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ORIGINAL RESEARCH

Delphi-Based Consensus on Treatment Intensification in Type 2 Diabetes Subjects Failing Basal Insulin Supported Oral Treatment: Focus on Basal Insulin + GLP-1 Receptor Agonist Combination Therapies

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ABSTRACT

Introduction: The aim of this study was to elaborate a consensus on treatment intensification strategies in patients with type 2 diabetes failing basal insulin supported oral therapy (BOT). The panel focused on glucagon-like peptide-1 receptor agonists (GLP-1RA) and basal insulin (BI) combinations.

Methods: The authors developed a Delphi questionnaire organized into ten statements and 77 items that focused on: the definition of BOT and BOT failure, intensification strategies, fixed-dose combinations in general and the BI/GLP-1RA fixed combination. The survey was administered in two rounds to a panel of 80 Italian diabetes specialists, who rated their level of agreement with each item on a 5-point Likert scale. Consensus was predefined as > 66% of the panel agreeing/disagreeing on any given item.

Results: Consensus was achieved for 71 of the 77 items. The panel agreed that the use of sulfonylureas in the BOT regimen is inappropriate. BOT failure was defined as individualized targets not being met for glycated hemoglobin, fasting plasma glucose and/or postprandial plasma glucose. There was agreement that postprandial hyperglycaemia and/or presence of nocturnal hypoglycaemia or weight gain define BOT failure. Addition of a GLP-1RA to BI therapy was considered to be the best option for BOT intensification. There was consensus for the use of BI/GLP-1RA fixed combinations as valuable options to increase compliance and safely improve glycaemic control. The panel agreed in considering the fixed-ratio combination insulin degludec/liraglutide (IDegLira) to be preferable to the fixed-ratio combination insulin glargine/lixisenatide (iGlarLixi) in the control of glycaemia, body weight and cardiovascular risk.

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Conclusion: According to this Delphi consensus, the addition of a GLP-1RA may be the best option to intensify BOT. The BI/GLP-1RA fixed combinations may increase compliance and optimize the advantages of each of these molecules.

Keywords: Basalinsulin + GLP-1RA combination therapies; Basal oral therapy; Delphi method; Expert consensus; Insulin intensification; Type 2 diabetes

Key Summary Points

Why carry out this study?

Glycaemic control is suboptimal in a large proportion of patients with type 2 diabetes (T2D), including those who have started insulin treatment, possibly due to clinical inertia in basal insulin uptitration and/or intensification.

The aim of this study was to elaborate a consensus on treatment intensification strategies in patients with T2D failing basal supported-oral therapy (BOT), focusing on the use of fixed combinations of basal insulin and glucagon-like peptide-1 receptor agonists (BI/GLP-1RA).

What was learned from the study?

The use of sulfonylureas in the BOT regimen is considered inappropriate.

BOT failure was defined as individualized targets not being met for glycated haemoglobin, fasting plasma glucose and/or postprandial glucose. Postprandial hyperglycaemia and/or presence of nocturnal hypoglycaemia or weight gain were also aspects contributing to BOT failure.

The fixed-ratio combination insulin degludec/liraglutide (IDegLira) was considered preferable to the fixed-ratio combination insulin glargine/lixisenatide (iGlarLixi) in the control of glycaemia, body weight and cardiovascular risk.

Addition of a GLP-1RA may be the best option to intensify BOT. The BI/GLP-1RA fixed combinations may increase compliance and optimize the advantages of using these molecules together.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13622792.

INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease requiring long-term management of hyperglycaemia aimed at improving clinical outcomes [1]. Current guidelines recommend achieving glycated haemoglobin (HbA1c) target levels of 6.5–7.0% (48–53 mmol/mol) or lower in most patients, provided that these targets are reached with medications associated with a very low risk of hypoglycaemia. Less stringent targets (< 8%; 64 mmol/mol) are suggested for patients with a history of severe hypoglycaemia, limited life expectancy, advanced micro- or macrovascular complications, comorbidities or long-standing diabetes [2, 3]. To reach HbA1c target levels, guidelines recommend using the sequential addition of second-line glucose-lowering agents to ongoing metformin therapy [2]. When individualized HbA1c targets are not achieved, and in the presence of clear signs of insulin deficiency, one of the intensification strategies is the initiation of basal insulin supported oral therapy (BOT) [4].

Despite these recommendations, glycaemic control remains suboptimal in a high proportion of T2D patients, including those who have started insulin treatment. Observational Italian data indicate that 2 years after starting insulin therapy, HbA1c values were still > 8% in almost 50% of patients surveyed [5]. This result is consistent with data from a large observational

study showing that only 28% of European and US insulin-naïve T2D patients had achieved HbA1c levels $\leq$ 7% (53 mmol/mol) 24 months after basal insulin (BI) initiation [6].

These observations clearly suggest a clinical inertia in BI therapy uptitration and/or intensification. In a cohort study evaluating data of 11,696 patients from UK Clinical Practice Research Datalink database, fewer than one third of BOT patients eligible for treatment intensification had their treatment regimen intensified, and the median time to intensification was 3.7 years [7].

BOT can be intensified by combining BI with rapid-acting insulin or by adding a glucagon-like peptide-1 receptor agonist (GLP-1RA) in a loose- or fixed-ratio combination. The addition of a GLP-1RA to ongoing BI therapy has consistently been shown to improve HbA1c and postprandial glucose (PPG) excursions and represents a useful alternative to uptitrating BI or starting a basal-bolus regimen [8]. Clinical trials have shown that this strategy, compared to basal-bolus regimens, allows equal or better glycaemic control with lower risk of hypoglycaemia, has a beneficial effect on body weight and results in a reduction in total daily insulin dose [9–13]. Furthermore, in this population of patients, GLP-1RA can reduce the risk of adverse cardiovascular outcomes [14].

The use of fixed-dose formulations entails a single daily injection, thus reducing the complexity of the therapeutic regimen and increasing treatment adherence. The slower titration of the GLP-1RA dose resulting from the use of these formulations reduces the occurrence of gastrointestinal adverse events and contributes to better treatment adherence and persistence [15, 16]. To date, two fixed-ratio combinations are available: IDegLira (insulin degludec and liraglutide) and iGlarLixi (insulin glargine and lixisenatide).

In this study, we used the Delphi method to elaborate a consensus among a panel of Italian diabetes specialists on treatment intensification strategies in patients with T2D failing BOT. The panel specifically focused on treatment intensification strategies involving the use of BI and GLP-1RA in combination.

METHODS

The Delphi method is a structured technique aimed at obtaining, by repeated rounds of questionnaires, a consensus opinion from a panel of experts in areas where evidence is scarce and opinion is important [17–19]. In the present study, the consensus process consisted of a two-step Delphi method, which took place between February and June 2020.

The online survey was developed by a panel of six physicians, all experts in diabetes management, identified here as key opinion leaders (KOLs) in the field of T2D in Italy. The KOLs identified ten statements involving a total of 77 items which were in serious need of clarification and debate, all focused on topics of BOT: BOT definition, BOT failure definition, insulin intensification strategies, fixed-dose combinations and fixed-dose combinations of BI and GLP-1RA (Table 1). Once developed, the survey was evaluated by 12 external validators to test its understandability and clarity, following which the questionnaire was distributed to 84 expert diabetologists via an online survey platform. The panellists were clinicians with solid experience in the field of diabetes, selected throughout the country among members of Diabetes Clinics Medical Staff, so that the whole country was homogeneously represented [18].

Panellists were asked to rate the level of their agreement or disagreement with each item on a 5-point Likert scale, scored as follows: 1, extremely disagree; 2, disagree; 3, agree; 4, mostly agree; and 5, extremely agree. All answers were categorized into two categories: for the purpose of this study, “extremely disagree” and “disagree” were categorized into category “Negative Consensus”; “agree”, “mostly agree” and “extremely agree” were categorized into “Positive Consensus”. A cutoff of 66% of agreement/disagreement was chosen a priori to represent positive or negative consensus, respectively. No consensus was reached when $<$ 66% of the answers fell in the same category [18, 19]. For the items on which consensus had not been achieved, panellists were asked to rate again in a second round their agreement/disagreement,

Table 1 List of consensus statements

Area	Statement/Item
BOT definition	Statement 1. In my clinical practice Basal Oral Therapy …
	1.1 includes, in addition to basal insulin, in most cases metformin and/or DPP-4 inhibitors
	1.2 does not include a long-acting insulin analogue of the latest generation
	1.3 includes, in addition to basal insulin, in most cases metformin and/or sulfonylureas
	1.4 includes, in addition to basal insulin, in most cases metformin and/or SGLT2 inhibitors
	1.5 is used in most cases in patients with chronic kidney disease
BOT definition	Statement 2. I believe that an appropriate Basal Oral Therapy…
	2.1 includes, in addition to basal insulin, in most cases metformin and/or SGLT2 inhibitors
	2.2 includes, in addition to basal insulin, in most cases metformin and/or sulfonylureas
	2.3 is used in most cases in patients with chronic kidney disease
	2.4 does not include a long-acting insulin analogue of the latest generation
	2.5 includes, in addition to basal insulin, in most cases metformin and/or DPP-4 inhibitors
BOT failure	Statement 3. I believe that the patient is in Basal Oral Therapy failure if …
	3.1 has fasting and postprandial blood glucose values above the individualized target according to patient age and comorbidity
	3.2 has HbA1c values above the target
	3.3 has nocturnal hypoglycaemic episodes
	3.4 has fasting blood glucose values in the target and HbA1c values above the target
	3.5 has a marked increase in body weight
	3.6 has fasting blood glucose and HbA1c values in the target and postprandial glycaemic excursions
	3.7 has fasting blood glucose levels above the target
BOT failure	Statement 4 Critical issues in patients in Basal Oral therapy are:
	4.1 Adherence to therapy
	4.2 Body weight control
	4.3 Costs
	4.4 Titration
	4.5 Achievement of the individualized glycaemic targets
	4.6 Risk of hypoglycaemia
	4.7 Control of postprandial blood glucose
Insulin intensification strategies	Statement 5 In a patient in Basal Oral Therapy not adequately controlled…
	5.1 I change the basal insulin
	5.2 I switch to multi-injection insulin therapy
	5.3 I titrate basal insulin
	5.4 I add another oral agent
	5.5 I carry out an educational reinforcement
	5.6 I change therapy by adding a GLP-1 receptor agonist
	5.7 I change therapy by replacing basal insulin with a fixed ratio association of basal insulin and GLP-1 receptor agonist
	5.8 I search areas of lipodystrophy
	5.9 I change therapy by replacing basal insulin with a GLP-1 receptor agonist
Insulin intensification strategies	Statement 6 I believe that the advantages of adding a GLP-1 receptor agonist to basal insulin are:
	6.1 Minimization of undesirable effects
	6.2 Synergy of the mechanisms of action of the individual molecules
	6.3 Control of body weight
	6.4 Cardiovascular protection
	6.5 Protection of kidney function
	6.6 Effective control of fasting and postprandial blood glucose
	6.7 Facilitating patient adherence to injection therapy

Table 1 continued

Area	Statement/Item
Fixed-dose combinations	Statement 7 In my opinion, fixed-dose combinations…
	7.1 have a better cost/effectiveness profile
	7.2 reduce the risk of mortality and hospitalization
	7.3 potentiate side effects of individual molecules
	7.4 prevent the optimization of the dosages of individual molecules
	7.5 are always an advantage
	7.6 help improving compliance and/or adherence
	7.7 offer little help compared to a loose dose combination
	7.8 maximize effectiveness of individual molecules
Fixed-dose combinations of basal insulin and GLP-1RA	Statement 8 I believe that the advantages of replacing basal insulin (in a patient in BOT failure) with a fixed dose combination of basal insulin and GLP-1 receptor agonist are:
	8.1 Control of body weight
	8.2 Efficacy in fasting and postprandial glucose control
	8.3 Protection of kidney function
	8.4 Reduction of insulin dosages
	8.5 Minimization of side effects of individual molecules
	8.6 Maximizing the efficacy of individual molecules
	8.7 Facilitating patient compliance with injection therapy
	8.8 Cost reduction
	8.9 Cardiovascular protection
Fixed-dose combinations of basal insulin and GLP-1RA	Statement 9 In my clinical practice IDegLira …
	9.1 is considered a strengthened basal insulin
	9.2 is an alternative to multi-injection insulin therapy (or basal bolus)
	9.3 guarantees cardiovascular protection
	9.4 helps achieving therapeutic targets
	9.5 is not preferred due to the need to reduce the initial insulin dosage
	9.6 limits hypoglycaemia episodes and weight gain
	9.7 is not preferred due to the limitations to the titration of the GLP-1 receptor agonist
	9.8 is an alternative to the loose dose combination of basal insulin and GLP-1 receptor agonist
	9.9 could be considered a useful therapeutic option in the patient with chronic kidney disease
	9.10 reduces the gastrointestinal side effects of the GLP-1 receptor agonist due to the gradual titration
Fixed-dose combinations of basal insulin and GLP-1RA	Statement 10 In my clinical practice iGlarLixi …
	10.1 limit hypoglycaemia episodes and weight gain
	10.2 is an alternative to the loose dose combination of basal insulin and GLP-1 receptor agonist
	10.3 helps achieving therapeutic targets
	10.4 is an alternative to multi-injection (or basal-bolus) insulin therapy
	10.5 is not preferred due to the limitations to the titration of the GLP-1 receptor agonist
	10.6 reduces the gastrointestinal side effects of the GLP-1 receptor agonist due to the gradual titration
	10.7 is considered a strengthened basal insulin
	10.8 could be considered a useful therapeutic option in the patient with chronic kidney disease
	10.9 guarantees cardiovascular protection
	10.10 is not preferred due to the need to reduce the initial insulin dosage

BOT Basal insulin supported oral therapy, *DDP-4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *IDegLira* fixed-ratio combination insulin degludec/liraglutide, *iGlarLixi* fixed-ratio combination insulin glargine/lixisenatide, *SGLT2* sodium-glucose co-transporter-2

after being provided with relevant literature on the topic, selected by the KOLs.

Descriptive statistics were used to summarize the results from rounds 1 and 2.

The study is based on a survey that does not involve the participation of human subjects nor patient data management and does not aim to modify the current clinical practice of participants. Consequently, this study did not require ethical approval.

RESULTS

In the first round of the Delphi survey, there were 80 respondents among the 84 invited panellists (response rate 95%). Round 2 was completed by all of the 80 panellists who responded to round 1. Mean age of the respondents was 48 years and 65% were female (Table 2). In round 1, consensus was reached for 62 of the 77 statements (80.5%). The second round was performed on the 15 items for which consensus had not been reached, and consensus was reached for nine of these 15 items. Overall, consensus was ultimately reached for 71 items of the Delphi survey (92.2%), while no consensus was reached for six items (Fig. 1).

Table 3 summarizes the statements and items and presents the percentage agreement for each.

Table 2 Characteristics of responders in the Delphi survey

Characteristics of responders	Values
Gender (female)	65%
Mean age (years)	48 ± 9.82
Age (years)	
≤ 40	28.8%
41–50	28.8%
> 50	42.5%
Italian region	
Northern Italy	41.3%
Central Italy	33.8%
Southern Italy	25.0%

Values in table are presented as a percentage or as the mean ± standard deviation,

BOT Definition

The panellists strongly agreed that, in clinical practice, BOT includes in most cases, in addition to BI, metformin and/or a dipeptidyl peptidase-4 (DPP-4) inhibitor (91%) or an sodium-glucose co-transporter-2 (SGLT2) inhibitor (98%). Panellists also strongly agreed to define appropriate BOT when metformin and/or SGLT2 inhibitors (99%) or DPP-4 inhibitors (93%) are given in combination with BI. Panellists agreed that the sulfonylureas are not commonly included as an option for their patients in BOT and that these options should not be considered an appropriate BOT strategy (78 and 83%, respectively). A negative consensus was reached on the item stating that in clinical practice BOT does not include a long-acting insulin analogue of the latest generation (70%).

There was no consensus on whether BOT is used preferentially or should be used in patients with chronic kidney disease (CKD).

BOT Failure

There was clear consensus on the definition of BOT failure; in particular, the panellists strongly agreed that a patient is in BOT failure when fasting plasma glucose (FPG), PPG and/or HbA1c levels are above the individualized targets (96%). Furthermore, panellists reached a consensus in defining BOT failure if nocturnal hypoglycaemic episodes are experienced (73%) or if there is a marked increase in body weight (70%).

There was consensus that all of the following aspects are critical in BOT: control of PPG (89%); achievement of the individualized glycaemic targets (82%); risk of hypoglycaemia (77%); body weight control (76%); insulin titration (75%); and adherence to therapy (70%). Costs of BOT were not considered to be a critical issue (71%).

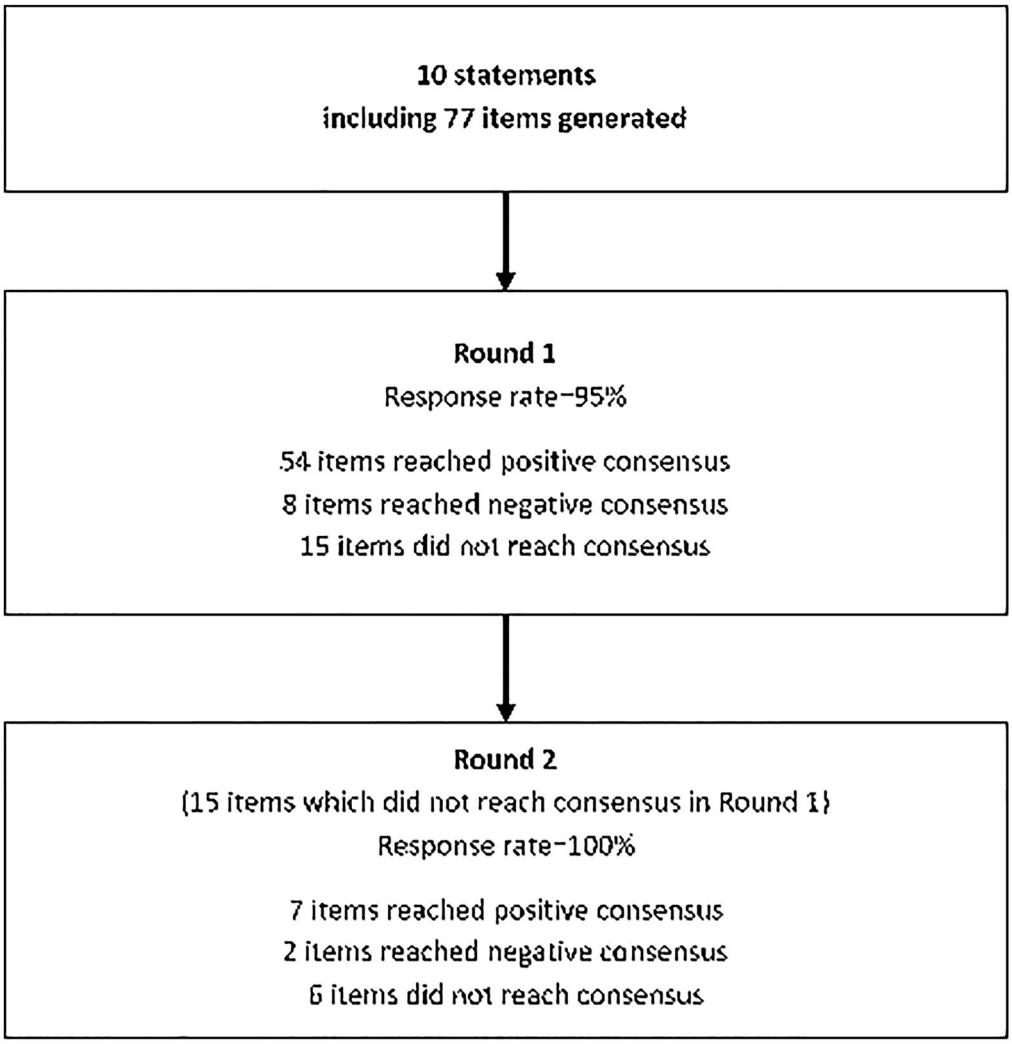

Fig. 1 Delphi survey flowchart

Insulin Intensification Strategies

Panellists strongly agreed on the strategies to adopt when BOT fails in a patient. The following therapeutic strategies were supported by the panellists, with agreement ranging between 95 and 99%: replacing BI with a fixed-dose combination of BI/GLP-1RA; adding a GLP-1RA to BI ongoing therapy; uptitrating insulin doses; providing educational reinforcement; and searching for areas of lipodystrophy. Consensus was also reached that the addition of another oral agent (81%) or a change of BI (75%) could be useful. Finally, agreement was reached on the replacement of BI with a GLP-1RA (69%) or the switch to multi-injection insulin therapy (68%).

Consensus on the advantages of adding GLP-1RA to ongoing BI therapy was almost unanimous. Panellists were in complete agreement that the advantage of the combination therapy is derived from the synergy of the mechanisms of action of the individual molecules, with an efficacy on both FPG and PPG, thereby providing both cardiovascular and kidney protection, and a positive effect on body weight. Furthermore, consensus was reached that the

Table 3 Results of the Delphi survey

Statement	Consensus score	
	Disagreement (score 1–2) (%)	**Agreement (score 3–5) (%)**
Statement 1. In my clinical practice Basal Oral Therapy …		
1.1 includes, in addition to basal insulin, in most cases metformin and/or DPP-4 inhibitors	9	91
1.2 does not include a long-acting insulin analogue of the latest generation	70	30
1.3 includes, in addition to basal insulin, in most cases metformin and/or sulfonylureas	78	23
1.4 includes, in addition to basal insulin, in most cases metformin and/or SGLT2 inhibitors	3	98
1.5 is used in most cases in patients with chronic kidney disease	46	54
Statement 2. I believe that an appropriate Basal Oral Therapy…		
2.1 includes, in addition to basal insulin, in most cases metformin and/or SGLT2 inhibitors	1	99
2.2 includes, in addition to basal insulin, in most cases metformin and/or sulfonylureas	83	18
2.3 is used in most cases in patients with chronic kidney disease	39	61
2.4 does not include a long-acting insulin analogue of the latest generation	90	10
2.5 includes, in addition to basal insulin, in most cases metformin and/or DPP-4 inhibitors	8	93
Statement 3. I believe that the patient is in Basal Oral Therapy failure if ……		
3.1 has fasting and postprandial blood glucose values above the individualized target according to patient age and comorbidity	4	96
3.2 has HbA1c values above the target	3	98
3.3 has nocturnal hypoglycaemic episodes	28	73
3.4 has fasting blood glucose values in the target and HbA1c values above the target	20	80
3.5 has a marked increase in body weight	30	70
3.6 has fasting blood glucose and HbA1c values in the target and postprandial glycaemic excursions	31	69
3.7 has fasting blood glucose levels above the target	29	71
Statement 4 Critical issues in patients in Basal Oral therapy are:		
4.1 Adherence to therapy	30	70
4.2 Body weight control	24	76
4.3 Costs	71	29

Table 3 continued

Statement	Consensus score	
	Disagreement (score 1–2) (%)	Agreement (score 3–5) (%)
4.4 Titration	25	75
4.5 Achievement of the individualized glycaemic targets	18	82
4.6 Risk of hypoglycaemia	24	77
4.7 Control of postprandial blood glucose	11	89
Statement 5 In a patient in Basal Oral Therapy not adequately controlled…		
5.1 I change the basal insulin	25	75
5.2 I switch to multi-injection insulin therapy	33	68
5.3 I titrate basal insulin	4	96
5.4 I add another oral agent	19	81
5.5 I carry out an educational reinforcement	3	98
5.6 I change therapy by adding a GLP-1 receptor agonist	3	98
5.7 I change therapy by replacing basal insulin with a fixed ratio association of basal insulin and GLP-1 receptor agonist	1	99
5.8 I search areas of lipodystrophy	5	95
5.9 I change therapy by replacing basal insulin with a GLP-1 receptor agonist	31	69
Statement 6 I believe that the advantages of adding a GLP-1 receptor agonist to basal insulin are:		
6.1 Minimization of undesirable effects	18	83
6.2 Synergy of the mechanisms of action of the individual molecules	0	100
6.3 Control of body weight	0	100
6.4 Cardiovascular protection	0	100
6.5 Protection of kidney function	1	99
6.6 Effective control of fasting and postprandial blood glucose	1	99
6.7 Facilitating patient adherence to injection therapy	5	95
Statement 7 In my opinion, fixed-dose combinations…		
7.1 have a better cost/effectiveness profile	13	88
7.2 reduce the risk of mortality and hospitalization	15	85
7.3 potentiate side effects of individual molecules	70	30
7.4 prevent the optimization of the dosages of individual molecules	49	51
7.5 are always an advantage	46	54
7.6 help improving compliance and/or adherence	1	99
7.7 offer little help compared to a loose dose combination	85	15

Table 3 continued

Statement	Consensus score	
	Disagreement (score 1–2) (%)	Agreement (score 3–5) (%)
7.8 maximize effectiveness of individual molecules	20	80
Statement 8 I believe that the advantages of replacing basal insulin (in a patient in BOT failure) with a fixed dose combination of basal insulin and GLP-1 receptor agonist are:		
8.1 Control of body weight	1	99
8.2 Efficacy in fasting and postprandial glucose control	1	99
8.3 Protection of kidney function	3	98
8.4 Reduction of insulin dosages	4	96
8.5 Minimization of side effects of individual molecules	8	93
8.6 Maximizing the efficacy of individual molecules	14	86
8.7 Facilitating patient compliance with injection therapy	1	99
8.8 Cost reduction	15	85
8.9 Cardiovascular protection	1	99
Statement 9 In my clinical practice IDegLira …		
9.1 is considered a strengthened basal insulin	20	80
9.2 is an alternative to multi-injection insulin therapy (or basal bolus)	11	89
9.3 guarantees cardiovascular protection	5	95
9.4 helps achieving therapeutic targets	0	100
9.5 is not preferred due to the need to reduce the initial insulin dosage	79	21
9.6 limits hypoglycaemia episodes and weight gain	0	100
9.7 is not preferred due to the limitations to the titration of the GLP-1 receptor agonist	79	21
9.8 is an alternative to the loose dose combination of basal insulin and GLP-1 receptor agonist	21	79
9.9 could be considered a useful therapeutic option in the patient with chronic kidney disease	0	100
9.10 reduces the gastrointestinal side effects of the GLP-1 receptor agonist due to the gradual titration	3	98
Statement 10 In my clinical practice iGlarLixi …		
10.1 limit hypoglycaemia episodes and weight gain	10	90
10.2 is an alternative to the loose dose combination of basal insulin and GLP-1 receptor agonist	18	83
10.3 helps achieving therapeutic targets	14	86

Table 3 continued

Statement	Consensus score	
	Disagreement (score 1–2) (%)	Agreement (score 3–5) (%)
10.4 is an alternative to multi-injection (or basal-bolus) insulin therapy	24	76
10.5 is not preferred due to the limitations to the titration of the GLP-1 receptor agonist	58	43
10.6 reduces the gastrointestinal side effects of the GLP-1 receptor agonist due to the gradual titration	16	84
10.7 is considered a strengthened basal insulin	33	68
10.8 could be considered a useful therapeutic option in the patient with chronic kidney disease	16	84
10.9 guarantees cardiovascular protection	51	49
10.10 is not preferred due to the need to reduce the initial insulin dosage	74	26

association leads to enhancement of patient adherence (95%) and minimization of side effects (83%).

Fixed-Dose Combinations

Panellists strongly agreed that fixed-dose combinations are useful for improving compliance and adherence (99%) and have a better cost/effectiveness profile (88%) than the individual components. There was also consensus on the utility of fixed-dose combinations for reducing the risk of mortality and hospitalization (85%) and their capacity to maximize the effectiveness of the individual molecules (80%). In addition, there was a negative consensus that loose-dose combinations are more useful than fixed-dose ones (85%) and that fixed-dose combinations can exacerbate side effects of individuals molecules (70%). However, no consensus was reached on whether fixed-dose combinations preclude optimization of the dosages of the individual components or whether they always have an advantage.

Fixed-Dose Combinations of BI and GLP-1RA

There was strong consensus that fixed-dose combinations of BI and GLP-1RA have all of the following benefits: control of body weight (99%); efficacy in FPG and PPG control (99%); facilitating patient compliance with injection therapy (99%); providing cardiovascular (99%) and kidney protection (98%); reducing insulin dosages (96%); minimizing side effects of individual molecules (93%); maximizing the efficacy of individual molecules (86%); and reducing costs (85%).

When the two available fixed-dose combinations were considered, there was consensus that both IDegLira and iGlarLixi are associated with a low risk for hypoglycaemic events and weight increase (100 and 90%, respectively) and are useful in achieving therapeutic targets (100 and 86%, respectively). Panellists also agreed that IDegLira and iGlarLixi could be considered useful therapeutic options in patients with CKD (100% and 84%, respectively).

Panellists agreed in considering IDegLira and iGlarLixi as strengthened BIs (80 and 68%, respectively), as alternatives to multi-injection insulin therapy (89 and 76%, respectively) or as

alternatives to loose-dose combinations of BI and GLP-1RA (79 and 83%, respectively). There was clear consensus that both fixed-dose combinations help reduce gastrointestinal side effects of the GLP-1RA (98% for IDegLira and 84% for iGlarLixi).

Panellists agreed that the need to reduce the initial insulin dosage is not one of the reasons why both fixed-dose combinations are not preferred (79% for IDegLira and 74% for iGlarLixi).

Finally, there was a strong consensus on the effectiveness of IDegLira on cardiovascular protection (95%). No consensus was reached on the cardiovascular protection provided by iGlarLixi.

Panellists disagreed that IDegLira is not preferred due to the limitations to the titration of the GLP-1RA (79%). The same item, but referring to iGlarLixi, did not reach a consensus among the Expert Panel.

DISCUSSION

The consensus reached in this Delphi study provides an overview of how diabetes specialists in Italy manage T2D patients whose BOT failed and gives a snapshot of issues that balance indications from guidelines and unmet needs from clinical practice. Consensus was reached on a variety of statements regarding treatment intensification after failure of BOT. Consensus was not reached on six of the 77 items, mainly due to heterogeneity in the management of patients at this disease stage in clinical practice.

DPP-4 inhibitors and SGLT2 inhibitors were the most widely used drugs associated with BI and metformin in clinical practice, while sulfonylureas were considered to be drugs that were no longer used or inappropriate in association with BI, which is in line with guidelines that recommend avoiding the use of sulfonylureas with BI and metformin due to the high risk of hypoglycaemia with this combination [3, 4]. However, data from the DARWIN T2D study documented that sulfonylureas were still a frequently adopted therapeutic option associated with BI [20].

There is a tendency to prefer newer second-generation insulin analogues since long and ultra-long BI analogues have a similar efficacy in terms of glycaemic control as the first-generation insulins, but with a lower risk of hypoglycaemia. The former have a more physiological pharmacokinetics profile that allows flexibility in the administration time [21].

The lack of agreement on the use of BOT in patients with CKD reflects different approaches in the treatment of this patient population, although recommendations do suggest using BI preferably in combination with a DPP-4 inhibitor in the presence of kidney impairment, especially in elderly patients [3]. CKD affects up to 40% of people with T2D and represents a significant health challenge in terms of management because the majority of glucose-lowering agents must be downtitrated or withdrawn with declining estimated glomerular filtration rate [22]. Therefore, BOT represents a rationale therapy when CKD is present. However, despite the current paucity of data on the use of long-acting BI in patients with T2D and CKD, observational studies have demonstrated that insulin glargine and insulin degludec are effective in reducing HbA1c with a low risk of hypoglycaemic events [23–25]. In a secondary analysis from the DEVOTE trial, a lower rate of severe hypoglycaemia was observed with degludec compared with insulin glargine, even in the presence of CKD [26]. The lack of consensus in our study could also reflect a progressive change, that is still ongoing, in the management of patients with T2D and CKD.

Reaching an agreement on the definition of BOT failure is a prerequisite to identifying strategies for therapy intensification. The panellists reached consensus to consider BOT failure not only in relation to the inability of the therapy to control the traditional glycaemic indicators (HbA1c, FPG, PPG), but also to the presence of side effects, such as nocturnal hypoglycaemia or weight gain.

Fear of hypoglycaemia is one of the determinants of suboptimal glycaemic control. It can be overcome by using an ultra-long-acting insulin analogue, such as degludec, which has been shown to result in a lower incidence of hypoglycaemia, with a reduction in FPG levels [27, 28]. Despite this evidence, newer second-generation insulins are still not used in a large

portion of patients treated with BI, and the risk of hypoglycaemia is still an issue.

The association of increase in body weight with BOT failure is still a debated issue. A meta-analysis of cardiovascular outcome trials on glucose-lowering drugs found that a decrease in bodyweight of 1 kg with glucose-lowering interventions led to a statistically significantly reduction of 5.9% in the relative risk of heart failure [29, 30]. Therefore, weight gain is considered to be a crucial aspect, representing an important challenge in the management of patients with T2D on insulin treatment [31].

The consensus that patients with T2D on BOT who experience hypoglycaemia or weight gain should require a change in therapy even if glycemic targets are met is revolutionary. At the present time, combination therapy with BI and GLP-1RA provides the possibility of reaching glycemic control with lower insulin doses, thereby dramatically limiting the risk of hypoglycaemia and without weight gain. This is one of the most important clinical messages from our survey.

Despite a consensus on the critical role of insulin titration in the BOT strategy, a modest titration of BI in the real-world setting has been observed, contributing to an inadequate glycaemic control [32, 33]. Data from Italian and international studies highlight that more than half of subjects with poorly controlled T2D receive low doses of insulin therapy, confirming a trend towards low insulin titration [6, 34, 37].

Combination therapies, such as BOT, often increase dosing frequency and the treatment burden in patients with T2D, leading to low adherence. In one study, the insulin adherence rate among people with T2D was found to be low, with one quarter of the patients initiating insulin therapy never refilling their prescription [35]. In another study, one third of patients reported insulin omission/non-adherence at least 1 day in the last month, and the majority of physicians reported that their patients did not take their insulin as prescribed [36].

Although costs were not considered to be a critical issue of BOT, it should be noted that a recent study in Italian setting on the two fixed combinations of BI and GLP-1RA showed that IDegLira was associated with improved clinical outcomes at higher costs relative to iGlarLixi. The higher costs were due to higher acquisition costs although these were partially offset by reduced complication-related treatment costs [37].

The consensus on changing BI therapy is in line with existing evidence when the BI is not an ultra-long-acting insulin analogue. Experimental and observational studies have demonstrated that switching to insulin degludec from other BI improved glycaemic control with a low risk of overall hypoglycaemia, irrespective of previous BI therapy [38, 39]. Even in vulnerable older patients, glargine 300 U/ml has demonstrated comparable efficacy to glargine 100 U/ml in terms of HbA1c reduction, associated with fewer nocturnal hypoglycaemic events [40].

Adding GLP-1RA to ongoing BI therapy has several advantages in terms of synergy of action of the individual molecules: efficacy on metabolic parameters; cardiorenal protection; minimization of side effects; and body weight control. There are several well-documented clinical benefits associated with this combination and it is considered to be a safe and effective treatment intensification option [41–43]. In addition, this therapeutic strategy has been found to reduce the risk of major cardiovascular events, as well as all-cause mortality, hospital admission for heart failure and kidney outcomes [44].

Finally, panellists agreed that the association of insulin and GLP-1RA can improve patient adherence. This aspect is fundamental to successful therapy as adherence is a predictor of metabolic control and diabetes complications [45].

As far as BOT intensification is concerned, it is not surprising that consensus was reached on the switch to multi-injection insulin. This consensus reflects physicians' persistent attitude to initiate multi-injection insulin more often than the combination of BI and GLP-1RA. A meta-analysis evaluating the efficacy of GLP-1RA as add-on to insulin in comparison with basal-plus/basal-bolus insulin regimens showed that insulin intensification with GLP-1RA is as effective as multi-injection insulin therapy on achieving the HbA1c target, with the added advantages of significant weight loss, reduced

risk of hypoglycaemia and sparing of insulin dose [41]. Furthermore, the association has been demonstrated to be less expensive than multi-injection insulin therapy when direct and indirect costs are considered [46, 47].

The lack of agreement for the items on whether fixed-dose combinations preclude optimization of the dosages of the individual components or whether they always have an advantage may depend on the personal clinical experience of the respondent with fixed-dose combinations. The latter do have some advantages, but sometimes lack flexibility in how dosages of the individual components are combined.

A loose-dose combination of BI and GLP-1RA could be chosen if the need for full-dose GLP-1RA is prioritized over intensification of the BI dose. It has been demonstrated that, although the loose- and the fixed-dose combinations similarly improved glycaemic control, the loose-dose combination significantly induced a greater body weight reduction than the fixed-dose combination, providing the possibility to use higher GLP-1RA doses. However, despite lower GLP-1RA doses, similar metabolic control was obtained due to the titration of insulin doses [48]. Furthermore, the slower titration of GLP-1RA in the fixed-dose combinations, which follows the titration schedule for the BI component, was found to result in less nausea compared with independent titration of GLP-1RA [49]. The advantages of the fixed-dose combination come from the synergy of the separate mechanisms of action of BI and GLP-1RA, resulting in improved glycaemic control compared with its mono-components given separately, thereby also improving patient compliance. An observational real-life data study reported that patients previously treated with a loose-dose combination of BI and GLP-1RA who switched to a fixed-dose combination showed increased adherence with a subsequent improvement in glycaemic control [50].

Results with liraglutide and insulin degludec in the respective cardiovascular outcome trials [51, 52] reflect the panellists' opinion: there was, in fact, a strong consensus on the potential effectiveness of IDegLira against cardiovascular events. Despite the lack of direct evidence on the safety and efficacy of IDegLira in the prevention of major cardiovascular events, data on the improvement in cardiovascular risk factors in patients treated with IDegLira compared to BI or basal-bolus are available [53]. The advantageous effects of IDegLira on cardiovascular risk factors are consistent with the results from the LEADER trial, even if the dose of liraglutide administered in the co-formulation IDegLira was lower than the dose of 1.8 mg used in the LEADER trial.

The lack of consensus reached on the cardiovascular protection of iGlarLixi probably resulted from a balance between the attitude of some respondents to consider the beneficial effects of GLP-1RA as a class effect and the findings of the ELIXA trial showing that treatment with lixisenatide, compared to placebo, did not provide protection from major adverse cardiovascular events in patients with T2D and recent acute coronary syndrome [54]. These results could be misleading as they might be largely influenced by the literature on the individual components rather than the actual experience of the respondents.

Of note, in the light of the different results from cardiovascular outcomes trials with various GLP-1RA, guidelines underline the importance to use, in the intensification algorithm, GLP-1RA with proven cardiovascular benefit [4].

The technical limitation in optimizing the dose of GLP-1RA with the fixed BI/GLP-1RA combination is overcome by the perception of the clinical benefits of the co-formulation; consequently, the unlikelihood of reaching the maximum GLP-1RA dose is not perceived as a limitation. In a European retrospective real-world study, after 6 months of treatment with IDegLira, HbA1c was significantly reduced by 0.9% in the subgroup of patients on BOT at baseline, with no increase in body weight, and a mean daily dose of IDegLira of 28.5 dose steps (corresponding to 1.03 mg of liraglutide) [55].

No consensus was reached among the Expert Panel on the same item referring to iGlarLixi. The panellists, in fact, believed that the limitations of GLP-1RA titration are not completely overcome by the clinical benefits or by manageability of iGlarLixi. This association offers reduced flexibility in terms of time of

administration in comparison with IDegLira since the daily dose should be administered within 1 h before a meal of the day due to the shorter half-life and duration of lixisenatide as compared to liraglutide. Furthermore, the clinical trial programme DUAL, which evaluated the efficacy and safety of IDegLira, is broader than the LIXILAN trials programme developed for the evaluation of iGlarLixi, and investigated multiple clinical situations, including comparisons of IDegLira with different comparators.

To date, no head-to-head studies with the two fixed-dose combinations are available. Indirect comparisons suggest that the efficacy of both co-formulations in terms of reduction of HbA1c is comparable, although iGlarLixi reduces PPG slightly more than IDegLira due to the action of the short-acting GLP-1RA lixisenatide on slowing gastric emptying. On the other hand, IDegLira has a greater effect on the reduction of FPG due to action of the long-acting GLP-1RA liraglutide [56].

There are some limitations to our study. Even when consensus is reached, there is no guarantee it is generalizable; results are dependent on the limited number and the composition of the respondents. However, to minimize the potential for selection bias, panellists were selected based on their experience in the field of diabetes and their distribution thoughout all regions of Italy. Furthermore, the attrition rates over the two rounds were extremely low, ensuring that the range of expert opinion was adequately represented, and the level of consensus was clearly specified a priori.

CONCLUSIONS

According to this Delphi consensus, failure of BOT is not only defined as not meeting glycemic endpoints, but also by the presence of hypoglycaemia or weight gain. The addition of a GLP-1RA to ongoing BI therapy is clearly identified as the best option to intensify BOT, and the BI/GLP-1RA fixed combinations may increase compliance and optimize the advantages of using these molecules together while providing similar glycemic control.

Some items for which consensus was not reached reflect open questions on which future clinical research will play an important role.

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