Diabetes Ther (2025) 16:1707–1725
https://doi.org/10.1007/s13300-025-01762-3

ORIGINAL RESEARCH

Oral Semaglutide as an Opportunity for an Appropriate Therapeutic Switch in People with Type 2 Diabetes: A Delphi Consensus

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Received: March 28, 2025 / Accepted: May 22, 2025 / Published online: June 20, 2025

ABSTRACT

Introduction: The expanding range of therapeutic options for type 2 diabetes (T2D) calls for a reassessment of clinical scenarios in which existing glucose-lowering therapies might be substituted with the oral glucagon-like peptide 1 receptor agonist (GLP-1 RA) semaglutide (OS). In light of the numerous unresolved questions, a panel of experts was convened to develop practical guidance for clinicians using the Delphi consensus method.

Methods: A panel of 13 experts formulated 31 statements addressing the following clinical scenarios: switch from injectable GLP-1 RA to OS; switch from sodium-glucose cotransporter 2 inhibitor to OS; switch from insulin to OS; switch from dipeptidyl peptidase 4 inhibitor (DPP4i) to OS; switch from "old" oral therapies

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(i.e., sulfonylureas, glinides, pioglitazone, acarbose) to OS. A panel of 28 diabetologists from the Emilia-Romagna region evaluated each statement by assigning a relevance score on a 9-point scale via a dedicated online platform. The RAND/UCLA Appropriateness Method was employed to determine the presence of disagreement among panelists.

***Results*:** Panelists showed agreement for all 31 statements, all considered relevant. Panelists agreed that in many circumstances OS can represent a valuable alternative to injectable GLP-1 RAs, other oral glucose-lowering drugs, and insulin. The selection of OS is justified by its proven effectiveness in reducing glycated hemoglobin and body weight, as well as its positive impact on cardiovascular outcomes and all-cause mortality. Furthermore, OS can allow a simplification of therapy in patients treated with insulin.

***Conclusion*:** In an ever-evolving therapeutic landscape, OS therapy stands as a valuable option in the management of patients with T2D.

Keywords: Type 2 diabetes; Expert consensus; Delphi method; Oral semaglutide

Key Summary Points

Why carry out this study?
The growing availability of therapeutic approaches to type 2 diabetes (T2D) requires a rethinking of the situations where ongoing glucose-lowering treatments could be replaced by the oral glucagon-like peptide 1 receptor agonist (GLP-1 RA) semaglutide.
The aim of the SWITCH (*S*martest *W*ay *I*n *T*he *C*ontrol of a *H*ypercomplex disease) project was to reach a consensus on strategies for a therapeutic switch to oral semaglutide from other glucose-lowering drugs in patients with T2D.
What was learned from the study?
Through a Delphi consensus, a panel of 28 diabetologists reached agreement on the clinical scenarios in which oral semaglutide may represent a valid alternative to injectable GLP-1 RAs, sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, insulin, and "old" oral glucose-lowering drugs.
Oral semaglutide can represent a valuable option in many circumstances where other glucose-lowering drug classes do not produce the expected benefits in terms of metabolic control, cardiorenal protection, or tolerability.

INTRODUCTION

The increase in the population exposed to chronic therapies, as well as the loss of patent protection for many drugs and the emergence of new drugs with overlapping therapeutic indications, has raised the issue of how safe, effective, and appropriate it is to switch between drug classes with the same therapeutic indication, without exposing the patient to any worsening of the drug therapy's benefit/harm profile [1].

Oral semaglutide has recently been introduced to the market. This first oral glucagon-like peptide 1 receptor agonist (GLP-1 RA) has been proven to be effective in improving glycemic control, weight, and cardiovascular risk factors [2, 3] in patients with type 2 diabetes (T2D). Cardiovascular safety of oral semaglutide has also been documented [4] and, recently, the results of the SOUL study, anticipated in a press release, confirmed the efficacy of oral semaglutide in reducing cardiovascular risk in people with T2D in secondary prevention [5].

Oral GLP-1 RA may therefore represent an opportunity in the context of different potential clinical scenarios where a therapeutic switch is needed, ensuring equal or greater therapeutic efficacy on glycemic and weight control, a similar or even greater effectiveness in terms of

cardiovascular protection, and, in specific contexts, a great opportunity to simplify therapy. In this sense, it becomes relevant to evaluate how, when, and in which clinical context a therapeutic switch to oral semaglutide can be considered appropriate.

The aim of the SWITCH (Smartest Way In The Control of a Hypercomplex disease) project was to reach a consensus, using a modified Delphi approach, on strategies for a therapeutic switch to oral semaglutide from other glucose-lowering drugs in patients with T2D. For this purpose, authors developed a specific questionnaire administered in two rounds to a panel of Italian diabetes specialists. Similar methodologies have been presented elsewhere [6].

METHODS

Development of Statements

Statements relative to the place of oral semaglutide in the treatment of people with T2D were identified by a steering group composed of 13 experts in diabetes management, operating in different healthcare districts of the Emilia-Romagna region. In a face-to-face meeting, chaired by a panel moderator experienced in facilitating group discussions and criteria development, the experts were asked to identify key aspects regarding the role of oral semaglutide in T2D relative to the following situations: switch from injectable GLP-1 RA to oral semaglutide; switch from sodium-glucose cotransporter 2 inhibitor (SGLT2i) to oral semaglutide; switch from insulin to oral semaglutide; switch from inhibitors of dipeptidyl peptidase 4 (DPP4i) to oral semaglutide; switch from "old" oral therapies (i.e., sulfonylureas, glinides, pioglitazone, acarbose) to oral semaglutide. A total of 31 statements were identified and grouped into five main topics (Table 1).

Participants

As a result of the nature of the topic, the initiative was limited to diabetes specialists, as GLP-1 RA therapy in Italy is almost exclusively managed by diabetologists. A panel of 28 diabetologists was selected, representing both university and non-university centers across the entire Emilia-Romagna region.

Rating of Statements

In May 2024, panel members were invited via email to participate in the project. Upon acceptance, they received personalized login credentials granting access to a dedicated website hosting the 31 statements developed by the steering group. Panelists were asked to evaluate each statement using a 9-point scale: scores of 1–3 indicated irrelevance (with 1 representing the highest level of irrelevance), scores of 7–9 indicated relevance (with 9 denoting the highest level of relevance), and scores of 4–6 were considered neutral.

Participants were also encouraged to provide brief comments explaining the rationale behind their ratings or to suggest alternative phrasing for any statement they found unclear or ambiguous. Following completion of the first round, responses were compiled and tabulated.

Statement ratings were analyzed quantitatively to evaluate the level of consensus among participants. Following the RAND/UCLA Appropriateness Method [7], the analysis began by assessing potential disagreement through a three-step process. First, the interpercentile range (IPR) was calculated, representing the range of responses between the 30th and 70th percentiles. Next, the interpercentile range adjusted for symmetry (IPRAS) was computed to account for asymmetry in the distribution of responses. Finally, the IPR and IPRAS values were compared: disagreement—indicating a lack of consensus—was considered present when IPR exceeded IPRAS [7].

Disagreement among participants automatically resulted in an uncertain outcome. In the absence of disagreement, the median score determined whether a statement was classified as relevant, irrelevant, or uncertain. A median within the 7–9 range indicated that the statement was relevant, suggesting its importance in informing clinical decisions. Conversely, a median within the 1–3 range signified that

Table 1 Results of Delphi process

	#	Statements	Median	30th percentile	70th percentile	IPRAS – IPR	Agreement	Decision
Switch from injectable GLP-1 RA to oral semaglutide	1	The switch is appropriate in patients with agoraphobia or reluctant to receive injectable therapies	9	8	9	14	Yes	Relevant
	2	The switch is appropriate in case of shortage/non availability of the injectable GLP-1 RA of the same class	8	8	9	12.125	Yes	Relevant
	3	The switch is appropriate if the patient is treated with low doses of injectable GLP-1 RA	7	6	8	5.5	Yes	Relevant
	4	The switch is appropriate in patients treated with "old" GLP-1 RA not meeting HbA1c target	8	7.1	9.8	10.2375	Yes	Relevant
	5	The switch is appropriate in patients treated with other injection therapies	7	7	8	8.375	Yes	Relevant
	6	The switch is appropriate in patients with difficulties managing injection therapy for musculoskeletal or neurological conditions, visual impairment/blindness or other disabilities in the absence of a caregiver	8	8	9	12.125	Yes	Relevant

Table 1 continued

	#	Statements	Median	30th percentile	70th percentile	IPRAS – IPR	Agreement	Decision
Switch from SGLT2i to oral semaglutide	7	The switch is appropriate in case of intolerance, genital infections, asthenia	9	8	9	12.125	Yes	Relevant
	8	The switch is appropriate if HbA1c > 7.5%, before evaluating the association of the two classes	8	7	8	8.375	Yes	Relevant
	9	The switch is appropriate if BMI > 30 kg/m^2	8	8	9	12.125	Yes	Relevant
	10	The switch is appropriate in patients with NASH/NAFLD	8	7.1	9	9.5375	Yes	Relevant
	11	The switch is appropriate in patients with peripheral artery disease or diabetic foot	7	7	8	8.375	Yes	Relevant
	12	The switch is appropriate in case of polyuria disturbing the quality of life	8	8	9	12.125	Yes	Relevant
	13	The switch is appropriate in patients with history of stroke	8	7	8	8.375	Yes	Relevant
	14	The switch is appropriate in patients with C-peptide < 0.7 ng/ml and risk of euglycemic ketoacidosis	8	7	8	8.375	Yes	Relevant

Table 1 continued

	#	Statements	Median	30th percentile	70th percentile	IPRAS – IPR	Agreement	Decision
Switch from insulin to oral semaglutide	15	The switch is appropriate in patients with BMI > 30 kg/m^2 and treated with low doses of insulin	9	8	9	12.125	Yes	Relevant
	16	The switch is appropriate in patients with established cardiovascular disease or multiple cardiovascular risk factors	8	8	9	12.125	Yes	Relevant
	17	The switch is appropriate to de-intensify/simplify therapy	8.5	7.1	9	9.5375	Yes	Relevant
	18	The switch is appropriate in patients experiencing hypoglycemia	8	7	8.9	9.1625	Yes	Relevant
	19	The switch is appropriate in patients with high cardiovascular risk, treated with insulin + SGLT2i (switch to SGLT2i + oral semaglutide)	8	7	9	9.25	Yes	Relevant
	20	The switch is appropriate in case of low dose basal bolus with C-peptide > 0.7 ng/ml (switch from basal bolus to basal Insulin + oral semaglutide)	8	8	9	12.125	Yes	Relevant
	21	The switch is appropriate in patients with visual impairment/blindness or other disabilities, in the absence of a caregiver, that do not allow the management of injection therapy and its monitoring	8.5	8	9	12.125	Yes	Relevant

Table 1 continued

	#	Statements	Median	30th percentile	70th percentile	IPRAS – IPR	Agreement	Decision
Switch from DPP4i to oral semaglutide	22	The switch is appropriate in patients with high cardiovascular risk	9	9	9	15	Yes	Relevant
	23	The switch is appropriate in patients with HbA1c not at target	9	9	9	15	Yes	Relevant
	24	The switch is appropriate in patients with BMI > 30 kg/m^2	9	8.1	9	12.4125	Yes	Relevant
	25	The switch is appropriate in patients with NASH/NAFLD	9	8	9	12.125	Yes	Relevant
	26	The switch is appropriate in patients without frailty	8	7	9	9.25	Yes	Relevant
	27	The switch is appropriate in patients treated with the combination of SGLT2i + DPP4i and with HbA1c not at target (switch to SGLT2i + oral semaglutide)	9	8	9	12.125	Yes	Relevant

Table 1 continued

	#	Statements	Median	30th percentile	70th percentile	IPRAS – IPR	Agreement	Decision
Switch from "old" oral agents to oral semaglutide	28	The switch is appropriate in patients treated with sulfonylureas/glinides (HbA1c not at target, CV risk/CV disease, BMI > 30 kg/m^2, hypoglycemia, eGFR < 30 ml/min)	9	9	9	15	Yes	Relevant
	29	The switch is appropriate in patient treated with pioglitazone (HbA1c not at target, BMI > 30 kg/m^2, lower limb edema/risk of heart failure)	9	9	9	15	Yes	Relevant
	30	The switch is appropriate in patients treated with acarbose (HbA1c not at target, high CV risk, side effects)	9	9	9	15	Yes	Relevant
	31	The switch is appropriate in patients treated with metformin in combination with SGLT2i, if intolerance to metformin or eGFR < 30 mg/dl (switch to SGLT2i + oral semaglutide)	8	8	9	12.125	Yes	Relevant

IPR interpercentile range, *IPRAS* interpercentile range adjusted for symmetry, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *HbA1c* glycated hemoglobin, *BMI* body mass index, *NASH/NAFLD* nonalcoholic steatohepatitis/non-alcoholic fatty liver disease, *CV* cardiovascular, *DPP4i* dipeptidyl peptidase 4 inhibitor, *eGFR* estimated glomerular filtration rate

the statement was irrelevant and not useful for clinical guidance. Medians falling within the 4–6 range led to an uncertain classification, reflecting ambiguity regarding the statement's clinical value.

After evaluating the level of consensus among participants, each panel member received a summary report including the frequency distribution of ratings across the 9-point scale, the overall median rating for each statement, and a record of their individual ratings. The ratings of other panelists remained anonymous. Each statement was also accompanied by an indication of whether agreement or disagreement had been observed on the basis of the panel's responses. Although second and third rounds were planned to promote consensus in cases of disagreement, full agreement was achieved in the first round for all statements, rendering further rounds unnecessary. The outcomes of the first round were subsequently shared and discussed with all 28 diabetologists during a dedicated meeting.

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.

Ethical Approval

In Italy, the activities of ethics committees are regulated by Legislative Decree of May 14, 2019, No. 52, which implements EU Regulation 536/2014 on clinical trials and defines the scope within which ethics committee evaluation is mandatory. It applies exclusively to studies involving medicinal products or medical devices and to experimental or observational research involving human subjects. Since our project is a simple opinion survey, is addressed to healthcare professionals, is completely anonymous, does not involve the collection of clinical, health-related, or identifiable personal data, does not involve patients or medical interventions, then it is not classified as "research involving human subjects" under current regulations and does not require ethics committee approval.

RESULTS

All the 28 invited panelists responded to the questionnaire (response rate 100%). After completion of the first round, panel members showed no significant disagreement (IPR < IPRAS) for any of the 31 statements, and all the statements were considered as relevant. Table 1 reports the results relative to individual statements, while Tables 2 and 3 summarize respectively the major evidence gaps and statements with higher level of consensus emerging from the Delphi process.

Switch from Injectable GLP-1 Receptor Agonist to Oral Semaglutide

All the panelists totally agreed (statement 1; median value 9) that it would be appropriate to switch from injectable GLP-1 RA to oral semaglutide in patients with agoraphobia or unwilling to be treated with injection therapy. A general agreement, with a median rating of 8, was reached regarding the possibility to switch to oral semaglutide in those circumstances where there is shortage or difficulty to have access to injectable GLP-1 RA therapy (statement 2).

Also, panelists agreed, albeit with a lower level of relevance, that the switch to oral semaglutide would be appropriate if the patient is treated with low doses of injectable GLP-1 RA (statement 3, median rating 7).

Another circumstance in which the switching to oral semaglutide was deemed appropriate was represented by the difficulty to reach the desired glycated hemoglobin (HbA1c) goal with injectable GLP-1 RAs exerting a lower glucose-lowering effect (statement 4, median rating 8).

Despite the agreement, a lower level of relevance was attributed to the possibility of switching from injectable to oral GLP-1 RA if the patient is receiving other injection therapies (statement 5, median rating 7).

Table 2 Evidence gaps emerging from the Delphi process (statements with score < 8)

Item #	Statement	Scoring	Comment
3	Switch from injectable GLP-1 RA to oral semaglutide is appropriate if the patient is treated with low doses of injectable GLP-1 RA	7	The switch to oral therapy would make the management of the disease less burdensome. On the other hand, patients with T2D are often treated with long-term, multiple oral therapies besides glucose-lowering drugs, thus increasing the risk of poor adherence
5	Switch from injectable GLP-1 RA to oral semaglutide is appropriate if the patient is treated with other injection therapies	7	
11	Switch from SGLT2i to oral semaglutide is appropriate in patients with PAD or diabetic foot	7	A note of caution arose from the findings of an increased risk of amputations in the CANVAS randomized trial. However, this was not a pre-specified endpoint and was not observed in the other SGLT2i trials or in long-term prospective studies. In addition, in post hoc analyses, these drugs had beneficial cardiovascular and renal effects in persons with PAD. Furthermore, treatment with semaglutide o.w. was associated with a reduction in MACE versus placebo, irrespective of PAD status

GLP-1 RA glucagon-like peptide 1 receptor agonist, *T2D* type 2 diabetes, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *PAD* peripheral artery disease, *MACE* major adverse cardiovascular events

Finally, panelists agreed that oral semaglutide would represent a valuable option in patients facing difficulties in managing an injection therapy (statement 6, median rating 8).

Switch from Sodium-Glucose Cotransporter 2 Inhibitor to Oral Semaglutide

There was strong agreement that oral semaglutide can represent an appropriate choice to replace therapy with SGLT2is when the latter are poorly tolerated or cause side effects (statement 7, median rating 9). Also, panelists agreed that oral semaglutide could be used to replace SGLT2i when the desired HbA1c target is not reached, before considering the option of adding on GLP-1 RA to ongoing SGLT2i therapy (statement 8, median rating 8). It was underlined that SGLT2i should be maintained in the presence of specific indications (i.e., heart failure, chronic kidney disease).

The switch from an SGLT2i to oral semaglutide was also considered appropriate in patients with obesity (statement 9, median rating 8) and those with nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) (statement 10, median rating 8).

Despite reaching the consensus of its relevance, a lower rating was assigned to the statement supporting the switch from SGLT2i to oral semaglutide in patients with peripheral artery disease (PAD) or diabetic foot (statement 11, median rating 7).

Table 3 Summary of the statements with high level of consensus (score ≥ 8)

Switch from injectable GLP-1 RA to oral semaglutide
The switch is appropriate in patients with agoraphobia or reluctant to receive injectable therapies (statement 1)
The switch is appropriate in case of shortage/non availability of the injectable GLP-1 RA of the same class (statement 2)
The switch is appropriate in patients treated with "old" GLP-1 RA not meeting HbA1c target (statement 4)
The switch is appropriate in patients with difficulties managing injection therapy for musculoskeletal or neurological conditions, visual impairment/blindness or other disabilities in the absence of a caregiver (statement 6)
Switch from SGLT2i to oral semaglutide
The switch is appropriate in case of intolerance, genital infections, asthenia (statement 7)
The switch is appropriate if HbA1c > 7.5%, before evaluating the association of the two classes (statement 8)
The switch is appropriate if BMI > 30 kg/m^2 (statement 9)
The switch is appropriate in patients with NASH/NAFLD (statement 10)
The switch is appropriate in case of polyuria disturbing the quality of life (statement 12)
The switch is appropriate in patients with history of stroke (statement 13)
The switch is appropriate in patients with C-peptide < 0.7 ng/ml and risk of euglycemic ketoacidosis (statement 14)
Switch from insulin to oral semaglutide
The switch is appropriate in patients with BMI > 30 kg/m^2 and treated with low doses of insulin (statement 15)
The switch is appropriate in patients with established cardiovascular disease or multiple cardiovascular risk factors (statement 16)
The switch is appropriate to de-intensify/simplify therapy (statement 17)
The switch is appropriate in patients experiencing hypoglycemia (statement 18)
The switch is appropriate in patients with high cardiovascular risk, treated with insulin + SGLT2i (switch to SGLT2i + oral semaglutide) (statement 19)
The switch is appropriate in case of low dose basal bolus with C-peptide > 0.7 ng/ml (switch from basal bolus to basal Insulin + oral semaglutide) (statement 20)
The switch is appropriate in patients with visual impairment/blindness or other disabilities, in the absence of a caregiver, that do not allow the management of injection therapy and its monitoring (statement 21)
Switch from DPP4i to oral semaglutide
The switch is appropriate in patients with high cardiovascular risk (statement 22)
The switch is appropriate in patients with HbA1c not at target (statement 23)
The switch is appropriate in patients with BMI > 30 kg/m^2 (statement 24)
The switch is appropriate in patients with NASH/NAFLD (statement 25)
The switch is appropriate in patients without frailty (statement 26)
The switch is appropriate in patients treated with the combination of SGLT2i + DPP4i and with HbA1c not at target (switch to SGLT2i + oral semaglutide) (statement 27)

Table 3 continued

Switch from "old" oral agents to oral semaglutide
The switch is appropriate in patients treated with sulfonylureas/glinides (HbA1c not at target, CV risk/CV disease, BMI > 30 kg/m^2, hypoglycemia, eGFR < 30 ml/min) (statement 28)
The switch is appropriate in patient treated with pioglitazone (HbA1c not at target, BMI > 30 kg/m^2, lower limb edema/risk of heart failure) (statement 29)
The switch is appropriate in patients treated with acarbose (HbA1c not at target, high CV risk, side effects) (statement 30)
The switch is appropriate in patients treated with metformin in combination with SGLT2i, if intolerance to metformin or eGFR < 30 mg/dl (switch to SGLT2i + oral semaglutide) (statement 31)

GLP-1 RA glucagon-like peptide 1 receptor agonist, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *HbA1c* glycated hemoglobin, *BMI* body mass index, *NASH/NAFLD* nonalcoholic steatohepatitis/non-alcoholic fatty liver disease, *CV* cardiovascular, *DPP4i* dipeptidyl peptidase 4 inhibitor, *eGFR* estimated glomerular filtration rate

The presence of polyuria disturbing the quality of life was considered another indication for switching from SGLT2i to oral semaglutide (statement 12, median rating 8).

Panelists agreed that patients with history of stroke should be candidates to switch from SGLT2i to oral semaglutide (statement 13, median rating 8).

Finally, panelists agreed that the switch from SGLT2i to oral semaglutide would be appropriate for patients with low residual beta cell function (C-peptide < 0.7 ng/ml), at risk of euglycemic ketoacidosis (statement 14, median rating 8).

Switch from Insulin to Oral Semaglutide

Agreement among panelists was documented for several circumstances in which it could be advisable to switch from insulin therapy to oral semaglutide. A high level of agreement was reached regarding the appropriateness of switching to oral semaglutide in the case of patients with obesity requiring low doses of insulin (statement 15, median rating 9). Similarly, it was agreed that patients with established cardiovascular disease or carrying multiple cardiovascular risk factors would benefit from substituting insulin therapy with oral semaglutide (statement 16, median rating 8).

Oral semaglutide was also considered a valuable option to de-intensify and simplify glucose-lowering therapy (statement 17, median rating 8.5). On the same line, the switch from insulin to oral semaglutide was deemed appropriate for patients experiencing hypoglycemia (statement 18, median score 8).

Also, in patients at high cardiovascular risk treated with the combination of insulin plus SGLT2i, panelists agreed that insulin could be replaced by oral semaglutide, while maintaining the therapy with SGLT2i (statement 19, median rating 8).

An agreement was also reached regarding the appropriateness of switching from rapid insulin to oral semaglutide in patients treated with low doses of insulin in a basal-bolus scheme and with C-peptide levels over 0.7 ng/ml (statement 20, median rating 8).

Finally, a strong consensus was reached regarding the appropriateness of switching from insulin to oral semaglutide in patients with visual impairment/blindness or other disabilities impeding, in the absence of a caregiver, the management of injection therapy and its monitoring (statement 21, median rating 8.5).

Switch from Dipeptidyl Peptidase 4 Inhibitor to Oral Semaglutide

Strong agreement among panelists was reached regarding the appropriateness of switching from DPP4i to oral semaglutide in patients at high cardiovascular risk (statement 22, median rating 9) and those with HbA1c not at target

(statement 23, median rating 9). Additional patient characteristics suggesting the opportunity to switch from DPP4i to oral semaglutide were obesity (statement 24, median rating 9), the presence of NASH/NAFLD (statement 25, median rating 9), and the absence of a condition of frailty (statement 26, median rating 9). Panelists also considered it appropriate to substitute DPP4i, when administered in combination with SGLT2i, when the desired therapeutic targets are not reached (statement 27, median rating 9).

Switch from "Old" Oral Agents to Oral Semaglutide

Panelists reached strong agreement regarding the appropriateness of switching from secretagogues (sulfonylureas, glinides) to oral semaglutide under many circumstances including poor metabolic control, high cardiovascular risk, obesity, experience of hypoglycemia, or reduced glomerular filtration rate (eGFR < 30 ml/min) (statement 28, median rating 9). Similarly, switching from pioglitazone to oral semaglutide was recommended in patients with HbA1c not at target, in those with obesity, and in those carrying the risk of heart failure (statement 29, median rating 9). Oral semaglutide was also considered a valuable alternative to acarbose in case of poor metabolic control, high cardiovascular risk, or poor tolerability of acarbose (statement 30, median rating 9). Finally, in patients treated with the combination of metformin plus SGLT2i, oral semaglutide can represent a valuable substitute of metformin, when this drug is poorly tolerated or in case of impaired renal function (eGFR < 30 ml/min) (statement 31, median rating 8).

DISCUSSION

This Delphi consensus indicates that diabetologists from a major Italian region perceive oral semaglutide as an appropriate opportunity for a switch from other glucose-lowering therapies in people with T2D.

Consensus was elicited for 31 statements regarding the switch to oral semaglutide from injectable GLP-1 RAs, SGLT2 inhibitors, insulin therapy, DPP4 inhibitors, and other "old" oral agents.

Panel members showed significant disagreement for any of the 31 statements, and all the statements were considered as relevant.

Panelists fully agreed that switching to semaglutide from injectable GLP-1 RA is appropriate in cases of needle phobia or unwilling to be treated with injection therapy. In this respect, it was emphasized that patients naïve to injectable therapy place great importance on the route of administration, preferring the oral route. However, the route of administration remains an important issue also for patients non-naïve to injection therapy [8]. Shortage or difficulty in having access to injectable GLP-1 RA therapy was also considered as a reason to switch to oral semaglutide. Unexpected drug shortages of the long-acting GLP-1 RAs emerged in late 2022 and have persisted through 2023 and 2024 [9, 10]. These shortages predominately occurred because of an unexpected increase in demand for GLP-1 RAs, without adequate adjustment in production. Panelists agreed that in these circumstances the switch from subcutaneous to oral GLP-1 RA is warranted. In fact, experimental data show that circulating levels of semaglutide are overlapping with oral versus injectable formulations [11], and real-world data confirm that oral and injectable formulations of semaglutide have similar glucose-lowering efficacy [12].

Also, it was agreed that oral semaglutide could represent a valuable option for patients unable to achieve their HbA1c target with other GLP-1 RAs. In this respect, data consistently show that oral semaglutide 14 mg o.d. has a better efficacy in terms of HbA1c reduction in comparison to other GLP-1 RAs [13, 14].

A lower level of consensus was obtained regarding the switch from other GLP-1 RAs to oral semaglutide in case of patients treated with low doses of injectable GLP-1 RA, or receiving other injection therapies. It was argued that the switch to oral therapy would make the management of the disease less burdensome. On the other hand, patients with T2D are often treated with long-term, multiple oral therapies besides glucose-lowering drugs, thus increasing the risk of poor adherence [15].

Strong agreement was reached on considering oral semaglutide as an alternative to a therapy with SGLT2is, in case of side effects or presence of polyuria disturbing the quality of life. Also, oral semaglutide was considered as a valuable substitute for SGLT2i when HbA1c targets were not met, before exploring the possibility of adding GLP-1 RA to SGLT2i therapy. This statement was supported by scientific evidence documenting a greater reduction of HbA1c levels with oral semaglutide compared to SGLT2i [16, 17]. However, participants agreed to maintain the SGLT2i treatment in the presence of specific clinical situations such as heart failure and chronic kidney disease. Obesity and presence of NASH/NAFLD were also considered as conditions supporting the switch from SGLT2i to oral semaglutide. A larger effect of oral semaglutide compared to SGLT2i on body weight was clearly documented [16, 18]. Regarding NASH/NAFLD, evidence suggests that semaglutide can represent an effective therapy [19, 20] although it is not currently approved as a treatment for NASH.

A lower level of consensus was reached for moving from a treatment with SGLT2i to oral semaglutide in patients with PAD or diabetic foot. A note of caution regarding the use of SGLT2i in patients with PAD arose from the findings of an increased risk of amputations in the CANVAS randomized trial [21]. However, this was not a pre-specified endpoint and was not observed in the other SGLT2i trials or in long-term prospective studies, as concluded in the ADA-EASD 2022 consensus report [22]. In addition, in post hoc analyses, these drugs had beneficial cardiovascular and renal effects in persons with PAD [23]. On the other hand, treatment with semaglutide o.w. was associated with a reduction in MACE versus placebo, irrespective of PAD status [24]. Panelists agreed that patients with history of stroke should be candidates to switch from SGLT2i to oral semaglutide. The recommendation was based on cumulative evidence showing that GLP-1 RA treatment reduces the risk of stroke [25], while no significant effect of SGLT2i on this outcome has emerged [26].

A low residual beta cell function was also considered as a condition where a switch from SGLT2i therapy to oral semaglutide should be considered highly appropriate. The statement was supported by evidence showing that euglycemic diabetic ketoacidosis secondary to SGLT2i in T2D is a rare but increasingly reported phenomenon [27]. In this respect, evaluating C-peptide was not considered necessary to initiate oral GLP-1 RA therapy. However, C-peptide evaluation was advised in patients receiving SGLT2 inhibitors when there is a need to rule out reduced beta cell function. In such cases, switching from SGLT2 inhibitors to oral semaglutide was recommended.

As for insulin therapy, panelists agreed that there are several situations in which a switch to oral semaglutide would be advisable. A switch from insulin therapy to oral semaglutide was considered appropriate in the case of patients with obesity requiring low doses of insulin.

The statement was supported by real-world evidence indicating that discontinuation of prandial insulin is achievable in approximately 50% of patients with T2D—particularly in those with greater residual beta cell function, such as younger individuals, or those with shorter disease duration, lower HbA1c levels, and reduced insulin requirements [28]. Panelists concurred that the introduction of oral semaglutide could facilitate the withdrawal of prandial insulin while maintaining glycemic control and enhancing quality of life, a position reinforced by a substantial body of literature [29, 30].

The switch from insulin to oral semaglutide was also considered appropriate in subjects with established cardiovascular disease or multiple cardiovascular risk factors. The statement was supported by scientific evidence demonstrating the benefits of oral semaglutide on cardiovascular outcomes and all-cause mortality [4]. In this direction, panelists agreed that in high cardiovascular risk patients treated with the combination of insulin plus SGLT2i, insulin could be replaced by oral semaglutide, while maintaining the therapy with SGLT2i, for the synergic effect of the two classes of glucose-lowering drugs on glucose and weight reduction, renal and cardiovascular protection, and benefits on mortality risk [31]. According to panelists, moving from insulin to oral semaglutide should also be considered to de-intensify and simplify glucose-lowering therapy. As individuals with T2D age, simplifying complex

insulin regimens may become appropriate because of a progressive decline in their ability to manage treatment independently. The goal of treatment simplification is to reduce therapeutic burden, which may include fewer daily injections and reduced frequency of blood glucose monitoring. Findings from randomized controlled trials suggest that transitioning from a basal-bolus insulin regimen to a combination of basal insulin and a GLP-1 RA can maintain or even improve glycemic control, while also reducing injection frequency, insulin dosage, and the risk of hypoglycemia, along with enhancing treatment satisfaction [30]. Supporting arguments for this approach include a lower risk of hypoglycemia, cardiorenal benefits, fewer daily injections, and a reduced need for intensive glucose self-monitoring.

Switching from insulin to oral semaglutide was also considered advisable in patients with visual impairment/blindness or other disabilities impeding, in the absence of a caregiver, the management of injection therapy and its monitoring.

A strong level of agreement was achieved for the switch from insulin to oral semaglutide in patients experiencing hypoglycemia and in patients treated with low doses of insulin in a basal-bolus scheme in the presence of C-peptide levels over 0.7 ng/ml, considered as indicative of a preserved beta cell reserve [32]. Furthermore, an improvement of beta cell function following semaglutide treatment has been described [33].

Strong agreement was reached regarding the need for switching from DPP4i to oral semaglutide in patients at high cardiovascular risk, based on the large amount of evidence supporting the cardiovascular protective role of GLP-1 RAs as opposed to the neutral effect of DPP4i. Also, on the basis of evidence of a greater glucose-lowering effect of oral semaglutide vs. DPP4i [18], the switch was deemed appropriate for patients not at HbA1c target. Also, the presence of obesity or NASH/NAFLD, and the absence of a condition of frailty, supported the switch from DPP4i to an oral GLP-1 RA. Regarding this last issue, it was noted that, although DPP4i can be better tolerated by frail patients, evidence suggests that GLP-1 RA can improve cardiovascular outcomes and mortality even among frail individuals [34].

In patients treated with the SGLT2i/DPP4i combination, panelists agreed that the transition from DPP4i to oral semaglutide should also be taken into consideration when the desired therapeutic targets are not reached. In this respect, it was reaffirmed that patients can benefit from the additive effect of SGLT2i and oral semaglutide on cardiorenal protection.

Participants strongly agreed on the desirability of switching from secretagogues to oral semaglutide in many circumstances including poor metabolic control, high cardiovascular risk, obesity, hypoglycemia experience, or chronic kidney disease. Existing evidence clearly documents the superiority of oral semaglutide versus secretagogues in all these situations [17]. The switch from pioglitazone to oral semaglutide was highly recommended in patients with HbA1c not at target, in those with obesity, and in subjects at high risk for heart failure. Moving form acarbose to oral semaglutide was suggested in case of poor metabolic control, high cardiovascular risk, or poor tolerability of acarbose. As a general comment, oral semaglutide shows a greater efficacy than “old” glucose-lowering drugs in terms of metabolic control, weight loss, risk of hypoglycemia, and cardiorenal protection. Finally, panelists underlined how in patients treated with the combination of metformin plus SGLT2i, oral semaglutide should substitute metformin, when this drug is not tolerated or in case of severe chronic kidney disease.

Our study has limitations. Firstly, although consensus was achieved, the findings inherently depended on the panel’s composition. To reduce the risk of selection bias, panel members were chosen on the basis of their extensive experience in diabetology and their broad geographic representation across the region. Moreover, all invited experts took part in the project, ensuring a comprehensive representation of expert opinions, and the consensus process followed a standardized, predefined methodology. Secondly, the panel was exclusively composed of diabetes specialists, without the involvement of primary care physicians. However, GLP-1 RA therapy in Italy is almost exclusively managed by diabetologists.

CONCLUSION

This consensus suggests clinical scenarios in which switching to oral semaglutide from other therapies should be considered, ensuring that the patient receives equal or greater therapeutic efficacy in glycemic and weight control and/or similar or even greater effectiveness in terms of cardiovascular protection. Also, the possibility of a switch to oral semaglutide for a simplification of therapy should not be overlooked.

It is important to emphasize that switching from other therapies to oral semaglutide can also have significant economic implications. Several studies have documented a favorable cost-effectiveness ratio associated with switching from SGLT2 inhibitors, DPP4 inhibitors, or injectable GLP-1 RAs to oral semaglutide 14 mg [35–40]. Although specific data on switching from insulin to oral semaglutide are lacking, it has been shown that once-weekly semaglutide is highly cost-effective compared to insulin aspart in the treatment of T2D [41]. Furthermore, it should be considered that socio-economic aspects are less relevant for the patient in the Italian context, since the national healthcare system fully covers the costs of diabetes treatment.

In conclusion, similar to other Delphi consensus [6, 42], this initiative offers indications that balance clinical recommendations with unmet patient needs, providing pragmatic guidance for our daily clinical practice and emphasizing how, in people with T2D, a "simple" switch to oral semaglutide from other therapeutic options could finally represent the "*S*martest *W*ay *I*n *T*he *C*ontrol of this *H*ypercomplex disease".

Medical Writing/Editorial Assistance. Editorial assistance was provided by Antonio Nicolucci. CORESEARCH SRL, Corso Umberto I, 103 65122 Pescara, Italy.

Author Contributions. Matteo Bruglia, Francesca Cardini, Raffaella Di Luzio, Stefania Fiorini, Antonella Guberti, Silvia Haddoub, Valentina Lo Preiato, Alessandra Luberto, Francesca Lugli, Massimiliano Maiello, Elisa Manicardi, Marco Marcello Marcellini, Marcello Monesi, Francesca Pellicano, Daniela Piani, Rosa Maria Trianni and Anna Vacirca: active participation in the Delphi process, reviewing and revising the manuscript critically for important intellectual content. Antonio Nicolucci: concept and design, data analysis, drafting of the manuscript. Paolo Di Bartolo: concept and design, drafting of the manuscript. All named authors have given final approval to the version to be published.

Funding. No funding or sponsorship was received for this study. The Rapid Service Fee was funded by the authors.

Data Availability. All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of Interest. Paolo Di Bartolo has served as a consultant or advisory board member for AstraZeneca, Boehringher Ingelheim, Eli Lilly and Company, and has also received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Abbott Diagnostic, Mundipharna and Sanofi. Antonio Nicolucci received research funding from AlfaSigma, Novo Nordisk, Sanofi, Theras, Shionogi and SOBI. All other authors (Matteo Bruglia, Francesca Cardini, Raffaella Di Luzio, Stefania Fiorini, Antonella Guberti, Silvia Haddoub, Valentina Lo Preiato, Alessandra Luberto, Francesca Lugli, Massimiliano Maiello, Elisa Manicardi, Marco Marcello Marcellini, Marcello Monesi, Francesca Pellicano, Daniela Piani, Rosa Maria Trianni and Anna Vacirca) have no conflicts of interest.

Ethical Approval. In Italy, the activities of ethics committees are regulated by Legislative Decree of May 14, 2019, No. 52, which implements EU Regulation 536/2014 on clinical trials and defines the scope within which ethics committee evaluation is mandatory. It applies exclusively to studies involving medicinal products or medical devices and to experimental or observational research involving human subjects. Since our project is a simple opinion survey, is addressed to healthcare professionals, is completely anonymous, does not involve the

collection of clinical, health-related, or identifiable personal data, does not involve patients or medical interventions, then it is not classified as "research involving human subjects" under current regulations and does not require ethics committee approval.

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