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ORIGINAL ARTICLE

Randomized Trial of Long-Acting Insulin Glargine Titration Web Tool (LTHome) Versus Enhanced Usual Therapy of Glargine Titration (INNOVATE Trial)

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Abstract

Background: Basal insulin titration in the real world is often unsuccessful. LTHome, a web tool, applies a rules engine-based algorithm providing insulin titration advice directly to the patient.
Methods: This pilot, randomized trial evaluates basal insulin glargine titration by LTHome compared to enhanced usual therapy ([EUT]—diabetes education program) over 12 weeks. Important inclusion criteria: 18–75 years, type 2 diabetes, computer literacy, and HbA1c >7.0%. Trial protocol was approved by ethics board.
Results: We randomized 139 subjects. The achievement of primary composite outcome (four out of seven fasting plasma glucose [FPG] within 5–7.2 mmol/L + mean for three consecutive FPG within 5–7.2 mmol/L + no severe hypoglycemia) was 15% in LTHome versus 41% in EUT (noninferiority not met, P-value = 0.92). Other outcomes were similar between the LTHome and EUT arms: alternate composite outcome achievement (last five FPG mean within the range of 5–7.2 mmol/L + no hypoglycemia, 47% and 51%, $P = 0.73$); A1c reduction (−1.0% and −1.1%, $P = 0.66$); proportion achieving A1c ≤7% (14% and 20%, $P = 0.36$); and hypoglycemia incidence (31% and 37%, $P = 0.4$), respectively. Patient satisfaction score improvements were greater in LTHome versus EUT (change in fear of hypoglycemia score $P = 0.04$ and change in diabetes distress score $P = 0.04$). The mean number of additional healthcare provider visits was 0.13 for LTHome and 1.22 for EUT ($P < 0.01$).
Conclusion: INNOVATE trial suggests clinical utility of LTHome compared to EUT in real-life settings. Further research is needed to evaluate the efficacy and safety of automated insulin titration algorithms.

Introduction

The progressive nature of type 2 diabetes (T2DM) requires treatment intensification over time, including insulin initiation in many patients.[1,2]

Despite significant improvements in insulin injection technology, several challenges persist for initiation in patients with T2DM. Insulin initiation is often delayed by many years resulting in a prolonged exposure to poorly controlled glycemia.[3]

In addition to the perceived adverse effects of hypoglycemia and weight gain, physician inertia to insulin initiation is often linked to insulin dosing complexity, time commitment for insulin titration, and scarcity of diabetes education resources in primary care. These perceived barriers result in a dependence on diabetologists and diabetes education programs (DEPs), increasing the financial burden on healthcare systems. Inadequate and often prolonged insulin dose titrations lead to low target achievement in general practice, despite use of simplified treat-to-target strategies.[3–5] As an example, a Canadian primary care chart audit found that only 25% patients had achieved a target A1C of ≤7% (53 mmol/mol) after a full year of basal insulin therapy.[3]

The long-acting insulin glargine titration web tool (LTHome, commercial name MyStar WebCoach®), containing a rules engine-based algorithm for titration and maintenance of insulin glargine, was developed to support the healthcare provider (HCP)-recommended dose progression of basal insulin glargine (Lantus®). It was developed to support the HCP-recommended dose progression of basal insulin glargine (Lantus), to be embedded in a range of platforms, from this first-generation

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web-based tool to glucometer and mobile options. Through the web-based platform, LTHome provides insulin titration advice directly to the patient, based on prior insulin dose, resulting fasting blood glucose (FBG), and incidental hypoglycemia during titration.

The INNOVATE trial is the first pilot trial using LTHome. INNOVATE is an investigator-initiated, open-label, parallel-group, randomized, multicenter trial that compares insulin titration utilizing either the LTHome web-based tool or a specialist HCP-driven diabetes education program (enhanced usual therapy [EUT]). The hypothesis of the trial is to show noninferiority of LTHome to EUT in achievement of glucose reduction efficacy and safety objectives in patients initiating or titrating basal glargine insulin.

Methods

The INNOVATE trial was conducted at seven LMC Diabetes & Endocrinology (LMC) centres in and near Toronto, Canada. LMC is a multisite, community-based, specialist-led, referral-based, multidisciplinary program. INNOVATE is an investigator-initiated trial, funded by Sanofi. The steering committee was solely and fully responsible for developing the protocol as well as analysis and was involved at all stages of trial development to achieve scientific integrity and objectivity. INNOVATE is a registered trial with ClinicalTrials.gov. The study was designed and monitored in accordance with Good Clinical Practice, the International Conference on Harmonization, and the Declaration of Helsinki. The protocol was reviewed by an independent research ethics board and each patient provided written informed consent.

Trial population

The key INNOVATE protocol inclusion criteria were as follows: subjects with T2DM between 18 and 75 years of age (inclusive), with body mass index $\leq 45\,kg/m^2$, who were scheduled to either initiate basal insulin (if insulin naive) or increase their dose of current basal insulin (if already on basal insulin), because of inadequate blood glucose control (defined by A1C >7.0% [>53 mmol/mol]) at screening AND mean self-monitored fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL) on three of the prior 7 days; stable oral antidiabetic agent/s (OAD) and/or GLP-1 receptor agonist therapy during the 4-week period before screening; and subjects who were computer literate with home access to a personal computer. The key exclusion criteria for the trial include the following: hypoglycemia unawareness, severe hypoglycemic episode within 90 days or hospitalization (for any reason) within 30 days before screening; current or anticipated use of mealtime (bolus) insulin during the time frame of the trial; and night shift workers.

Randomization and study procedures

Eligible subjects were randomly allocated via an interactive, computer-generated system to LTHome or EUT in a 1:1 ratio. A balanced representation of randomized subjects was maintained between the two randomized arms among insulin initiation and insulin titration subgroups. In the EUT arm, insulin dosing and titration instructions were provided by certified diabetes educators (CDE) according to a standard protocol—where patients were advised to increase by 1 U every day until their FBG <7.0 mmol/L, based on INSIGHT protocol.[6] In addition, CDE could titrate the insulin dose by up to 10% at each visit (scheduled every 4 weeks).

In the LTHome arm, instructions on insulin administration and dosing, as well as the use of the web-based LTHome tool, were provided by delegated non-healthcare professionals. For subjects initiating insulin, the suggested starting dose was 10–20 U at bedtime based on physician discretion. Morning only (AM) or twice daily (BID) dosing was not allowed. All patients were counseled on lifestyle modification; study visits were scheduled at 4-week intervals for both arms but additional telephone encounters could be initiated by subjects at any time.

There were no scheduled physician visits during the 12-week insulin titration period, but physicians were available for any medical need, including adverse effects, hyperglycemia, or hypoglycemia. Irrespective of randomization assignment, study subjects' OAD regimen could be adjusted during the trial period as per physician discretion, to achieve an appropriate individualized glycemic goal as per Canadian guidelines.[1] Both trial arms were supported by detailed instructions on the use of blood glucose monitor and unlimited availability of blood glucose monitoring supplies (BG Star®), as well as counseling on hypoglycemia treatment.

The LTHome algorithm utilized in this trial was adapted from a number of treat-to-target trials and modified significantly to avoid hypoglycemia. As depicted in Table 1, the LTHome algorithm's suggested dose titrations are based on the three-day fasting median value for self-monitoring of blood glucose (SMBG), any documented hypoglycemia, or hypoglycemia symptoms.

Trial outcomes

The prespecified primary outcome for the trial was the composite of the following parameters before the end of the 12-week trial period: (i) at least four out of seven FPG within the 10-day period in the range of 5–7.2 mmol/L or 90–129.6 mg/dL (inclusive); (ii) mean FPG for three consecutive prior FPG within the 10-day period in the range of 5–7.2 mmol/L or 90–129.6 mg/dL (inclusive); and (iii) no severe hypoglycemia during the 7–10-day period—defined as requiring third-party intervention for management. Because of unanticipated low levels of achievement of primary outcome, as well as no episode of severe hypoglycemia observed after 82 patients were enrolled, secondary FPG efficacy and composite outcomes were added to the protocol subsequently. Alternate FPG efficacy outcome was defined as the proportion of patients achieving mean of the last five FPG within the range of 5–

Table 1. Titration Rules for Insulin Glargine as Per LTHome

Assessment rules (median FPG based on three consecutive results)	*Resultant dose adjustment*
>10.0 mmol/L (180 mg/dL)	+4 U
7.3–9.9 mmol/L (131.4–178.2 mg/dL)	+2 U
5.0–7.2 mmol/L (90–129.6 mg/dL)	0
3.9–4.9 mmol/L (70.2–88.2 mg/dL)	−2 U or 5%
<3.9 mmol/L (70.2 mg/dL) or any hypoglycemia symptoms	−4 U or 10%

FPG, fasting plasma glucose.

Table 2. Baseline Characteristics

	LTHome (n = 72)		*EUT (n = 67)*	
	Mean	*SD*	*Mean*	*SD*
Age (years)	56.4	8.1	56.4	8.4
BMI (kg/m^2)	32.1	6.0	33.7	5.8
Duration of diabetes	11.1	6.0	12.9	7.5
A1C	8.8	1.3	8.8	1.4
Insulin dose among titration group (U)	26.2	21.6	28.5	26.2
	N	%	N	%
Insulin titration group	47	65%	47	70%
Insulin initiation group	25	35%	20	30%
Education	N	%	N	%
Attended secondary school	4	6%	5	8%
Completed secondary school	10	15%	9	14%
Completed postsecondary	30	44%	29	46%
Attended university	24	35%	20	32%

EUT, enhanced usual therapy; BMI, body mass index.

7.2 mmol/L or 90–129.6 mg/dL (inclusive) before the end of 12-week trial. Alternate composite outcome was defined as meeting alternate FPG efficacy outcome target, with no documented hypoglycemia. The secondary objectives of this study were to assess A1C reduction effectiveness and proportion of patients achieving target A1C ≤7% (53 mmol/mol), hypoglycemia safety, as well as satisfaction score changes with LTHome versus EUT-directed glargine titration. Patient satisfaction score changes were calculated from randomization visit to end of trial at 12 weeks—Diabetes Treatment Satisfaction Questionnaire, Fear of Hypoglycemia Survey, WHO-5 well-being index, and Diabetes Distress Scale (DDS).[7–10] All primary and secondary safety and efficacy outcomes were analyzed separately for insulin initiation versus titration. Survey responses were also collected for subjects randomized to the LTHome arm.

Statistical considerations

Primary analysis and sample size calculations were based on the proportion of subjects meeting the primary outcome. The *z*-test was used to test noninferiority of the LTHome arm to the EUT arm with a noninferiority margin of 15%. Analysis population was the intention-to-treat (ITT) population. We assumed a 10% loss to follow-up for individuals. The proposed sample size of 138 subjects provides 80% power to conclude noninferiority of the LTHome arm to the EUT arm for the 15% margin if there was a true difference in favor of the LTHome of 10%. All analyses were performed using SAS version 9.2 software (SAS, Inc., Cary, NC), and *P*-values <0.05 were considered statistically significant.

Results

One hundred thirty-nine subjects were randomized in the INNOVATE trial (LTHome = 72 and EUT = 67) between December 2013 and December 2014. Baseline characteristics were generally balanced and are outlined in Table 2. Nineteen patients (13 in LTHome arm and six in EUT arm) were nonevaluable for the primary and alternate efficacy outcomes (permanent discontinuation, lost to follow-up, or no FPG record during the last 10 days before end of 12-week trial period). Mean number of days that trial subjects checked their FPG was 112 (±31) days.

The proportion of patients meeting the primary outcome was 15% in LTHome and 41% in EUT (Table 3). The test of noninferiority of LTHome to EUT for reaching primary outcome was not met (*P* value = 0.92). None of the patients had severe hypoglycemia. The alternate FPG efficacy outcome was achieved in 44% patients in LTHome and 54% in EUT arms (*P* value = 0.27). Alternate composite outcome achievement was also similar among the trial arms, that is, among subjects who experienced no hypoglycemia during the trial, alternate FPG efficacy outcome was achieved in 18/38 subjects (47%) in LTHome and 19/37 subjects (51%) in EUT arms (*P* = 0.73). Rolling 3-day FPG improved over the trial period for both arms. There was no significant difference in average A1C reduction between the LTHome and EUT arms (−1.0% ± 0.9 and −1.1% ± 1.2, respectively; *P* = 0.66). In addition, the proportion of patients achieving target A1C <7% (53 mmol/mol) at 12 weeks was similar between EUT and LTHome (14% and 20%, respectively; *P* = 0.36).

The proportion of subjects having at least one hypoglycemia, at least one nocturnal hypoglycemia, at least one daytime hypoglycemia, at least one symptomatic hypoglycemia, as

Table 3. Glucose Reduction Efficacy and Safety Outcomes

	LTHome (%)	*EUT (%)*	P-*value*
Proportion achieving primary composite outcome[a]	15	41	0.92[b]
Proportion achieving alternate FPG efficacy outcome[c]	44	54	0.27
Proportion achieving alternate composite outcome[d]	47	51	0.73
Mean change in A1c from baseline to 12 weeks (SD)	−1.0 (0.9)	−1.1 (1.2)	0.66
Proportion of patients reaching A1c ≤7% at 12 weeks	20	14	0.36
Overall hypoglycemia	31	37	0.40
Nocturnal hypoglycemia	6	1	0.18
Daytime hypoglycemia	28	33	0.52

[a]Primary composite outcome = at least four out of seven FPG within a 10-day period in the range of 5–7.2 mmol/L or 90–129.6 mg/dL (inclusive) + mean FPG for three consecutive prior FPG within a 10-day period in the range of 5–7.2 mmol/L or 90–129.6 mg/dL (inclusive) + no severe hypoglycemia.
[b]Test of noninferiority of LTHome to EUT, with a 15% noninferiority margin.
[c]Alternate FPG efficacy outcome = mean of the last five FPG within the range of 5–7.2 mmol/L or 90–129.6 mg/dL (inclusive).
[d]Alternate composite outcome = alternate FPG efficacy outcome in target, with no hypoglycemia.
LTHome, web-tool.

well as at least one asymptomatic hypoglycemia was similar between EUT and LTHome arms (Table 3), with no significant difference between groups.

Subjects randomized to LTHome arm had a significantly greater improvement in fear of hypoglycemia (hypoglycemia fear score [HFS] change 0.0 in LTHome vs. 4.1 on EUT; $P = 0.04$) and in diabetes distress (DDS −8.8 in LTHome vs. −3.1 in EUT; $P = 0.04$) on an average (Table 4). The DDS score reduction reported by the subjects in the LTHome arm was mainly driven by a perceived reduction of emotional burden as well as reduced regimen distress.

Survey responses suggested a high degree of satisfaction with the home-based web tool use: only 39% of the respondents found it somewhat constraining to have to use the system every day; 84% rarely missed entering SMBG; and 74% affirmed that ''every day'' was their preferred frequency for entering the SMBG data—instead of less frequently. Seventy-nine percent of users stated that they are very likely to recommend this web-based home titration model to other people with diabetes on insulin therapy and 71% of respondents felt empowered by using the system as it gave them more control over their disease.

Outside of the scheduled study visits (4, 8, and 12 weeks), significantly less number of patients needed additional HCP visits in LTHome compared to EUT by the 12-week trial end. The number of subjects attending one additional visit was four in LTHome versus 12 in EUT. Furthermore, in the EUT arm, 11 subjects sought two additional visits, while 10 needed >2 additional visits; the corresponding number of subjects was 2 and 0 in LTHome arm for 2 or >2 additional visits, respectively. Overall, the mean number of additional HCP visits was 0.13 for LTHome and 1.22 for EUT ($P < 0.01$).

Table 4. Patient Satisfaction Score Changes from Randomization to Twelve Weeks

		Mean	*SD*	P *value*
Change DTSQs	LTHome	3.2	7.1	0.69
	EUT	2.7	5.0	
Change HFS	LTHome	0.0	9.6	**0.04**
	EUT	4.1	12.5	
Change total DDS score	LTHome	−8.8	17.5	**0.04**
	EUT	−3.1	13.5	
Change emotional burden	LTHome	−3.1	5.9	**0.03**
	EUT	−1.1	4.2	
Change physician distress	LTHome	−0.9	4.9	0.10
	EUT	0.4	4.2	
Change regimen distress	LTHome	−4.3	5.6	**0.02**
	EUT	−2.0	5.0	
Change interpersonal distress	LTHome	−0.5	3.6	0.61
	EUT	−0.3	2.7	
Change WHO5 score	LTHome	1.1	3.8	0.83
	EUT	1.3	3.9	
Change WHO5 percentage	LTHome	4.5	15.3	0.83
	EUT	5.1	15.6	

DTSQ, diabetes treatment satisfaction questionnaire; HFS, hypoglycemia fear score; DDS, diabetes distress score; WHO5, WHO-5 well-being index. Boldfaced *P* values are statistically significant ($P < 0.05$).

Discussion

The results of the randomized, pilot INNOVATE trial suggest clinical utility of LTHome-based insulin glargine titration, together with greater improvement in patient satisfaction scores and less resource utilization, compared to traditional HCP-diabetes educator-directed insulin titration (EUT arm).

Overall, we observed the following results: (i) successful implementation of LTHome in a community-based, multicenter trial; (ii) the predefined primary outcome did not meet statistical noninferiority in the LTHome arm compared to EUT, whereas all the other clinical parameters of glucose-lowering efficacy (alternate FPG efficacy outcome, alternate composite outcome, A1C reduction, and proportion reaching target A1C) were similar in LTHome and EUT arms; (iii) no statistically significant differences in hypoglycemia endpoints between LTHome and EUT; (iv) subjects in the LTHome arm perceived less fear of hypoglycemia (on HFS) as well as a greater reduction in emotional burden and regimen distress on DDS compared to EUT; and (v) reduced HCP resource utilization was observed in LTHome compared to EUT arm.

The use of health information technology (HIT) in clinical practice, similar to the LTHome web-tool used in INNOVATE, may help overcome practical barriers to hyperglycemia control in T2DM. Indeed, a recent United States evidence report titled ''Enabling patient centered care (PCC) through Health Information Technology'' asserted that particular attention needs to be given to studies that directly examine the effects of HIT applications on measures of PCC, including shared decision-making, patient–clinician communication, and responsiveness to the preferences of individual patients.[11]

Few studies have been published using computer-assisted insulin titration. In a pilot usability study among four patients with no prior experience with a web-based self-management system for insulin titration (PANDIT), Simon et al. found that patients were capable of consulting the web-based system without encountering significant usability problems.[12] In another limited 4-week pilot study of 10 randomly recruited patients with T2DM,[13] even though patients were observed to have enough knowledge of the need for insulin adjustment, the insulin self-titration system helped them additionally to verify their reasoning.

In the proposed Di@log randomized control trial,[14] Roek et al. hypothesize that multiple benefits in terms of increases in treatment satisfaction, quality of life, as well as self-efficacy based on the self-regulation theory of Leventhal will be achieved by an Internet-based intervention for self-titration of insulin therapy.[15,16] Notably, in the INNOVATE trial, improved patient satisfaction score changes—with less fear of hypoglycemia (on HFS) as well as a greater reduction in emotional burden and regimen distress on DDS—were indeed observed among patients randomized to LTHome. In addition, the INNOVATE trial suggests potential benefits of cost-saving as well as prudent use of scarce diabetes education resources—by letting delegated non-healthcare professionals train patients on the web-based LTHome tool for basal glargine insulin titration. Indeed, automated basal insulin titration led to reduced HCP resource utilization in our trial.

Despite these potential benefits of HIT, we acknowledge that computer-assisted insulin self-titration systems mainly focus on helping patients overcome barriers related to the cognitive components of insulin titration. Yet, other

barriers (e.g., psychological or physical) could still impede effective clinical use of such systems and need to be investigated further.[17]

INNOVATE trial results have potential implications for design as well as analyses of future research trials utilizing HIT for insulin titration. Composite outcomes in the INNOVATE trial included both FPG target achievement and avoidance of hypoglycemia. FPG targets have been achieved to a higher degree in previous randomized trials for basal insulin titration[18–20] than those achieved in INNOVATE, which may be explained by ''real-world'' insulin titration steps used in our trial compared to the forced titration algorithms in treat-to-target trials.

In addition, minimizing the risk of hypoglycemia is considered an important clinical goal for insulin titration. The risk of developing hypoglycemia is generally proportional to the attained level of glycemic control.[21–23] Major clinical studies in both type 1 diabetes (DCCT) and T2DM (ACCORD) demonstrate about a threefold increase in severe hypoglycemia on therapy intensification.[24,25] However, in terms of frequency, a meta-analysis of 13 randomized controlled trials found that severe hypoglycemia occurs in 5% of subjects treated for an average of 5 years.[26]

Extrapolating to INNOVATE, it was not surprising that there was no severe hypoglycemia in either trial arm during the trial. Because of the aforementioned reasons, additional outcomes analyzed in INNOVATE (alternate mean of the last five FPG target achievement, alternate composite outcomes, A1C reduction, as well as proportion achieving A1C ≤7% [53 mmol/mol]) may be preferred for glucose-lowering efficacy comparisons in further trials of LTHome to help guide future clinical usage.

One further strength of this multicenter trial is the use of a single community-based group of endocrinology specialist clinics, which share electronic medical records and standardized resources and staffing, to optimize the homogeneity of protocol procedures and data collection methods.

One of the limitations of INNOVATE is the restricted generalizability of LTHome (and other HIT platforms) usage to patient populations that may be less computer proficient, for example, populations of old age, lower education level or computer literacy, and cognitive impairment.

Second, the EUT arm in this trial (using a specialist HCP-driven DEP) may be considered as exceeding standard of care compared to the majority of community-based general physician practices and did receive more HCP resources compared to LTHome. Because of the protocol followed, INNOVATE signals important savings on cost as well as resource utilization for DEPs and HCP.

In addition, a 12-week duration may be considered limited time for follow-up in the INNOVATE pilot trial. It is possible that subjects, especially among the insulin naive group, may take several weeks to get sufficiently familiar with a new web-based tool while learning the new tasks of insulin administration. Indeed, within INNOVATE, fewer patients had reached a stable insulin dose over the last 7 days before the 12-week end of trial visit in EUT versus LTHome arm (data not shown) indicating the possibility of ongoing dose titration. On the contrary, it is also plausible that patients may grow tired of this technology use over time and hence lose clinical efficacy. Future trials with longer duration can help clarify this question.

Finally, usability statistics of LTHome could also have affected the achievement of glucose reduction efficacy outcomes, as the dose recommendations for this web-tool are dependent on daily frequency of glucometer testing as well as data entry into the web-based algorithm. It should be emphasized that, despite this possible shortcoming, we adhered to the pre-defined ITT analysis for analyzing all outcomes in this trial.

INNOVATE is the largest, completed randomized controlled trial in application of HIT—to our knowledge—addressing web-based insulin titration to support patient-centered glucose control in the convenience of their home. Further research is urgently needed in this growing area of technology use in healthcare, including the possibility to improve algorithms for HIT titration and ascertain the non-inferiority of glucose reduction efficacy—together with safety parameters—of the LTHome rules engine for titration of long-acting insulin glargine. In addition, to trials with LTHome web-tool, we suggest that titration algorithms incorporated within a glucometer or via using mobile devices (which may be more generalizable and less cumbersome) should undergo similar efficacy and safety trials.

Once this information on safety and efficacy of HIT is confirmed, the clinical usage of such technology has the potential to transform real-world insulin management in three ways: (i) reduce physician and patient barriers related to complexity of titration or lack of physician time/resources; (ii) improve timeliness of basal insulin titration leading to greater A1C goal achievement than currently seen in clinical practice[3,27]; and (iii) reduce the resources required for basal insulin initiation and titration such as specialized physicians and diabetes education centers. Future research on the costs of HIT use, for example, LTHome, will need to take into consideration the specific economic perspective of stakeholders, including patients, clinicians, HCPs, and healthcare insurers.

Author Contributions

H.B. participated in the trial concept and protocol design, trial supervision, data analysis, interpretation of data, wrote and revised the manuscript. K.V. participated in the trial concept and protocol design and reviewed/edited the manuscript. C.Y. performed the statistical verification and analysis of data, contributed to the discussion, and reviewed/edited the manuscript. R.A. participated in the trial concept and protocol design and contributed to revising the manuscript. Dr. H.B. 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.

Author Disclosure Statement

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