These were estimated by extrapolating and bootstrapping individual patient data in a probabilistic cost-effectiveness analysis with 10,000 iterations using a per intervention arm validated probabilistic Markov diabetes model (10,30–33). Progression of diabetes complications was based on the formula $\beta^{HbA_1c/10}$ (10,31,34). We adjusted for the natural increase in $HbA_{1c}$ over time, ageing of patients, and the age-related increase in complication risk, accounting for uncertainties by including distributions in values of input variables, including $HbA_{1c}$ at the end of the trial and mortality risk (10,31). We only discounted costs (3%) and did not discount QALYs (32,33). Costs and health outcomes of the probabilistic analyses are presented as point estimates with 95% CIs.

**Statistical analysis**

The primary and secondary outcomes by $HbA_{1c}$ strata were compared using ANOVA for continuous normally distributed variables (mean and SD, such as $HbA_{1c}$ and age), the Kruskal-Wallis test for continuous nonnormally distributed variables (median or interquartile range), like duration of diabetes, as well as the $\chi^2$ test for categorical variables (numbers, sex, etc.). All tests were two tailed, and the limit of statistical significance was defined as $P < 0.05$. An intention-to-treat analysis was performed in this study. We used SPSS version 11.0 (SPSS Inc., Chicago, IL) and Excel version 9.0 (Microsoft, Seattle, WA).

**RESULTS**

Participant flow, for each arm and for each stratum is provided in the CONSORT 2010 flow diagram online. The trial was completed after 1 year of follow-up as planned. There was no reason to stop or end prematurely. Baseline characteristics of the participating and nonparticipating hospitals were similar as were the baseline characteristics of subjects in the two arms, patient-centered and usual care, apart from $HbA_{1c}$ (Table 1). Baseline characteristics of subjects in the three strata were also comparable, apart from longer duration of diabetes and more insulin use in the highest $HbA_{1c}$ stratum (Table 1).

A summary of the continuous outcomes in each trial arm according to stratum ($HbA_{1c}$ reduction, QALYs, and costs) as well as the effect size representing their contrast (differences between patient-centered and usual care and the ICERs) and their 95% CIs are presented in Table 2.

**Health effects ($HbA_{1c}$), costs, and cost-effectiveness at 1 year**

Change and distribution of $HbA_{1c}$ are depicted in Fig. 1. Over 1 year, the ICER for patient-centered care was highest in the highest $HbA_{1c}$ stratum (Table 2). In general,

### Table 2—$HbA_{1c}$ reduction and extra costs for patient-centered and usual care after the 1st year, and QALYs and extra costs over a lifetime

| Effect $HbA_{1c}$ reduction (mean [95% CI]) | Stratified according to $HbA_{1c}$ at baseline |  |
|-------------------------------------------|---------------------------------------------|---|
|                                          | $<7$ (53 mmol/mol)                          | $7–8.5$ (53–69 mmol/mol) | $>8.5$ (69 mmol/mol) |
| Usual care (UC), % mmol/mol               | −0.42 (0.43 to −0.42)                      | −0.31 (−0.31 to −0.30) | 0.24 (0.23–0.25) |
| Patient-centered guideline-based care (PC), % mmol/mol | −0.22 (0.23 to −0.22) | −1.0 (−1.0 to −9) | 0.17 (1.06–1.08) |
| Difference between PC and UC, % mmol/mol | 0.08 (0.07–0.09)                          | 0.49 (0.48–0.49)       | 0.83 (0.81–0.84) |
| Costs                                     |                                                                 |
| Usual care (UC)                           | 115 (112–117)                              | −4 (−6 to −2)           | −80 (−83 to −77) |
| Patient-centered care (PC)               | 14 (11–17)                                 | 4 (1–6)                 | 119 (116–121) |
| Difference between PC and UC              | −101 (−105 to −97)                         | 9 (4–12)                | 199 (194–202) |
| ICER (USD/$HbA_{1c}$ %)                   |                                                                 |
| Patient-centered care over usual care     | −1.262 (−2.022 to 4.862)                   | 18 (10–27)              | 261 (235–288) |
| Effect QALY not discounted (mean [95% CI]*) |                                                                 |
| Usual care (UC)                           | 10.61 (8.90–12.32)                        | 10.41 (9.33–11.48)     | 10.13 (8.71–11.55) |
| Patient-centered care (PC)               | 10.36 (8.34–12.38)                        | 10.64 (9.39–11.89)     | 10.67 (9.30–12.04) |
| Difference between PC and UC              | −0.24 (−0.66 to 0.18)                     | 0.24 (0.07–0.41)       | 0.54 (0.30–0.78) |
| Costs discounted at 3% (USD)             |                                                                 |
| Usual secondary care (UC)                 | 21,114 (17,183–25,044)                    | 21,511 (18,900–24,122) | 23,290 (19,013–27,567) |
| Patient-centered care (PC)               | 25,782 (19,345–32,219)                    | 26,243 (22,236–30,250) | 26,772 (22,209–31,334) |
| Difference between PC and UC              | 4,688 (3,504–5,832)                       | 4,731 (4,259–5,205)    | 3,482 (2,706–4,258) |
| ICER (USD/QALY)                           |                                                                 |
| Patient-centered care over usual care     | Indecisive                                 | 20,086 (5,979–34,193)  | 6,443 (3,199–9,686) |

*A minus sign denotes an increase in $HbA_{1c}$ to allow a reduction being positive in the cost-effectiveness plane.*
the ICERs were quite low. Bootstrapping the results of the individual patients and plotting the gain in a cost-effectiveness plane confirmed this (Fig. 2). The scatter plots at lower baseline HbA1c were in the two lower quadrants and with higher HbA1c at baseline in the upper right quadrant. Hence, for the highest stratum (baseline HbA1c > 8.5 [69 mmol/mol]), patient-centered care showed a reduction in HbA1c at higher costs (dots above the x-axis). For patients with baseline HbA1c = 7–8.5% (53–69 mmol/mol), patient-centered care showed an HbA1c reduction and was cost saving in 45% of cases. For patients with a baseline HbA1c < 7% (53 mmol/mol), the health effects were uncertain as points were divided over the left and right sides of the y-axis. With 64% of the points falling below the x-axis, there is a reasonable chance that patient-centered care would be dominant or cheaper than usual care.

**Lifetime extrapolation of costs and effects**

The difference in total lifetime QALYs between patient-centered care and usual care varied according to the baseline HbA1c stratum (Table 2), and the difference was positively associated with HbA1c. The gain achievable from patient-centered care was greatest in patients with an HbA1c > 8.5% (0.54) (69 mmol/mol) (0.36) and lowest in patients with an HbA1c < 7% (53 mmol/mol). In both arms, costs were higher, the higher the baseline HbA1c, and the difference was lowest in the highest stratum. Hence, the ICER of patient-centered over usual care was most favorable in patients with HbA1c > 8.5% (69 mmol/mol) (6,443 USD/QALY). The higher cost-effectiveness ratio of 20,086 USD/QALY measured in the second stratum (7 < HbA1c < 8.5 [53–69 mmol/mol]) was below prevailing thresholds used to decide whether or not an intervention is cost-effective (e.g., 50,000 USD for the U.S.) (35). The lowest stratum (HbA1c < 7 [53 mmol/mol]) showed uncertain health gains and an unfavorable ICER.

The cluster design did not change the outcomes of the analyses. The intraclass correlation for reduction in HbA1c and other long-term parameters was low and varied, except for HbA1c < 7% (53 mmol/mol) for life years and QALYs. The latter was 0.06.

Analyses were only performed according to predefined protocol. No adverse events, harms, or unintended events were reported.

**CONCLUSIONS**—Stratification is an important tool to optimize effectiveness and efficiency. Patient-centered care is more effective when targeted at a subgroup defined by higher baseline HbA1c. Over a lifetime, patient-centered care is particularly effective and a “better buy” for patients with baseline HbA1c > 8.5% (69 mmol/mol) and does not provide value for patients with baseline HbA1c < 7% (53 mmol/mol). This suggests that patient-centered care should focus on
patients with a baseline HbA1c >8.5% (69 mmol/mol), be considered for those with HbA1c = 7.0–8.5% (53–69 mmol/mol), and not be implemented in those with baseline HbA1c <7% (53 mmol/mol).

This article transforms intuition into evidence and quantifies the benefits of targeting the patient-centered care intervention by baseline HbA1c. Exploring additional criteria for stratification, as well as additional interventions aimed at the high-risk patient groups, seems warranted.

Our study is among the first to stratify patients with type 2 diabetes according to baseline risk in order to optimize lifetime benefits and lower costs. Our results are consistent with the recent literature on cost-effectiveness of interventions in people at high risk for diabetes and stratified analyses in other diseases (18,34,36–40). A recent Cochrane review suggests a benefit of individual education on glycemic control when compared with usual care in a subgroup of those with a baseline HbA1c >8% (64 mmol/mol) in an at least 6-month follow-up (+11). We extend these findings over a lifetime and show that such benefits persist.

Several limitations should be acknowledged. Further studies should replicate and refine these analyses and include other risk profiles to account for heterogeneity among patients. This would also provide a more comprehensive picture of the additional key risk factors impacting the development of complications. Also, further studies should include primary care settings since treatment of chronic diseases like type 2 diabetes tends to occur in primary care settings. In addition, longer follow-up will be needed. We assumed that the level of improvement seen after 1 year would be maintained over a lifetime (as shown in the UK Prospective Diabetes Study [UKPDS]). This is especially relevant for the stratum with HbA1c >8.5% (69 mmol/mol). Another potential limitation could relate to the generalizability of our findings. Although it is likely that our findings apply to other European and North American hospital settings, since the prevalence, characteristics, treatment strategies, and costs of type 2 diabetes are similar (37), the intensity of care might vary. Finally, more complex models might be needed that include side effects and disutilities related to insulin and oral medication use and other health care costs (related to patient admissions, primary care, or specialist visits).

Further insight can be achieved by replication of the present approach in larger completed studies hypothesizing gradients or threshold levels below which patient-centered care is not cost-effective and above which it is cost saving. Moreover, a study using a priori stratification would provide valuable confirmatory evidence for the findings of our exploratory study. Conceptually, the terminology and emphasis of patient-centered care has evolved over the years. At the time of our study, it referred to care in which the patient through the use of self-monitoring was more involved in decision making than those enrolled in usual care. The current concept of patient-centered care is one where the patient plays a much more active role.

For now, our results have several implications. When faced with the question of whether intervention A is effective and cost-effective relative to intervention B, the answer may be “it depends” instead of an unequivocal “yes” or “no,” when referring to the average patient. Targeting treatments at specific risk groups may result in better outcomes and better use of resources. Targeting those with HbA1c >8.5% (69 mmol/mol), those who are most in need, is preferable to targeting those who have little to gain. Especially in low- and middle-income countries, targeted implementation might reduce health care expenditures (3).

Future research should confirm our findings in primary care and investigate risk profiles other than HbA1c. These might include BMI or waist circumference or cardiovascular risk factors that predict cardiovascular events.

Targeting interventions to the highest risk population may allow resources to be better used, costs to be reduced, and negative side effects to be reduced by avoiding unnecessary use of medications. Focusing on HbA1c and examining a variety of HbA1c reduction strategies is valuable for patients, health care organizations, and the economy.

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dited the manuscript. R.F.D. collected and researched the data, contributed to the discussion, and reviewed and edited the manuscript. L.W.N. collected and researched the data, contributed to the discussion, and reviewed and edited the manuscript. L.W.N. 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.

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