Feasibility of Simplification From a Basal-Bolus Insulin Regimen to a Fixed-Ratio Formulation of Basal Insulin Plus a GLP-1RA or to Basal Insulin Plus an SGLT2 Inhibitor: BEYOND, a Randomized, Pragmatic Trial

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Diabetes Care 2021;44:1353–1360 | https://doi.org/10.2337/dc20-2623

OBJECTIVE

BEYOND trial evaluated the feasibility of either basal insulin plus glucagon-like peptide 1 receptor agonist (GLP-1RA) or basal insulin plus sodium–glucose cotransporter 2 inhibitor (SGLT2i) to replace a full basal-bolus insulin (BBI) regimen in participants with type 2 diabetes and inadequate glycemic control.

RESEARCH DESIGN AND METHODS

Participants were randomized (1:1:1) to *1*) intensification of the BBI regimen ($n = 101$), *2*) fixed ratio of basal insulin plus GLP-1RA (fixed-combo group; $n = 102$), and *3*) combination of basal insulin plus SGLT2i (gliflo-combo group; $n = 102$). The primary efficacy outcome was change from baseline in HbA_{1c} at 6 months.

RESULTS

Baseline characteristics were similar among the three groups (mean HbA_{1c} was 8.6% [70 mmol/mol]). At 6 months, patients experienced similar reduction in HbA_{1c} level ($-0.6 \pm 0.8\%$, $-0.6 \pm 0.8\%$, and $-0.7 \pm 0.9\%$, mean ± SD, respectively; noninferiority $P < 0.001$ vs. BBI), and the proportion of patients with $HbA_{1c} \leq 7.5\%$ was also similar (34%, 28%, and 27%, respectively; $P = 0.489$). Total insulin dose increased in the BBI group (62 units/day) and decreased both in the fixed-combo and gliflo-combo groups (27 units/day and 21 units/day, respectively; $P < 0.01$). The proportion of patients with hypoglycemia was 17.8%, 7.8%, and 5.9%, respectively ($P = 0.015$). There were 12 dropouts in the fixed-combo group, 9 in the gliflo-combo group, and none in the BBI group.

CONCLUSIONS

BEYOND provides evidence that it is possible and safe to switch from a BBI regimen to either a once-daily fixed-combo injection or once-daily gliflozin added to basal insulin, with similar glucose control, fewer insulin doses, fewer injections daily, and less hypoglycemia.

Type 2 diabetes is a progressive chronic disease responsible for long-term vascular complications and mortality worldwide. According to the last estimates of the

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Received 23 October 2020 and accepted 1 March 2021

Clinical trial registry no. NCT04196231, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.14140991

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts

D.G. and M.L. share first authorship.

International Diabetes Federation, 463 million people were living with diabetes in 2019, a number projected to rise to 700 million in 2045 (1). Given the natural history of diabetes and the progressive decline in β-cell function, use of insulin is often required. However, insulin therapy is burdened by challenging issues, such as the risk of hypoglycemia, weight gain, and the complexity of injectable treatment (2). Nowadays, about one-fourth of people with type 2 diabetes are currently on insulin therapy (3,4). However, only 50% of patients with type 2 diabetes who use insulin achieve an optimal glucose control (HbA_{1c} <7%), and the percentage of patients with HbA_{1c} ≥9% is rapidly increasing (3,5).

According to the current Standards of Medical Care in Diabetes released by the American Diabetes Association, an intensification of injectable therapy can be considered when basal insulin dose is >0.5 units/kg/day and HbA_{1c} remains above the target level, either with association of glucagon-like peptide 1 receptor agonists (GLP-1RAs) or multiple doses of insulin rapid analogs (6). The combination therapy of basal insulin with a GLP-1RA represents a synergic and complementary therapeutic strategy, resulting in robust glucose-lowering effects and reduced body weight and risk of hypoglycemia as compared with intensified insulin regimens (7–9). There is evidence from meta-analyses of randomized controlled trials that regimens based on basal insulin plus GLP-1RA, as separate preparations of each component or as a fixed-ratio combo, significantly improve glycemic control in terms of HbA_{1c} reduction and number of patients at target (HbA_{1c} <7%), with weight loss and similar hypoglycemic risk compared with other injectable therapy (9,10). Two different once-daily fixed-ratio combinations of basal insulin plus a GLP-1RA are available after November 2016: insulin glargine plus lixisenatide (IGlarLixi) and insulin degludec plus liraglutide (IDegLira). The use of a fixed-ratio combo, which allows both drugs to be administered in a single injection, may be valuable to patients on basal insulin therapy in whom HbA_{1c} is not sufficiently controlled, when there is no need or willingness to increase the number of daily injections.

The inhibitors of sodium–glucose cotransporter 2 (SGLT2i) or gliflozins (canagliflozin, dapagliflozin, and empagliflozin) inhibit glucose reabsorption in the proximal convoluted tubule of the kidneys, increasing urinary glucose excretion and lowering blood glucose levels without risk of hypoglycemia. They showed beneficial effects in promoting weight loss and lowering blood pressure, with a significant amelioration of cardiovascular outlook (11–13). Moreover, the combination of basal insulin and SGLT2i has proved to be safe and effective, leading to a better glycemic control and weight loss, without increasing risk of hypoglycemic events (14).

A basal-bolus insulin (BBI) regimen still represents the ultimate chance for many patients with type 2 diabetes who do not achieve the desired level of glycemic control (15). A simplification of intensive insulin treatment, if possible, is advisable for these patients in order to improve medication adherence and quality of life (16,17). We designed a randomized trial in patients with type 2 diabetes to evaluate the effects of replacing a BBI regimen with either a fixed- combo of insulin plus GLP-1RA or a combination of basal insulin plus SGLT2i.

RESEARCH DESIGN AND METHODS

Durability of Combination of Insulin and GLP-1 Receptor Agonist or SGLT-2 Inhibitors Versus Basal-Bolus Insulin Regimen in Type 2 Diabetes (BEYOND) is a 6-month, randomized, pragmatic, parallel-group, active-control, open-label, single-center trial that evaluates the efficacy and safety of either basal insulin plus GLP-1RA or basal insulin plus SGLT2i to replace a full BBI regimen in participants with type 2 diabetes experiencing inadequate glycemic control (HbA_{1c} >7.5% [58 mmol/mol]), with or without metformin. The active control group consisted of patients with type 2 diabetes continuing the BBI regimen by their usual diabetes care. The study protocol has been built up according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (18), approved by the Medical Ethics Committee of the University of Campania "Luigi Vanvitelli" (number 1_11_07_2019) and registered on ClinicalTrials.gov (NCT04196231). The protocol complies with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All participating patients provided signed informed consent at the first visit in the presence of the medical staff of the study, confirming that they understood all of the procedures.

Study Population

Recruitment for the trial started in July 2019 among subjects with type 2 diabetes admitted to the inpatient and outpatient departments of the Division of Endocrinology and Metabolic Diseases at the University of Campania "Luigi Vanvitelli" in Naples, Italy. However, preselection of patients started earlier (March 2019) in order to verify the eligibility criteria valid for recruitment and accelerate the subsequent randomization. The key eligibility criteria at screening were age >35 years, HbA_{1c} >7.5% (58 mmol/mol), and current use of a full BBI regimen (four injections daily), with or without metformin, for at least 6 months. Exclusion criteria were type 1 diabetes or latent autoimmune diabetes in adults, history of diabetes secondary to pancreatitis or pancreatectomy, use of GLP-1RA, SGLT2i, or dipeptidyl peptidase 4 inhibitor within the last 3 months, history of diabetic ketoacidosis or pancreatitis, impaired kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), liver insufficiency, pregnancy or planned pregnancy, and history of cancer within 5 years prior to baseline.

Trial Design

After the screening visit, patients who were eligible for the study and willing to participate in the trial were randomized, by simple randomization using a computer-generated sequence, 1:1:1 to: *1*) intensification of the BBI regimen (three injections of rapid insulin analog at meals and one injection of basal insulin at bedtime), *2*) fixed-ratio combination of basal insulin plus GLP-1RA (fixed-combo), and *3*) combination of basal insulin plus SGLT2i (gliflo-combo). A further 1:1 randomization was performed for participants assigned to the fixed-combo group, based on a similar degree of effectiveness of the two formulations

(9,10). Similarly, participants assigned to the gliflo-combo group were further randomized to one of the three SGLT2i with 1:1:1 ratio. Patients of the fixed-combo group discontinued all insulin injections and started a single daily injection of one of the two combinations (IDegLira or IGlarLixi) at the starting recommended doses. Patients of the gliflo-combo group discontinued all rapid insulin injections at meals, while preserving the basal insulin injection at bedtime and adding an SGLT2i (canagliflozin, empagliflozin, or dapagliflozin) as a single full dose at the main meal of the day.

Owing to its pragmatic nature, this trial did not follow a treat-to-target methodology. In contrast, patients of the three groups were advised to titrate diabetes medications according to the current clinical practice. In particular, patients continuing the BBI regimen received information on how to titrate both basal and rapid insulin on the basis of self-monitored blood glucose measurements, but no detailed algorithm was offered, except when fasting glucose was greater than that of the day before. In this case, an increase of 2–4 units was suggested depending on the degree of glycemic increment (>20 mg/dL plus 2 units and >40 mg/dL plus 4 units). Patients of the fixed-combo group and gliflo-combo group were advised to titrate the daily injectable dose on the basis of prebreakfast self-monitored blood glucose measurements, according to the manufacturer's instructions. All of the included patients were strictly monitored with weekly phone call visits during the first 30 days after the randomization; moreover, patients could contact medical staff by phone calls or visit at site when glucose values, either pre- or postprandial, were >40 mg/dL with respect to the previous values or anytime they required a front-office visit.

Procedures

Height and weight were recorded using a Seca 200 scale (Seca, Hamburg, Germany) with attached stadiometer; BMI was calculated as weight in kilograms divided by the square of height in meters; waist circumference was measured in orthostatic position on the horizontal plane at the superior border of iliac crest, using an appropriate graduated tape; and arterial blood pressure was measured three times, at the end of the physical examination with the patients in sitting position, after a rest of 15 min.

Participants in the study were instructed to correctly use a glucometer and to monitor glucose levels through capillary pick by self-monitoring blood glucose at different times according to the specific arms: patients in the combo groups perform at least one fasting glucose reading per day; in contrast, patients in the BBI group do four measurements per day (one at fasting and the other three 2 h after meals).

HbA_{1c}, plasma glucose, lipid, and creatinine levels were measured by routine laboratory methods. eGFR was calculated using the MDRD formula. Screening for microalbuminuria (urinary albumin-to-creatinine ratio 30–299 mg/24 h) and macroalbuminuria (urinary albumin-to-creatinine ratio ≥300 mg/24-h values) was performed on 24-h urine sampling.

Medication adherence in the gliflo group was calculated as the ratio between the number of pills taken by a patient in a given time divided by the number of pills prescribed by the physician in the same time. A ratio >80% indicates good adherence to treatment (19). Medication adherence in the BBI and the fixed-combo groups was assessed by interview. The validated eight-item Italian version of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) assesses variations in patients' satisfaction related to therapy modifications and is also useful for comparing levels of satisfaction in subjects using different treatment strategies (20). It consists of eight items: items 1, 4, 5, 6, 7, and 8 are summed to form a treatment satisfaction score; and items 2 and 3, which measure the perceived frequency of hyper- and hypoglycemia, are scored as separate items on scales ranging from 0 to 6.

Data Collection and Management

Data were collected from all participants enrolled in the study at baseline and at 3 and 6 months postrandomization. All of the measures were assessed at the Diabetes Unit of University of Campania "Luigi Vanvitelli" by medical staff and project workers specifically trained in the study protocol. All data were stored on an internal electronic secure database accessible to the medical staff only. The study team was responsible for data entry in the database, contacting patients for missing data, ensuring the project proceed as intended, and discussing with the principal investigator all raised issues with the protocol. The internal data monitoring was the responsibility of the study medical staff. The principal investigator is the guarantor of this work and, as such, has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Adverse Events and Withdrawal

Study staff reviewed the occurrence of adverse events at regularly scheduled trial visits, kept records of any events or complaints, and addressed them as needed, according to the local Institutional Review Board protocol. Level 1 hypoglycemia was defined as a blood glucose level <70 mg/dL (<3.9 mmol/L) associated with symptoms or signs (sweating, tremor, and tachycardia); level 2 hypoglycemia as a blood glucose level <54 mg/dL (<3.0 mmol/L); and level 3 (severe) as a blood glucose level <50 mg/dL (<2.8 mmol/L) or needing the assistance of a third party. The study drugs will be suspended if the participant becomes pregnant or withdraws consent. The investigators may suspend the medication for safety reasons or for uncontrolled hyperglycemia (i.e., HbA_{1c} higher than the baseline value in the first assessment). Participants in both the gliflo-combo and fixed-combo groups who withdrew from the study due to lack of treatment efficacy returned to the BBI therapy.

Outcomes

The primary efficacy outcome was change from baseline in HbA_{1c} at 6 months. Secondary outcomes of the study were the proportion of participants with HbA_{1c} ≤7.5% (58 mmol/mol) or ≤8.0% (64 mmol/mol) at 6 months, the percentage of participants with a decrease in HbA_{1c} from baseline ≥0.5% (5 mmol/mol) at 6 months, total daily insulin doses at 6 months, number of daily injections at 6 months,

percentage of participants with hypoglycemia from randomization to 6 months, changes from baseline in body weight and fasting plasma glucose at 6 months, and the level of satisfaction in participants assigned to the different arms.

Statistical Analyses

Sample size calculation was made on the primary end point. Assuming an expected treatment group difference of 0 for HbA_{1c}, a SD of 0.6% (0.6 mmol/mol), and a noninferiority margin of 0.3% (0.3 mmol/mol), a total sample size of 258 participants (86 in each group) was enough to test for noninferiority, with a power of 90% and one-sided significance level of 0.025. Assuming a withdrawal rate of 15%, a total of 305 participants were randomly assigned.

Categorical variables are expressed as frequencies and proportions and continuous variables as mean ± SD (variables normally distributed) or median and interquartile range (variables not normally distributed). The efficacy population consisted of all participants randomized to study treatment. Statistical differences in the primary outcome at 6 months were assessed by ANCOVA with treatment as fixed effect and baseline levels as covariates. The proportions of patients analyzed for secondary outcomes were assessed by contingency tables and χ^2 test. Differences between baseline parameters and 6 months are assessed by two-sample test for comparisons within groups. The safety population consisted of participants who received at least one dose of randomized study medication. P values <0.05 were deemed statistically significant. We conducted all analyses using SPSS version 26.0 (SPSS Inc., Chicago, IL).

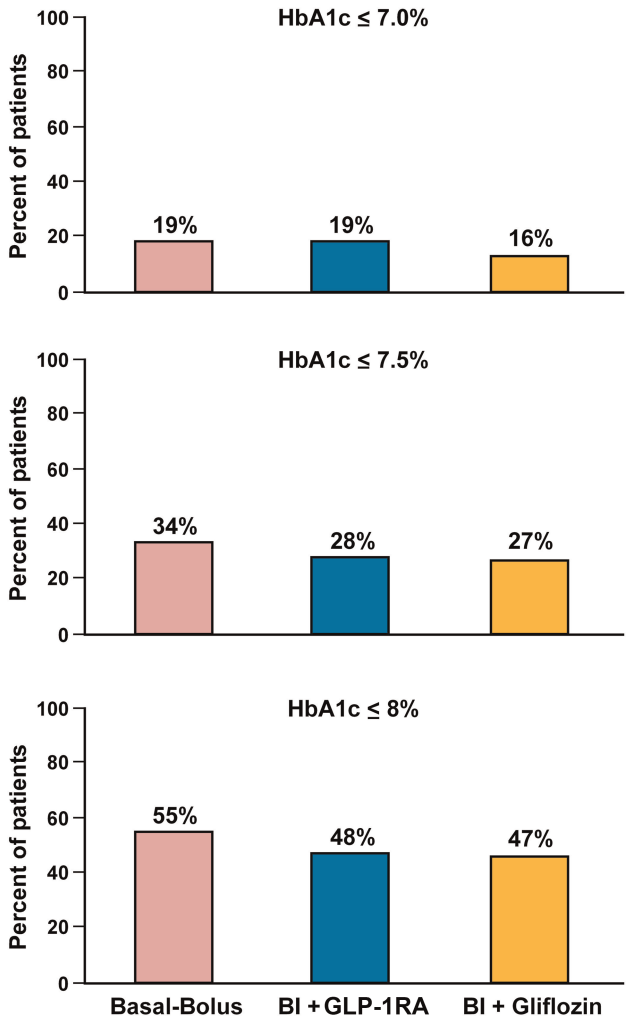

Figure 1—Proportion of patients achieving HbA_{1c} ≤7.0% (top), ≤7.5% (middle), or ≤8% (bottom) after 6 months of treatment in the BBI group (Basal-Bolus), the fixed-combo group (basal insulin [BI] + GLP-1RA), and the gliflo-combo group (BI + Gliflozin).

RESULTS

Participants and Baseline Characteristics

In all, 101 participants were randomly assigned to intensification of BBI, 102 to the fixed-combo (basal insulin plus GLP-1RA) group, and 102 to the gliflo-combo (basal insulin plus gliflozin) group, of whom 94% (100% in the BBI group, 88% in the fixed-combo group, and 91% in the gliflo-combo group) completed the study (Supplementary Fig. 1).

Table 1 shows the baseline characteristics of the patients enrolled in the study. Baseline characteristics were similar among the three groups: the mean age was 61 years, the mean duration of diabetes was 17 years, and mean HbA_{1c} was 8.6% (70 mmol/mol). In the fixed-combo group, IGlarLixi was used by 55 patients and IDegLira by the other 47; in the gliflo-combo group, canagliflozin was used by 37 patients, empagliflozin by 33, and dapagliflozin by 32. There was no difference between the baseline characteristics of patients according to any single drug of the fixed-combo or gliflo-combo groups (data not shown); therefore, the patients are presented all together within each group.

Primary End Point

At 6 months, the mean changes from baseline in HbA_{1c} were −0.6%, −0.6%, and −0.7% in the three groups (BBI, fixed-combo, and gliflo-combo, respectively; $P = 0.356$) (Table 2 and Supplementary Fig. 2); the mean differences between fixed-combo and BBI or gliflo-combo and BBI were −0.09% (95% CI −0.18 to 0.28) and 0.08% (95% CI −0.10 and 0.25), respectively (noninferiority, $P < 0.001$ for both). Within the fixed-combo group, there was no difference in the HbA_{1c} values at 6 months between patients assigned to either IDegLira or IGlarLixi (data not shown). The mean dose of the GLP-1RA at 6 months in the fixed-combo groups was 0.9 ± 1.2 mg liraglutide for IDegLira and 13.5 ± 2.0 μg lixisenatide for IGlarLixi.

Other End Points

The proportion of patients achieving HbA_{1c} ≤7.0% (53 mmol/mol), ≤7.5% (58 mmol/mol), and ≤8.0% (64 mmol/

Table 1—Baseline characteristics of patients

Variables	BBI (n = 101)	Basal insulin plus GLP-1RA (n = 102)	Basal insulin plus gliflozin (n = 102)	P
Males, *n* (%)	40 (39.6)	42 (41.1)	44 (43.1)	0.205
Age, years	62.1 ± 10.2	62.6 ± 9.6	60.5 ± 10.3	0.210
Duration of diabetes, years	17.3 ± 8.1	17.0 ± 9.6	16.9 ± 8.7	0.465
Weight, kg	86.9 ± 10.7	89.3 ± 12.9	86.7 ± 10.4	0.193
BMI, kg/m^2	31.9 ± 3.7	32.6 ± 4.9	31.6 ± 4.3	0.128
Fasting glucose, mg/dL	174.2 ± 48.5	172.8 ± 47.7	171.0 ± 39.7	0.148
HbA_{1c}, %	8.5 ± 1.1	8.5 ± 1.0	8.7 ± 1.1	0.478
Total daily insulin dose, units	49.3 ± 21.2	53.4 ± 27.6	47.8 ± 21.4	0.398
Basal	25.6 ± 11.3	27.3 ± 10.7	24.9 ± 10.5	0.268
Prandial	23.7 ± 10.1	26.1 ± 9.8	23.3 ± 9.6	0.091
SBP, mmHg	134.2 ± 21.2	133.2 ± 17.5	131.3 ± 12.5	0.190
DBP, mmHg	77.6 ± 7.8	78.2 ± 8.2	79.2 ± 11.1	0.664
Total cholesterol, mg/dL	166.5 ± 31.0	173.5 ± 37.0	175.7 ± 37.1	0.562
HDL cholesterol, mg/dL	48.1 ± 13.1	47.7 ± 13.5	46.8 ± 11.4	0.943
LDL cholesterol, mg/dL	94.6 ± 24.8	95.3 ± 25.1	97.8 ± 19.7	0.874
Triglycerides, mg/dL	164.5 ± 53.8	163.8 ± 62.3	170.2 ± 59.9	0.176
Creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.4	0.9 ± 0.3	0.514
eGFR, mL/min/1.73 m^2	73.6 ± 22.8	76.2 ± 22.0	81.7 ± 18.9	0.410
Diabetic retinopathy, *n* (%)	40 (39.6)	39 (38.2)	37 (36.2)	0.266
Diabetic kidney disease, *n* (%)	30 (29.7)	31 (30.3)	29 (28.4)	0.371
Diabetic neuropathy, *n* (%)	33 (32.6)	34 (33.3)	32 (31.3)	0.250
Prior cardiovascular event, *n* (%)	34 (33.6)	36 (35.1)	32 (31.3)	0.842
Metformin users, *n* (%)	56 (55.4)	53 (51.9)	50 (49.0)	0.290
Statin users, *n* (%)	61 (60.3)	59 (57.8)	56 (55.0)	0.310
ACE-i users, *n* (%)	38 (37.6)	39 (38.2)	40 (39.2)	0.308
β-Blocker users, *n* (%)	36 (36.6)	37 (36.2)	35 (34.3)	0.578

Data are mean ± SD unless otherwise indicated. ACE-i, ACE inhibitor.

mol) was not significantly different among the three groups (P = 0.189) (Fig. 1). Moreover, the proportion of patients achieving an HbA_{1c} change ≥0.5% from baseline was 43% in the BBI group, 39% in the fixed-combo group, and 44% in the gliflo-combo group (P = 0.769). According to the protocol, all patients randomly assigned to the intervention groups (fixed-combo and gliflo-combo) abandoned the rapid insulin injections and maintained the basal insulin injection. Total insulin increased in the BBI group and decreased both in the fixed-combo and gliflo-combo groups (superiority, $P < 0.01$ for both, as compared with BBI group) (Fig. 2). In both the fixed-combo and gliflo-combo groups, the dose of basal insulin did not change significantly over time. The number of daily injections remained unchanged at 6 months, with four insulin injections daily in the basal-bolus group (one shot of basal insulin plus three shots of rapid insulin) and one injection daily in both fixed-combo and gliflo-combo groups (Fig. 2).

Patients continuing the BBI regimen exhibited significant (superiority) amelioration in fasting plasma glucose (Table 2). Patients in the fixed-combo group also showed significant improvements in fasting glucose and also a significant reduction in body weight (Table 2). Patients in the gliflo-combo group behaved as those in the BBI group as fasting plasma glucose decrease is concerned. Lipid changes in the three arms are described in the Supplementary Table 2. There was no significant difference among the three groups for parameters of glucose control, arterial pressure, and lipids; body weight reduction was significantly greater in the fixed-combo group only (superiority, P = 0.02).

Hypoglycemia and Adverse Events

The proportion of patients presenting at least one episode of level 1 hypoglycemia (blood glucose level <70 mg/dL with symptoms or signs) was 17.8%, 7.8%, and 5.9% in the BBI, fixed-combo, and gliflo-combo groups, respectively, with a significant difference among them (P = 0.015). Less than 5% of patients in the three groups experienced level 2 (blood glucose level <54 mg/dL) or 3 hypoglycemia (severe: blood glucose level <50 mg/dL or needing the assistance of a third party).

The incidence of adverse events (excluding hypoglycemia) while on therapy was low. In total, 15% of the 305 patients reported 49 adverse events during treatment. There was no event of acute pancreatitis in the fixed-combo group. There were 12 dropouts in the fixed-combo group, 9 in the gliflo-combo group, and none in the BBI group. The dropouts were mainly due to inefficacy of maintaining the HbA_{1c} level below the baseline value at 3 months: eight participants in the fixed-combo group and six participants in the gliflo-combo group

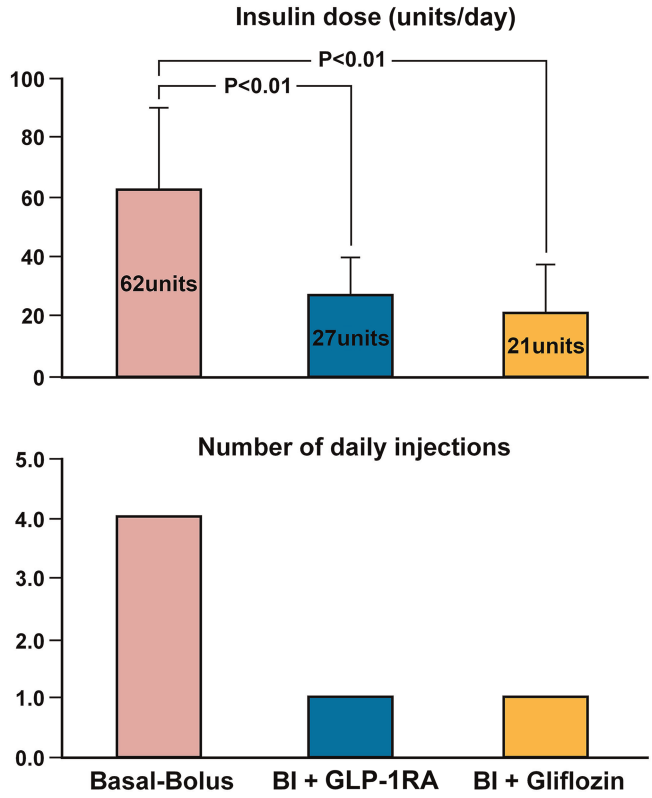

Figure 2—Insulin daily doses (top) and number of injections daily (bottom) after 6 months of treatment in the BBI group (Basal-Bolus), the fixed-combo group (basal insulin [BI] + GLP-1RA), and the gliflo-combo group (BI + Gliflozin).

discontinued for inefficacy. Four participants in the fixed-combo group and three in the gliflo-combo group discontinued for adverse events, mostly gastrointestinal in the fixed-combo and genital mycotic in the gliflo-combo. The baseline clinical characteristics between people with type 2 diabetes who continued the study and those withdrawing from the study did not significantly differ, except for weight, which was greater in the latter (94.8 ± 19.8 vs. 88.7 ± 17.2 kg; $P = 0.045$).

The baseline DTSQ scores were 16.3 ± 5.5, 17.4 ± 6.1, and 15.9 ± 5.8 in the three groups, respectively (BBI, fixed-combo, and gliflo-combo). At 6 months, DTSQ scores increased to 34.2 ± 3.7 ($P < 0.001$) and 33.8 ± 4.1 ($P < 0.001$) in the fixed-combo and gliflo-combo groups, respectively, but remained unchanged in the BBI group (15.7 ± 5.9; $P = 0.345$).

CONCLUSIONS

To our knowledge, our study is the first trial to assess the role of simplification of complex insulin regimen in patients with type 2 diabetes in their current clinical practice, beyond any structured support system associated with classical randomized controlled trials. In this setting, substituting a complex and ineffective BBI regimen with the simple strategy of either a fixed-combo (basal insulin plus GLP-1RA) or gliflo-combo (basal insulin plus gliflozin) achieved glucose control similar to intensification of the previous BBI, with the added benefits of weight loss (fixed-combo only), less insulin doses and daily injections, and less hypoglycemia (both fixed-combo and gliflo-combo).

According to inclusion criteria, no patients with type 2 diabetes enrolled in the trial had HbA_{1c} <7.5% (58 mmol/mol) at baseline. At the end of the trial, a percentage of patients ranging approximately from one-fourth (22%, gliflo-combo group) to one-third (37%, BBI group) reached the HbA_{1c} target of ≤7.5% (58 mmol/mol). Although this may be considered not optimal in term of target achievement, nonetheless, it represents the result of a simple therapeutic algorithm to be used in clinical practice both in outpatient or inpatient departments, beyond the complexity of somewhat discouraging titration protocols. In one recent randomized trial (21), the once-weekly GLP-1RA albiglutide was able to be substituted for prandial insulin in about one-half of people with type 2 diabetes inadequately controlled with a multiple daily insulin injections regimen. However, the change needed a somewhat complex protocol lasting 8 weeks, including starting with halving of the regular insulin dose, discontinuation of regular insulin at 4 weeks, and eventual reintroduction of regular insulin at 8 weeks in case of inefficacy of treatment. Lastly, the intensification of BBI resulted in 61% of patients achieving HbA_{1c} <7% (53 mmol/mol) at the expense of 130 units of daily insulin doses and 75% of patients with severe or documented hypoglycemia.

Besides their practical utilization in the real life of type 2 diabetes, these studies (21 and the current study) represent a step toward simplification of complex insulin regimen by substituting all prandial insulin with a daily or weekly GLP-1RA. Of note, the DUAL VII randomized controlled trial has demonstrated that, in patients with uncontrolled type 2 diabetes on basal insulin and metformin, the fixed-combo IDegLira produced HbA_{1c} reductions comparable to BBI therapy, with lower hypoglycemia rates and weight loss (22). These results have been confirmed by more recent meta-analysis (10).

Our trial is unique at exploring another way of simplification (i.e., the substitution of regular insulin [three shots daily] with a single pill of a gliflozin taken at the main meal of the day). This approach also resulted in a glucose control similar to that of an intensifying BBI regimen, with less total insulin dose, less injections per day, less hypoglycemia, and no weight gain. Noteworthy is that both simplification regimens need one shot daily (i.e., one injection of fixed-combo or one shot of basal insulin in the gliflo-combo). At last, whatever the choice, and besides the metabolic benefits, patients will save three injections daily. This may be an option for the estimated 20 million people with type 2 diabetes worldwide who are likely to be on a BBI regimen (23).

Our approach also allowed us to detect nonresponders early in the course

Table 2—Results at 6 months

	BBI (n = 101)		Basal insulin plus GLP-1RA (n = 102)		Basal insulin plus gliflozin (n = 102)	
Variables	Change vs. baseline	P	Change vs. baseline	P	Change vs. baseline	P
HbA_{1c}, %	−0.6 ± 08	0.005	−0.6 ± 0.8	<0.001	−0.7 ± 0.9	<0.001
Fasting glucose, mg/dL	−18 ± 51	0.011	−24 ± 43	<0.001	−21 ± 36	<0.001
Weight, kg	0.3 ± 1.5	0.159	−1.9 ± 4.3	0.001	−0.6 ± 1.9	0.855
Daily insulin dose, units	12.3 ± 7.4	0.041	−27.1 ± 14.2	<0.001	–26.8 ± 12.4	0.001
SBP, mmHg	1.9 ± 12.4	0.188	0.85 ± 15.7	0.489	−3.4 ± 17.2	0.114
DBP, mmHg	0.8 ± 6.2	0.260	0.12 ± 8.6	0.932	0.8 ± 10.1	0.824
Creatinine, mg/dL	0.03 ± 0.2	0.167	0.01 ± 0.2	0.538	0.02 ± 0.1	0.835
eGFR, mL/min/1.73 m^2	3.1 ± 17.1	0.145	−1.4 ± 15.6	0.424	3.1 ± 14.1	0.102

Data are mean ± SD. The P values indicate difference of changes from baseline.

of the trial: withdrawal for inefficacy occurred in both the fixed-combo group and gliflo-combo group in the first 3 months and was <10% of the total randomized population. Moreover, withdrawal for adverse events also occurred in the first 3 months. This may be important for clinicians in order to have a rapid assessment of the propensity to respond and/or tolerate the simplification. The dropout rates were higher in the two exchange groups than the BBI group. This was quite expected, as the BBI regimen represented either the rescue for those not responding to the exchange regimens or the only available option in the current clinical practice at the top of type 2 diabetes management.

This study has strengths and limitations. Its simple design is a strength because it allows us to evaluate the efficacy of interventions in real-life daily practice conditions and produce results that can be applied in routine practice settings. Moreover, the trial is randomized, which bypasses a major limitation of real-life studies. Furthermore, simplification of BBI therapy is based on an "all or nothing" procedure, in which only basal insulin is maintained and the other drug (GLP-1RA or a SGLT2i) is added. Finally, the addition of a drug with proven cardiorenal benefits (24) may be seen as a further potential merit of the combination strategy.

A limitation of this trial is monocentricity, so its results could be confined to the type of population investigated (White, Caucasian, and living in the Campania County). Moreover, its 6-month duration does not tell whether the metabolic benefits of the simplifications will be durable; however, the scheduled 2-year extension of BEYOND hopefully will tell us the whole story. Finally, its open-label design is a further limitation. Of note, physicians' clinical inertia may have contributed, in the absence of a treat-to-target protocol, to the modest results obtained in the exchange groups, showing its impact also in pragmatic trials (16).

The results of BEYOND seem to confute the dogma about the untouchability of BBI regimen in type 2 diabetes (15) by providing evidence that it is possible and safe to switch from a BBI regimen to either a once-daily fixed-combo injection or once-daily gliflozin pill added to basal insulin. This simplification strategy may work, in terms of significant and clinically relevant reduction of HbA_{1c}, in many patients who maintain their results for at least 6 months. If BEYOND results last more than the present 6-month window of the trial, they will facilitate the role of the physician, will be appreciated by the patient, and hopefully will provide better guidance to practitioners in the choice of medications.

Acknowledgments. The authors thank Francesco Caiazzo, Carla Carbone, Raffaela Carotenuto, Laura Castellano, Lucia Digitale Selvaggio, Daniela Forestiere, Chiara Porcellini (Division of Endocrinology and Metabolic Diseases, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy), Paolo Cirillo, Antonietta Maio, Vlenia Pernice, Annalisa Sarnataro (Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy), and Filomena Castaldo (Division of Endocrinology and Metabolic Diseases, University of Campania "Luigi Vanvitelli," Naples, Italy) for composition of the BEYOND study.

Funding. This study was funded in part by the Associazione "Salute con Stile" (no. 1.2020) (Naples, Italy).

Duality of Interest. D.G. received honoraria for speaking at meetings from Novartis, Sanofi, Eli Lilly and Company, AstraZeneca, and Novo Nordisk. M.I.M. received honoraria for speaking at meetings from AstraZeneca, Novo Nordisk, Bruno Farmaceutici, Mundipharma, and Sanofi. K.E. received honoraria for speaking at meetings from Novartis, Sanofi Aventis, Eli Lilly and Company, AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.G., M.L., M.I.M., and K.E. designed the research. D.G., M.L., R.D.F., L.S., M.G., M.P., G.B., M.I.M., and K.E. conducted the research. M.L., P.C., and L.S. collected data in the electronic database. D.G., M.L., and M.I.M. performed statistical analysis. D.G., M.L., G.B., M.I.M., and K.E. wrote the paper. All authors commented critically and approved the final manuscript. D.G. is the guarantor of this work and, as such, had full access to all of 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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