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ORIGINAL RESEARCH

Clinical Effectiveness and Safety of Analog Glargine in Type 1 Diabetes: A Systematic Review and Meta-Analysis

Lays P. Marra · Vania E. Araújo · Thales B. C. Silva · Leonardo M. Diniz · Augusto A. Guerra Junior · Francisco A. Acurcio · Brian Godman · Juliana Álvares

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ABSTRACT

Introduction: The use of insulin analogs for the treatment of type 1 diabetes mellitus (T1DM) is widespread; however, the therapeutic benefits still require further evaluation given their higher costs. The objective of this study was to evaluate the effectiveness and safety of analog insulin glargine compared to recombinant DNA (rDNA) insulin in patients with T1DM in observational studies, building on previous reviews of randomized controlled trials comparing neutral protamine Hagedorn insulin and insulin glargine.

Methods: A systematic review with a meta-analysis was performed. The review included cohort studies and registries available on PubMed, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL), as well as manual and gray literature searches. The meta-analysis was conducted in Review Manager 5.3 software. The primary outcomes were glycated hemoglobin (Hb1Ac), weight gain, and hypoglycemia. Methodological quality was assessed using the Newcastle-Ottawa scale.

Results: Out of 796 publications, 11 studies were finally included. The meta-analysis favored insulin glargine in HbA1c outcomes (adult

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L. P. Marra (✉) · V. E. Araújo · T. B. C. Silva · A. A. Guerra Junior · F. A. Acurcio · J. Álvares
School of Pharmacy, Graduate Program in Medicines and Pharmaceutical Assistance, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil
e-mail: laysmarra@yahoo.com.br

L. M. Diniz
School of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil

B. Godman
Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

B. Godman
Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

B. Godman
Liverpool Health Economics Centre, University of Liverpool Management School, Liverpool, UK
e-mail: Brian.Godman@ki.se

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patients) and hypoglycemic episodes ($P < 0.05$), but without reaching glycemic control (Hb1Ac to approximately 7%). The methodological quality of the studies was moderate, noting that 45% of studies were funded by pharmaceutical companies.

Conclusion: Given the high heterogeneity of the studies, the discrete value presented by the estimated effect on effectiveness and safety, potential conflicts of interest of the studies, and the appreciable higher cost of insulin glargine, there is still no support for recommending first-line therapy with analogs. The role of analogs in the treatment of T1DM could be better determined by further observational studies of good methodological quality to assess their long-term effectiveness and safety, as well as their cost-effectiveness.

Keywords: Comparative effectiveness research; Glargine; Insulin; Meta-analysis; Systematic review; Type 1 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to changes in insulin secretion or altered action of insulin, or both. Type 1 DM (T1DM) results from the destruction of pancreatic beta cells mediated by cellular autoimmune responses [1].

The treatment of patients with T1DM consists of repositioning of insulin that is not produced endogenously. This involves administering either rapid-acting insulin, more intermediate or long-acting insulin. Recombinant DNA (rDNA) insulin and neutral protamine Hagedorn (NPH), which has an intermediate-acting time, are typically first-line choices among the insulins used for basal glycemic control [2, 3]. Glargine, a long-acting insulin analog, is used as an alternative to rDNA insulin. It is a molecule structurally similar to human insulin and is developed by modification of the amino acid sequence, with the aim of prolonging the duration of the effect and decreasing intra-individual variability [4].

Metabolic control through active management of patients with T1DM is based on three fundamental principles: adequate food, weight, and glycemic control. These provide benefits to patients and decrease the risk of complications [5, 6]. The glycated hemoglobin (HbA1c) level is the average glycemic level of an individual over a period of 2–3 months prior to the test day. Consequently, it can be used to evaluate glycemic control and the effectiveness of current treatments. Glycemia tests indicate blood glucose levels during testing. Both these methods are important, since the information they provide is complementary and helps to obtain a more global evaluation of glycemic control. When used together, they provide safer and more accurate results, thereby minimizing possible interferences due to the different technical methodologies used [7].

T1DM may cause acute and chronic complications, with hypoglycemia one of the most important acute complications that can occur. Microvascular (causing retinopathy, nephropathy, and neuropathy) and macrovascular (causing peripheral arterial disease, carotid disease, and coronary artery diseases) are the most prevalent chronic complications [1].

The studies and systematic reviews performed to date to compare rDNA insulin with long-acting analogs, including the authors' own systematic review of randomized

controlled trials (RCTs), did not show any significant differences in the clinical benefits obtained between the different formulations of insulin although there can be considerable differences in costs [3, 8–10]. Published studies though, including observational studies, have reported better effectiveness of insulin analogs compared with human insulin [11–13]. However, the published studies that have evaluated the performance of different insulins in non-controlled situations do appear inconclusive when combined. It is important to address this confusion given, as mentioned, the considerable differences in costs that can occur between the different formulations, for example, in Brazil, the cost of treating a patient with insulin glargine is 536% that of treatment with NPH insulin [3].

Consequently, the aim of this study was to evaluate the clinical effectiveness of insulin glargine through a systematic review of observational studies, which was not addressed in the authors' original systematic review [3], and as a result, help to determine the performance of long-acting insulins versus NPH and other insulins in the real-world in non-controlled situations to provide future guidance. It is not about assessing the effectiveness of different interventions to encourage the prescribing of particular insulin formulations.

METHODS

This review was conducted in accordance with the recommendations of the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) guidelines [14]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Study Search

Electronic searches of relevant articles published until June 2015 in MEDLINE (PubMed), Latin American and Caribbean Health Sciences (LILACS), and Cochrane Library were performed. Various combinations of terms were used, including terms related to the disease and type of intervention study (Table 1).

Hand searching was conducted in the references of all included studies and the electronic journal *Diabetes Care* from 2003 until March 2015. *Diabetes Care* was chosen as this is a reputable publication for studies involving patients with diabetes. The search for studies in the grey literature was also made among the theses and dissertations database of the Coordination for the Improvement of Higher Education Personnel (CAPES), the Digital Library of Theses and Dissertations of the Universidade Federal de Minas Gerais (UFMG), and ProQuest Dissertations and database thesis to ensure that the authors did not miss out important observational studies. These included lectures, publications and academic theses, government, congress, books, and reports.

Eligibility Criteria

Prospective and retrospective cohort studies and database records of patients with T1DM were selected. Studies that evaluated the insulin glargine preparations in comparison with rDNA insulin to assess the effectiveness and safety outcomes were included.

Studies that assessed the dosage, intervention methods, pregnant patients, clinical protocols, reviews, case reports, animal studies, in vitro studies, pharmacodynamics

Table 1 Search strategies

Databases	Search strategies	Studies
LILACS	((mh:"Diabetes Mellitus Tipo 1" AND "CetoacidoseDiabética") OR (tw:dmid OR dmt1 OR (diabet$ tip$I) OR (diabet$ tip$1) OR (diabet$ tip$ I) OR (diabet$ tip$ 1) OR (Diabetes Auto-Imune) OR (C18.452.394.750.124) OR (C19.246.267) OR (C20.111.327) OR (Diabetes Mellitus Instável) OR (Diabetes Mellitus Insulino-Dependente) OR (Diabetes Mellitus Dependente de Insulina) OR (Diabetes Mellitus de InícionaJuventude) OR (Diabetes Mellitus com Tendência à Cetose) OR (Diabetes Mellitus de InícioSúbito))) AND NOT (mh:"Diabetes Insípido" OR tw:(diabet$ insipid$)) AND (("Insulina" OR "Insulina NPH" OR D06.472.699.587.200.500.625 OR D12.644.548.586.200.500.625 OR D06.472.699.587.200.300.200) OR (tw: glargin$ OR insulin$ OR isofan$ OR nph OR isophane) OR (ti: glargin$ OR insulin$ OR isofan$ OR nph OR isophane) OR (ab: glargin$ OR insulin$ OR isofan$ OR nph OR isophane)) AND ((mh:Cohort Studies) OR tw: Seguimento$ OR tw:coort$ OR (tw:Análise de Coortes) OR tw:incidenc$ OR (tw:Observational study OR EstudioObservacional OR Estudoobservacional OR V03.200.650)) AND NOT ((tw: cat$ OR dog$ OR anima$ OR mice OR rat OR rabbits) OR ab:Prevalence OR ti:Guideline$ OR (ab:Cross-Sectional Study) OR (tw:case report))	381
Medline (via PubMed)	((((((((((((((((((((Diabetic Ketoacidosis[MeSH Terms]) OR Diabetes Mellitus, Type 1[MeSH Terms]) OR Diabetes Mellitus, Insulin*Dependent[Text Word]) OR Insulin-Dependent Diabetes Mellitus[Text Word]) OR Juvenile-Onset Diabetes Mellitus[Text Word]) OR Type 1 Diabetes Mellitus[Text Word]) OR Sudden-Onset Diabetes Mellitus[Text Word]) OR Diabetes Mellitus, Type I[Text Word]) OR IDDM[Text Word]) OR Insulin*Dependent Diabetes Mellitus 1[Text Word]) OR Juvenile*Onset Diabetes[Text Word]) OR Brittle Diabetes Mellitus[Text Word]) OR Ketosis-Prone Diabetes Mellitus[Text Word]) OR Diabetes, Autoimmune[All Fields] OR Autoimmune Diabetes[Text Word]) NOT diabetes insipidus[MeSH Terms]))))) AND ((((((Insulin, Isophane[MeSH Terms]) OR Isophane Insulin[Text Word]) OR NPH Insulin[Text Word]) OR NPH[Text Word]) OR Protamine Hagedorn Insulin[Text Word]) OR Neutral Protamine Hagedorn Insulin[Text Word]))) AND (((((((glargine[Supplementary Concept]) OR glargine[Text Word]) OR lantus[Text Word]) OR insulin glargine[Text Word]) OR HOE*901[Text Word])) OR "Insulin, Long-Acting"[Mesh]))) AND ((("Cohort Studies"[Mesh]) OR (((cohort$[Text Word]) OR controlled clinical trial[Publication Type]) OR epidemiologic methods))))	231

Table 1 continued

Databases	Search strategies	Studies
Cochrane	#1MeSH descriptor: [Diabetic Ketoacidosis] explode all trees #2MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees#3 Diabetes Mellitus, Insulin$Dependent (Word variations have been searched) #4Insulin-Dependent Diabetes Mellitus (Word variations have been searched)#5 Juvenile-Onset Diabetes Mellitus (Word variations have been searched)#6 Type 1 Diabetes Mellitus (Word variations have been searched)#7 Sudden-Onset Diabetes Mellitus (Word variations have been searched)#8 Diabetes Mellitus, Type I (Word variations have been searched)#9 Insulin$Dependent Diabetes Mellitus 1 (Word variations have been searched)#10 Brittle Diabetes Mellitus (Word variations have been searched)#11 Ketosis-Prone Diabetes Mellitus (Word variations have been searched)#12 Diabetes, Autoimmune (Word variations have been searched) #13Autoimmune Diabetes (Word variations have been searched)#14 insulin$* depend$ (Word variations have been searched)#15Type 1 diabetes (Word variations have been searched)#16 {or #1-#15} #17 MeSH descriptor: [Insulin, Long-Acting] explode all trees#18glargine (Word variations have been searched)#19 lantus (Word variations have been searched)#20 insulin glargine (Word variations have been searched)#21HOE$901 (Word variations have been searched) #22{or #17-#21} #23 MeSH descriptor: [Insulin, Isophane] explode all trees#24 Isophane Insulin (Word variations have been searched)#25 NPH (Word variations have been searched)#26 Protamine Hagedorn Insulin (Word variations have been searched)#27 Neutral rotamineHagedorn Insulin (Word variations have been searched)#28 {or #23-#27} #34 #28 or #33 #35 #22 and #34 #36#16 and #35 #37 MeSH descriptor: [Cohort Studies] explode all trees #38cohort$ (Word variations have been searched)#39 epidemiologic methods #40controlled clinical trial:pt (Word variations have been searched)#41 {or #37-#40} #42#36 and #41	184

and/or pharmacokinetics studies, studies that included patients with T2DM, studies that evaluated concomitant oral therapies with insulin therapy for patients with T1DM, studies that evaluated less than or equal to 30 participants as deemed as too small for meaningful comparisons, or studies that had a follow-up time of less than 4 weeks were excluded.

Data Collection and Assessment of Methodological Quality

The studies found in the electronic databases were brought together in a single database for deleting duplicates. The selection was carried out in three stages by two independent reviewers and included the analysis of titles, abstracts, and full texts. Disagreements were resolved by a third reviewer. Data including methodological quality, information of participants, duration of treatment, efficacy, and safety data were extracted and collected in duplicate in an Excel form developed for this purpose and previously tested.

For the assessment of methodological quality, the authors used the Newcastle-Ottawa scale for observational studies [15]. On this scale, each study was measured in three dimensions: selection of study groups, comparability of groups, and determination of the results of interest. The

total score is nine, with studies considered of high methodological quality if above six. In addition, funding sources were identified to verify potential sources of bias. The possibility of publication bias was assessed by analysis of the funnel plot [16]. It was felt there was conflict of interest in the study when somewhere in the text there was commentary on conflict of interest, it referred to sources of industry funding, or when there was some link of the study authors with the pharmaceutical industry.

Summary of the Findings and Statistical Analysis

Assessed outcomes included the concentration of HbA1c, or capillary blood glucose plasma fasting and episodes of severe hypoglycemia. Secondary outcomes included the impact on body mass index (BMI), weight gain, and the occurrence of adverse reactions.

Data from the studies were combined using random effects model the Review Manager (RevMan) software version 5.3. The authors chose RevMan as this is a typical software program used for preparing and maintaining Cochrane Reviews. It was developed through a continuous process of consultation with its users and Cochrane methodologists, to support standards and guidelines for Cochrane Reviews, and provide analytic methods, access to 'online' help, and validation mechanisms. RevMan is free to use for authors preparing a Cochrane Review or for purely academic use. The results are presented as mean difference (MD) for continuous variables with a 95% confidence interval (CI). Analysis with an $I^2 > 40\%$ and a P value of Chi square test <0.10 were considered significant heterogeneity. Sensitivity analyses were conducted to investigate the causes of any heterogeneity, excluding a study each time and recorded the changes in I^2 and P values.

RESULTS

Study Inclusion

Seven-hundred and ninety-six publications were found in the electronic database. After excluding duplicates, 626 articles were selected for title assessment, 40 for abstract assessment, and 18 to be read in their entirety. After assessing the entire papers, 7 studies were included and another 4 were added from the manual check; therefore, a total of 11 studies were included in the meta-analysis (Fig. 1).

Study Characteristics

From the 11 included observational studies, 1 comprised a database record and 10 were cohort studies, with 8 being retrospective design studies and 3 prospective studies. The follow-up time varied from 6 to 54 months. Only one study did not have any conflict of interest, while five stated conflicts of interest. Three studies did not report any financial sources, and the remaining four were supported by pharmaceutical companies (Table 2). To evaluate the clinical effectiveness and safety of insulin glargine compared with rDNA insulin, 11,426 participants were evaluated from the 11 included studies.

Concerning the patients' characteristics, the average age varied between 11 and 57 years. Four studies assessed adult patients [12, 13, 17, 18], five pediatric patients [19–23], and two studies assessed both adults and children [24, 25]. The total sample included an average of 55% males. The average time duration of the disease varied between 2 and 19 years. The

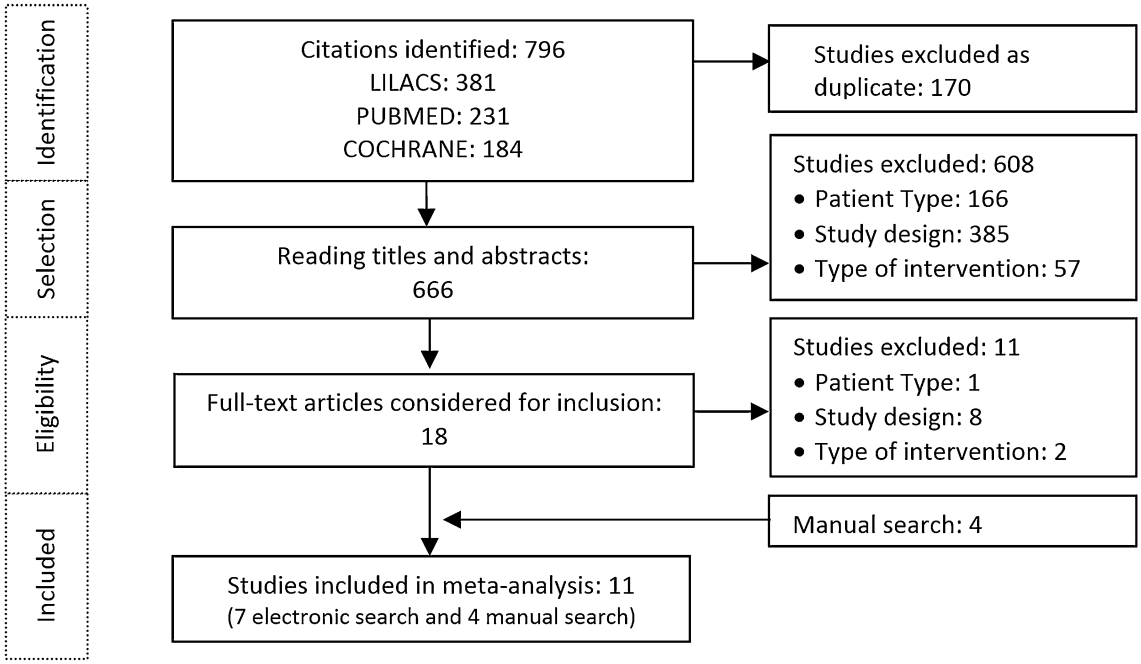

Fig. 1 The process of study selection

sample size varied between 43 and 10,469 participants (Table 2).

Methodological Quality

The methodological quality assessment of the studies using the Newcastle-Ottawa scale indicated that none of the studies obtained the maximum score corresponding to nine stars, while four studies scored eight, four scored seven, and three had a score of six (Table 2). Overall, the studies were of moderate quality. There was no asymmetry in the funnel chart for the HbA1c outcome, suggesting an absence of publication bias (Fig. 2).

Date Synthesis

To evaluate the effectiveness and safety of the outcomes of the HbA1c values, the insulin total dosage, severe hypoglycemia, patient weight gain, and BMI were evaluated. Concerning the adverse effects night hypoglycemia events and fasting capillary glycemia, only the results presented in each study were described since the data discussed in the studies could not be combined in the meta-analysis.

Primary Outcomes

The outcome of HbA1c was assessed in two subgroups: with pediatric patients [19–24] and with adult patients [12, 13, 17, 18, 24]. The meta-analysis of the pediatric subgroup of patients did not show significant differences between the groups (MD = −0.38; 95% CI −0.79, 0.04; $P = 0.07$; $I^2 = 86\%$), and the adult patients subgroup favored insulin glargine (MD = −0.26; 95% CI −0.48, −0.04; $P = 0.02$; $I^2 = 53\%$). In the total combination of subgroups, the estimate of the effect favored insulin glargine and the heterogeneity was high and significant (MD = −0.33; 95% CI −0.54, −0.12; $P = 0.002$; $I^2 = 81\%$; Table 3; Fig. 3). In

Table 2 General characteristics of the included studies by date of publication

Study	Type of study	Participants[a]	Place of study	Study scope	Conflict of interest	Funding sources	Follow-up (months)	Duration classification	Total score in the Newcastle-Ottawa scale
Hathout et al. [21]	Retrospective cohort	60 (60/60)	USA	SC	NR	NR	9	Long	7
Garg et al. [17]	Retrospective cohort	196 (98/98)	USA	SC	Yes	The Children's Diabetes Foundation in Denver	13	Long	7
Dixon et al. [20]	Prospective cohort	128 (64/64)	USA	SC	NR	The Children's Diabetes Foundation in Denver	6	Intermediary	8
Colino et al. [19]	Prospective cohort	80 (80/80)	NR	SC	NR	INERGEN C03/05	6	Intermediary	8
Yamamoto-Honda et al. [18]	Retrospective cohort	83 (83/83)	Japan	SC	NR	NR	12	Long	8
Herwig et al. [24]	Prospective registry	142(74/68)	Germany	SC	Yes	Sanofi Aventis	19	Long	6
Schreiber et al. [12]	Retrospective cohort	65 (65/65)	Germany	SC	Yes	Sanofi Aventis	30	Long	6
Päivärinta et al. [22]	Retrospective cohort	62 (62/62)	Finland	SC	NR	NR	12	Long	7
Johansen et al. [13]	Retrospective cohort	43 (43/43)	Norway	SC	Yes	Novo Nordisk	18	Long	7
Salemyr et al. [23]	Retrospective cohort	98 (49/49)	Sweden	SC	No[b]	Samaritan Foundation	12	Long	8

Table 2 continued

Study	Type of study	Participants[a]	Place of study	Study scope	Conflict of interest	Funding sources	Follow-up (months)	Duration classification	Total score in the Newcastle-Ottawa scale
Haukka et al. [25]	Retrospective cohort	10,469 (3359/7110)	Finland	MC	Yes	Novo Nordisk	54	Long	6

MC multi center, *NR* not reported, *SC* single center

[a] The value in brackets indicates (n_i/n_c) where, n_i = the number of participants in the intervention group (glargine), and n_c = the number of participants in the control group (neutral protamine Hagedorn)

[b] The authors declared no conflicts of interest

the sensitivity analysis, exclusion of three studies [17, 20, 24] reduced the heterogeneity, but did not change the outcome.

Only two studies [19, 21] evaluated the fasting capillary glycemia, and their results did not reveal significant differences between the groups (Table 3).

For the meta-analysis of severe hypoglycemic episode occurrence, four studies [17, 19, 24, 25] were included. Data revealed an estimated difference in the means of −0.58 (95% CI −0.99, −0.16; $P < 0.007$; $I^2 = 95\%$), favoring analog glargine. In the sensitivity analysis, the exclusion of Colino et al. [19] decreased the heterogeneity, without changing the direction of the outcome (Table 3; Fig. 4).

Analysis of the Subgroup: Follow-up Time of the Study

The impact on HbA1c levels was assessed according to the follow-up time of the studies. Studies considered intermediate [19, 20] revealed an insignificant difference in the mean values between the insulin formulations (MD = −0.05; 95% CI −0.92, 0.82; $P = 0.91$; $I^2 = 95\%$). In studies of a longer duration [12, 13, 17, 18, 21–24], the difference in the means was estimated at −0.37 (CI −0.61, −0.13; $P = 0.003$; $I^2 = 70\%$), thereby favoring insulin glargine. The consolidation of the above-mentioned groups revealed an estimated difference in the means of −0.29, favoring insulin glargine (95% CI −0.51, −0.08; $P = 0.008$; $I^2 = 80\%$) with a high heterogeneity pattern (Table 3; Fig. 5). In the sensitivity analyses, the individual exclusion of the studies affected neither the direction of the outcomes nor the significance of the heterogeneity.

Subgroup Analysis: Conflict of Interest

The impact on HbA1c levels was evaluated in the subgroups to determine the presence of

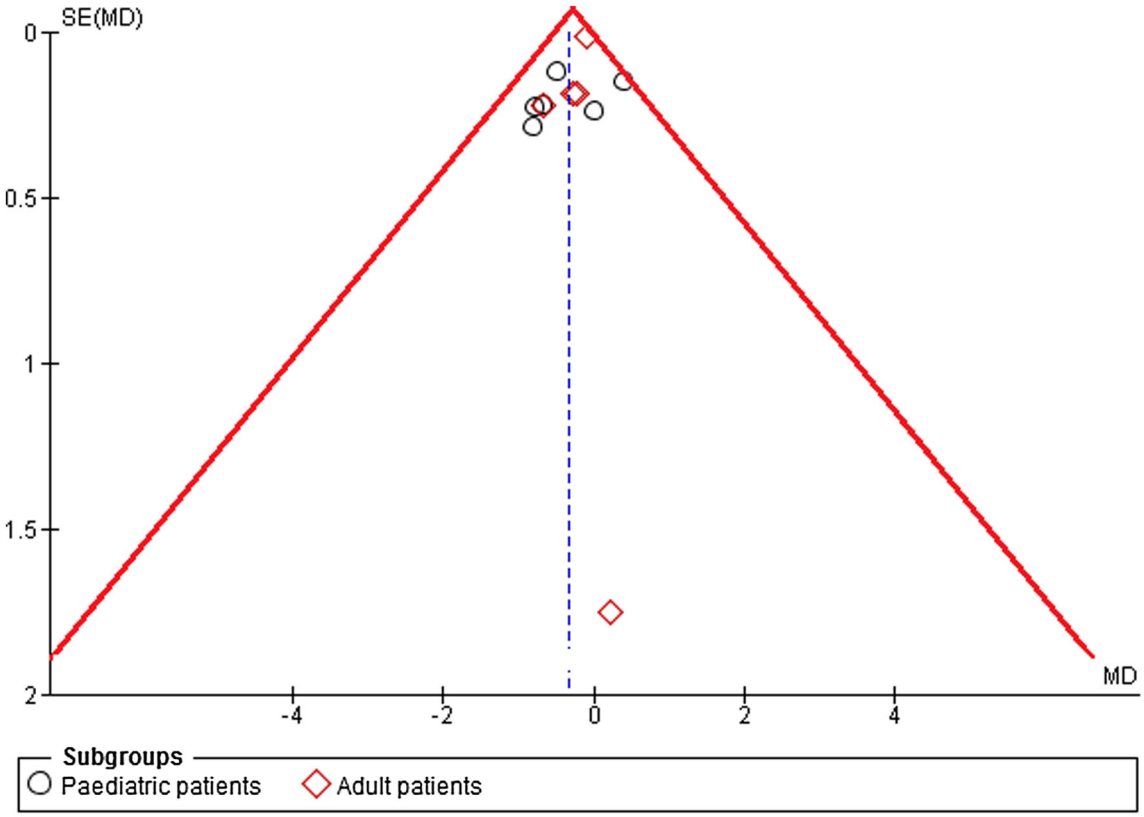

Fig. 2 Funnel plot of MD in HbA_{1c}. *MD* mean difference, *SE* standard error

conflicts of interest on the findings. The subgroup without any conflict of interest [18–23] revealed an insignificant difference in means (MD = −0.31; 95% CI −0.70, 0.07; $P = 0.11$; $I^2 = 85\%$). In the subgroup with conflicts of interest [12, 13, 17, 24], the difference in the means was estimated at −0.30 (95% CI −0.59, −0.01; $P = 0.05$; $I^2 = 41\%$), favoring insulin glargine. The total result revealed an estimated difference in means of −0.31, favoring insulin glargine (95% CI −0.56, −0.05; $P = 0.02$; $I^2 = 76\%$) with a high heterogeneity pattern (Table 3; Fig. 6). In the sensitivity analyses, the exclusion of the two studies [20, 24] affected the direction of the outcome (Table 3; Fig. 6).

Secondary Outcomes

The meta-analysis that evaluated the BMI (in kg/m^2) [10, 11, 13, 15] revealed an insignificant difference in the means (MD = −0.15; 95% CI −0.71, 0.40; $P = 0.59$; $I^2 = 74\%$; Table 3). The sensitivity analyses excluding the study conducted by Dixon et al. [20] resulted in a statistical heterogeneity equal to zero, without changing the direction of the outcome.

Concerning the impact on body weight gain (in kg), the study results [12, 13, 17, 18, 22, 23] revealed that there was no significant difference between the different insulins (MD = −1.38; 95% CI −4.86, 2.10; $P = 0.44$; $I^2 = 91\%$). In the sensitivity analyses that excluded the study conducted by Garg et al. [17], a statistical heterogeneity equal to zero was observed,

Table 3 Outcomes evaluated in the meta-analysis

Outcomes	Studies, *n* [reference(s)]	Participants	Estimated effect (95% CI)	*P* value	I^2 (%)
1.1 HbA1c, %	10 [12, 13, 17–24]	1422	−0.33 (−0.54, −0.12)	0.002	81
Pediatric patients	6 [19–24]	702	−0.38 (−0.79, 0.04)	0.07	86
Adult patients	5 [12, 13, 17, 18, 24]	720	−0.26 (−0.48, −0.04)	0.02	53
1.2 HbA1c, %	10 [12, 13, 17–24]	1280	−0.29 (−0.51, −0.08)	0.008	80
Intermediate duration studies	2 [9, 24]	288	−0.05 (−0.92, 0.82)	0.91	95
Long-duration studies	8 [12, 13, 17, 21–24]	992	−0.37 (−0.61, −0.13)	0.003	70
1.3 HbA1c, %	10 [12, 13, 17 24]	1280	−0.31 (−0.56, −0.05)	0.02	76
With conflict of interest	4 [12, 13, 17, 24]	554	−0.30 (−0.59, −0.01)	0.05	41
7.5	6 [18–23]	726	−0.31 (−0.70, 0.07)	0.11	85
1.4 Severe hypoglycemic, episodes/person-year	4 [17, 19, 24, 25]	10,967	−0.58 (−0.99, −0.16)	0.007	95
1.5 BMI, kg/m^2	4 [13, 19–21]	494	−0.15 (−0.71, 0.40)	0.59	74
1.6 Weight, kg	6 [12, 13, 17, 18, 22, 23]	670	−1.38 (−4.86, 2.10)	0.44	91
1.7 Insulin total dosage, U/kg/day	10 [12, 13, 17–24]	1350	−0.03 (−0.09, 0.04)	0.37	84
Pediatric patients	6 [19–24]	702	−0.01 (−0.12, 0.09)	0.83	88
Adult patients	5 [12, 13, 17, 18, 24]	648	−0.06 (−0.14, 0.02)	0.16	72

without any change in the direction of the outcome (Table 3).

For the total dosage of the analog or insulin (in U/kg/day), the subgroups of pediatric [19–24] and adult patients [12, 13, 17, 18, 24] were evaluated. Data revealed that there was no significant difference in any of the groups (MD = −0.01; 95% CI −0.12, 0.09; $P = 0.83$; $I^2 = 88\%$; and MD = −0.06; 95% CI −0.14, 0.02; $P = 0.16$; $I^2 = 72\%$, respectively). The total result of the meta-analysis also did not show a significant difference (MD = −0.03; 95% CI −0.09, 0.04; $P = 0.37$; $I^2 = 84\%$; Table 3). In the sensitivity analyses of the adult patient subgroup, exclusion of Yamamoto-Honda et al. [18] changed the heterogeneity and the direction of the outcome, favoring insulin glargine (MD = −0.09; 95% CI −0.12, −0.06; $P < 0.00001$; $I^2 = 0\%$).

Night-time hypoglycemic events were not evaluated in this meta-analysis, since the final studies did not present data that could be combined statistically. Only three studies described this outcome [18, 20, 22]. In the study by Dixon et al. [20], the night hypoglycemic events in the insulin glargine group decreased from 12 to 1 during the study period. However, in the studies by Päivärinta et al. [22] and Yamamoto-Honda et al. [18], the results revealed that there was no significant difference between the different insulins.

Asymptomatic hypoglycemic episodes were assessed in two studies [20, 21]. In the study by Dixon et al. [20], the asymptomatic hypoglycemic events did not present significant

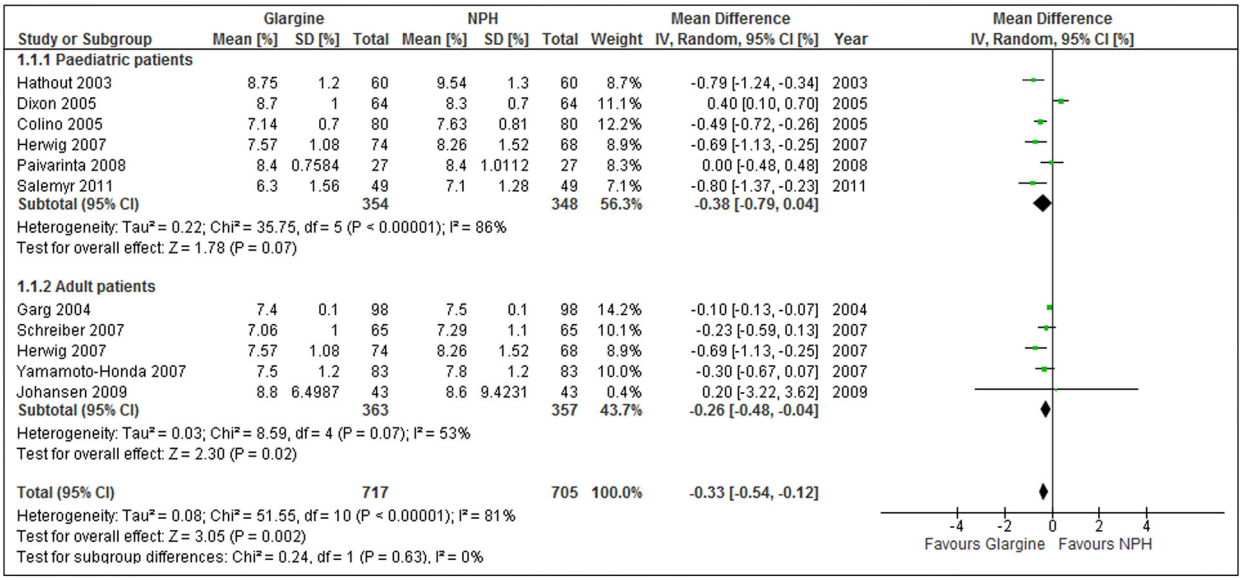

Fig. 3 Glycated hemoglobin meta-analysis: age subgroup. *CI* confidence interval, *df* degrees of freedom, *NPH* neutral protamine Hagedorn, *SD* standard deviation, *Method IV* Method based on an iterative estimate and a closed form confidence interval

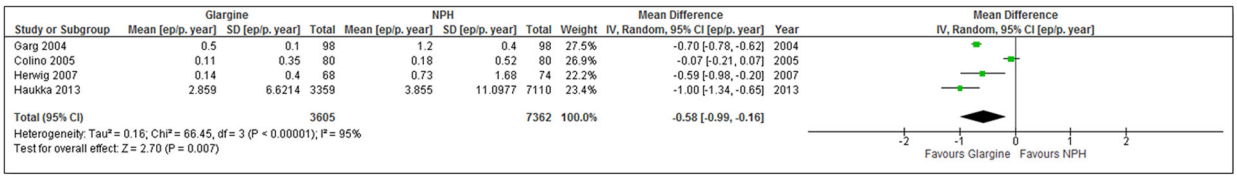

Fig. 4 Meta-analysis: episodes of severe hypoglycemia. *CI* confidence interval, *df* degrees of freedom, *NPH* neutral protamine Hagedorn, *SD* standard deviation, *Method IV* Method based on an iterative estimate and a closed form confidence interval

differences between the insulin glargine and rDNA insulin groups (2.3 ± 1.3 and 2.3 ± 1.5, respectively; $P > 0.05$). In the study by Hathout et al. [21], the average frequency of hypoglycemia decreased from 10.6% to 9.2% after 9 months' treatment with insulin glargine; however, it was not statistically significant for all the groups under study ($P = 0.3$). The decrease was more evident in very small children with pre- and post-glargine hypoglycemic events of 20% and 15%, respectively.

Adverse reactions were assessed in four studies [13, 18, 19, 24]. In the studies by Colino et al. [19] and Herwig et al. [24], there was no significant difference between the insulin groups. Several patients reported that they felt more pain during the insulin glargine injection, but this did not result in the discontinuation of the treatment [19]. In the study by Johansen et al. [13], a patient developed edema and pain in the articulations immediately after the beginning treatment with analog glargine, but this did not result in the suspension of the treatment. The results by Yamamoto-Honda et al. [18] revealed that insulin glargine was well tolerated by all the patients, except for five episodes of failure in the injection system.

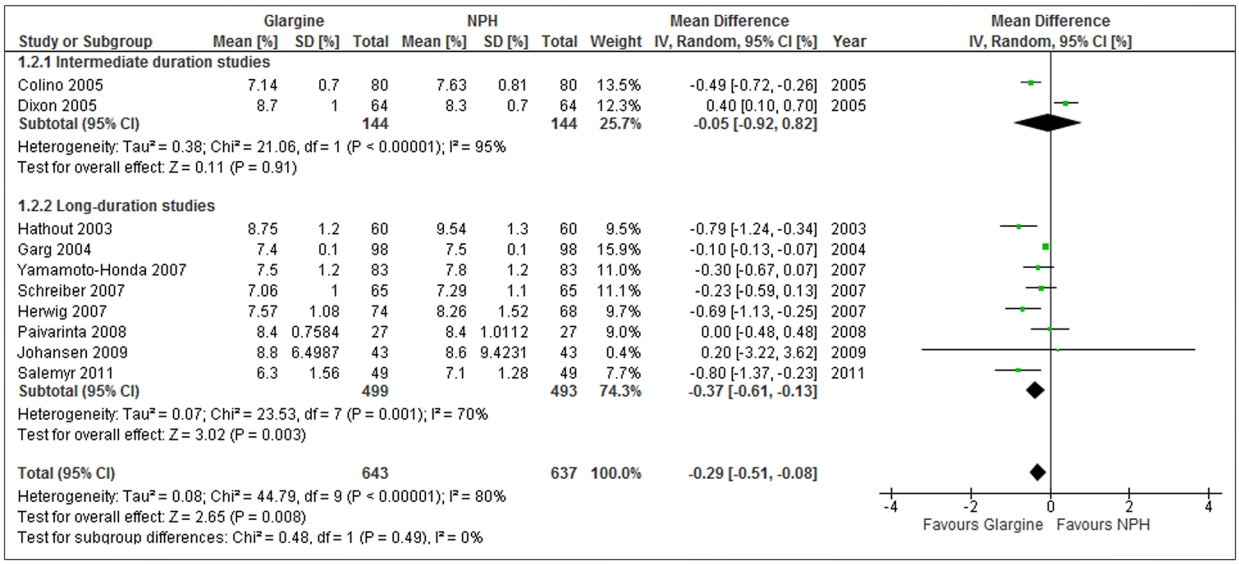

Fig. 5 Glycated hemoglobin meta-analysis: duration of the study subgroup. *CI* confidence interval, *df* degrees of freedom, *NPH* neutral protamine Hagedorn, *SD* standard deviation, *Method IV* Method based on an iterative estimate and a closed form confidence interval

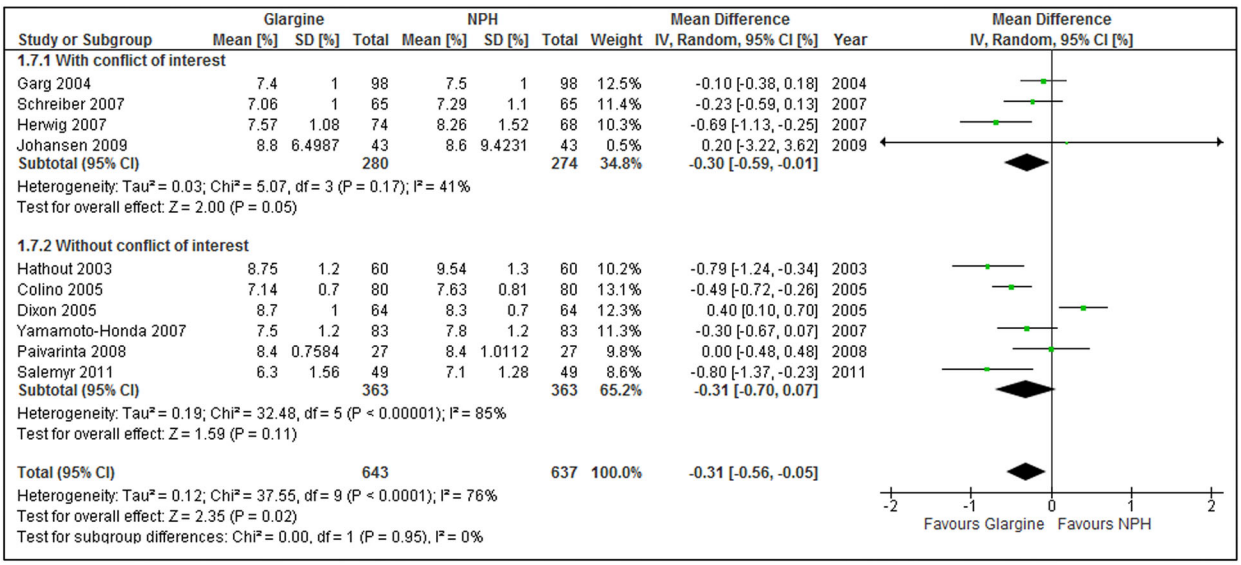

Fig. 6 Glycated hemoglobin meta-analysis: conflict of interest subgroup. *CI* confidence interval, *df* degrees of freedom, *NPH* neutral protamine Hagedorn, *SD* standard deviation, *Method IV* Method based on an iterative estimate and a closed form confidence interval

DISCUSSION

The introduction of analogs as therapeutic options to treat T1DM presented hope to millions of patients to obtain greater glycemic control and prevent both microvascular and macrovascular complications associated with hyperglycemia as well as potential injury caused by hypoglycemic episodes. In this systematic review with meta-analysis, the

authors aimed to assess evidence of the improved effectiveness and safety of analog glargine compared to rDNA insulin for the treatment of patients with T1DM obtained through observational studies, that is, the real word [26], thus building on their previous systematic review of RCTs [3]. It is important to emphasize that, despite the fact that they provide robust evidence regarding the efficacy of interventions, RCTs can have low external validity, that is, extrapolation of the results to the community at large including patients with greater co-morbidities can be limited [27, 28].

The HbA1c evaluation was performed on 1422 participants, comparing insulin glargine with rDNA insulin, and the result of the meta-analysis favored insulin glargine; however, this was without HbA1c control. Furthermore, for the pediatric subgroup of patients, the results of the difference in means did not show any significance. It should be emphasized that the discrete value of this result, which involved not achieving ideal control of HbA1c by the patients, established by the Brazilian Diabetes Society guidelines, was lower than 7.5% [29].

In the study by Warren et al. [30], a systematic review of the efficacy of analog glargine showed it to be more effective than rDNA insulin in decreasing fasting blood glucose, but not for reducing the HbA1c level. Another outcome assessed in the study involving 10,967 participants was the reduction of severe hypoglycemic episodes, with the findings favoring rDNA insulin [30]. The study by Siebenhofer et al. [31] showed similar results.

The follow-up period in the reported studies were divided into short duration (up to 3 months), intermediate (more than 3 months and up to 6 months), and long (more than 6 months) duration. Short-duration studies were not included since this parameter reflects the average glycemic control obtained in the period from three to 4 months, based on the red blood cell life cycle [32]. Very short studies of one-month duration, for example, detected only 50% of the estimated variation in the glycemic control [33], a fact that could introduce bias in the results. The intermediate duration studies [19, 20] did not demonstrate significant statistical differences. Most studies included in this systematic review were of long duration [12, 13, 17, 18, 21–24] and showed significant results favoring insulin glargine.

In this systematic review, it was observed that insulin glargine showed better effectiveness results compared with rDNA insulin. Vardi et al. [34] showed similar results in their systematic review, but the analysis suggested only a modest clinical benefit using long-acting analogs instead of intermediate acting insulin preparations for patients with T1DM. Its effect was more prominent for the control of night hypoglycemia [34].

Only one study reported the reason why insulin glargine treatment was discontinued [22], which was observed in 9% of the patients who discontinued treatment before completing 1 year of follow-up. The reasons for interrupting therapy were night hypoglycemia ($n = 2$), failure to reach good glycemic control ($n = 3$), patients considered the multiple injection therapy too laborious ($n = 2$), and pain associated with the application ($n = 1$). After interruption, two of the patients continued their treatment with an insulin pump and five with rDNA insulin.

The authors believe it is worth highlighting the conflict of interest associated with research, especially in regards to its ethical and bioethical aspects. According to Thompson [35], conflict of interest is a group of conditions in which professional judgment could be improperly

influenced by interests such as financial gain. Conflicts of interest include, for instance, omission of sponsorship or financial involvement when publishing a scientific paper or presenting results at congresses, avoiding disclosing negative results or delaying this disclosure with the aim of protecting a potential market [36]. Publications confirm that financial relations between the industry, scientific researchers, and academic institutions can be persuasive affecting studies and utilization patterns [37, 38] and may influence important aspects of biomedical research [39]. In this systematic review when assessing the results of HbA1c, the subgroup of studies in which there was no conflict of interest did not demonstrate significant statistical difference between the findings from either insulin glargine or rDNA insulin. On the other hand, in the subgroup that reported conflicts of interest, the findings were favorable for insulin glargine (Fig. 6).

The studies selected in this systematic review and meta-analysis may have been influenced by publication bias, which is the tendency of the results published being systematically different from reality. For example, examination of clinical trials with a registered protocol in the registry database ClinicalTrials.gov revealed that <70% of the studies are eventually published [40], which may be due to a variety of reasons [41]. For instance, in a review of published studies comparing different atypical antipsychotics, in 90% of the studies supported by pharmaceutical companies the reported overall outcome was in favor of the sponsor's drug [42]. However, in this systematic review, the analysis of the funnel chart did not show asymmetry, suggesting the absence of publication bias. Having said this, there were differences in results between the reviewed studies with and without conflicts of interest (Fig. 6). In addition, the majority of studies that showed little precision were generally performed with small samples and distributed symmetrically in the largest part of the funnel. Only the study by Johansen et al. [13] showed greater precision and was situated in the narrowest part of the funnel.

This systematic review included only cohort and patient record studies, which is one of the limitations of systematic reviews of observational studies, that is, referring to selection bias inherent to this type of study design and to non-controlled confounding factors. Some studies did not present complete and accurate information to be included in the quantitative analysis, thereby affecting the explanation of the high heterogeneity found in some comparisons. Differences in the number of participants between the groups were also observed as well as during the follow-up period. Despite this fact, observational studies have the advantage of potentially large patient groups and represent real-world conditions since they are performed in non-controlled conditions without the strict confines of RCTs [27].

Another limitation in the interpretation of the results was the statistical heterogeneity among the studies found in the meta-analysis. The small number of studies included in the comparisons, in addition to the lack of complete and accurate information in these studies, hindered the explanation of the sources of heterogeneity. In the sensitivity analysis, the inclusion and exclusion of studies in each comparison did not change the direction of a majority of the outcomes, with alterations in heterogeneity. It should be highlighted that the studies that significantly changed heterogeneity [17–20, 24, 36] were all sponsored by the pharmaceutical industry, with the exception of Yamamoto-Honda et al. [18].

The absence of other published systematic reviews on the effectiveness and safety of the different insulins in 'real-world' conditions hinders any comparison with the results from this review. Typically, systematic reviews evaluate efficacy studies, that is, patients enrolled into RCTs, as seen by ours and other published reviews [3, 8, 31, 34, 43], rather than including real-world studies. Overall, any recommendation of the insulin analogs as first-line therapy should still be considered with caution, considering the small difference between the outcomes in the meta-analyses that have been performed including this study, potential conflict of interests, and the appreciable differences in treatment costs in comparison with therapeutic alternatives that are available.

CONCLUSIONS

Taking into account the high heterogeneity of the published studies, the discrete value shown by assessing the effectiveness and safety outcomes, the potential conflict of interest of the included studies, and treatment costs in contrast to the therapeutic alternatives available, there is evidence of improved effectiveness with the analogs. However, these results need to be treated with caution as there were differences in findings between studies where conflicts of interest were reported and those without conflict of interest. The role of the analogs in T1DM treatment should be better determined through more studies with good methodologies to assess their effectiveness and safety profile over a long duration as well as well-conducted economic evaluations focusing on available therapies. This is particularly important where there are considerable acquisition cost differences between available insulin formulations. In view of these controversies, the authors are currently performing their own analysis of the effectiveness of insulin glargine in real life amongst a Brazilian population. They hope to report on this shortly.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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