



# The “Early Treatment” Approach Reducing Cardiovascular Risk in Patients with Type 2 Diabetes: A Consensus From an Expert Panel Using the Delphi Technique

Giuseppina Russo · Matteo Monami · Gianluca Perseghin ·  
Angelo Avogaro · Pasquale Perrone Filardi · Michele Senni ·  
Claudio Borghi · Aldo P. Maggioni

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## ABSTRACT

**Introduction:** There is no consensus on the optimal therapeutic approach to adopt in patients with newly diagnosed type 2 diabetes mellitus (T2DM) to prevent cardiovascular disease (CVD). The study aimed to gather an expert consensus on the hypoglycemic treatment and CV risk management in patients with newly

diagnosed T2DM through the Delphi methodology.

**Methods:** To address this issue, a list of 30 statements concerning the definition of “early T2DM patient”, early treatment, CV risk in T2DM, treat-to-benefit approach, and indications for treatment with glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors was

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G. Russo (✉)  
Department of Clinical and Experimental Medicine,  
University of Messina, Messina, Italy  
e-mail: giuseppina.russo@unime.it

M. Monami  
Unit of Diabetology and Metabolic Disease, Careggi  
Teaching Hospital and University of Florence,  
Florence, Italy

G. Perseghin  
Department of Medicine and Surgery, University of  
Milano Bicocca, Milan, Italy

G. Perseghin  
Department of Medicine and Rehabilitation,  
Policlinico di Monza, Monza, Italy

A. Avogaro  
Department of Medicine, Section of Diabetes and  
Metabolic Diseases, University of Padova, Padova,  
Italy

P. Perrone Filardi  
Department of Advanced Biomedical Sciences,  
Federico II University of Naples and Mediterranean  
Cardio Center Clinic of Naples, Naples, Italy

M. Senni  
Division of Cardiology, ASST Papa Giovanni XXIII  
Hospital, Bergamo, Italy

C. Borghi  
Medical and Surgery Sciences Department,  
Dyslipidemia and Atherosclerosis Research Unit,  
Alma Mater Studiorum University of Bologna,  
Bologna, Italy

A. P. Maggioni  
ANMCO Research Center, Florence, Italy

developed. Using a two-round Delphi methodology, the survey was distributed to 80 Italian diabetes specialists who rated their level of agreement with each statement on a 5-point Likert scale. Consensus was predefined as more than 66% of the panel agreeing/disagreeing with any given statement.

**Results:** A total of 27/30 statements achieved consensus. A patient was defined as “early” according to pathophysiological or clinical interpretation, and/or the timing of the diagnosis. There was agreement on the importance to reach the lowest possible HbA1c level, since diagnosis, also using combination therapy with hypoglycemic drugs with a proven CV benefit. There was a consensus that a treat-to-benefit approach involves the addition of a glucose-lowering agent with proven CV benefits to metformin since diagnosis. The use of GLP-1RAs and SGLT2 inhibitors was considered a key strategy in this approach and the benefits were recognized also for patients with T2DM without established CVD. GLP-1RAs should be used at an earlier stage than SGLT2 inhibitors to prevent CVD, especially in patients with evidence of subclinical atherosclerotic disease.

**Conclusion:** This Delphi consensus recognized the importance to adopt a tailored hypoglycemic treatment of patients with T2DM according to their CVD risk and the key role of glucose-lowering agents with proven CV efficacy, GLP-1RAs and SGLT2 inhibitors, in the context of an early treat-to-benefit approach.

**Keywords:** Delphi method; Expert consensus; GLP-1 receptor agonists; Glucose-lowering agents; SGLT2 inhibitors; Type 2 diabetes

## Key Summary Points

### Why carry out this study

Current guidelines and consensus recommend the use of hypoglycemic drugs with proven CV benefit for patients with type 2 diabetes (T2DM) and established CVD, heart failure, and/or chronic kidney disease.

Clear recommendations for the treatment of patients with newly diagnosed T2DM to prevent cardiovascular disease are not yet available.

The study aims to provide expert opinion on the hypoglycemic treatment and CV risk management in patients with newly diagnosed T2DM.

### What was learned from the study?

Italian diabetologists consider the importance of adopting a personalized approach for patients with T2DM and CV risk factors.

GLP-1RAs and SGLT2 inhibitors were recognized as key strategies in the treat-to-benefit approach.

A paradigm shift should be implemented to focus clinicians’ attention not only on metabolic control but also on the long-term CV benefits, even at early stages.

## 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.14135225>.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by overt hyperglycemia, due to insulin resistance and various degree of beta cell dysfunction. However, the pathophysiology of T2DM is complex, involving several organs and apparatus, including the cardiovascular system [1]. Several of these changes may occur long before T2DM diagnosis, being already detectable in prediabetes states and healthy siblings of subjects with T2DM [2, 3].

Current local [4] and international diabetes guidelines recommend an HbA1c target of less than 6.5% for patients with T2DM with a short duration of disease, without comorbidities, and/or with long life expectancy [5, 6]. However, there is no consensus on the best therapeutic strategy to reach HbA1c goals in these patients. A stepwise treatment intensification has been the standard approach to achieve glycemic control using metformin monotherapy as the preferred first-line therapy for the treatment of patients with a recent diagnosis of T2DM, followed by treatment intensification to achieve HbA1c targets [7]. Several glucose-lowering agents can effectively reduce glucose levels, without the risk of hypoglycemia [8]. Furthermore, for some of them, additional beneficial effects on cardiovascular disease (CVD) risk factors and on major adverse cardiovascular events (MACE) have been demonstrated. In particular, in the cardiovascular outcomes trials (CVOTs), liraglutide, semaglutide, albiglutide, dulaglutide, empagliflozin, dapagliflozin, and canagliflozin were demonstrated to reduce MACE, although with some differences [9–19].

Accordingly, the Italian, as well as international, guidelines recommend the use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors in patients with a previous CVD event, heart failure (HF), and/or chronic kidney disease (CKD) [4, 5, 7, 8]. Notably, the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) study demonstrated the CVD beneficial effects of GLP-

1RAs also in patients at relatively lower CV risk [12].

While for patients with high CV risk, established CVD, HF, or CKD the recommended second-line therapy consists in the addition of a glucose-lowering agent with proven CV benefit, such as an SGLT2 inhibitor or a GLP-1RA, the second-line treatment to recommend for subjects with T2DM but without overt CV/CKD/HF is still debated [7].

In this context, several clinical trials have demonstrated that the early combination therapy with an innovative glucose-lowering agent in addition to metformin can significantly increase the number of patients achieving HbA1c targets compared to the respective monotherapies, without increasing the incidence of hypoglycemia [20–23].

Moreover, increasing benefits on glucose control and weight management have been recently reported with the early introduction of glucose-lowering therapies with proven CV benefits, i.e., SGLT2 inhibitors and GLP-1RAs, simultaneously or soon after the failure with metformin [7, 20–24].

With this background in mind, the purpose of the study was to perform a Delphi survey among a panel of Italian diabetes specialists to gather an expert consensus on the treatment of patients with newly diagnosed T2DM, as well as generate expert ideas on the optimal early CV risk management in this population.

## 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 wherein evidence is scarce and opinion is important [25–27]. In the present manuscript, the consensus process consisted of a two-step web-based Delphi method, which took place between June and October 2020.

The survey was developed by a panel of eight physicians (four diabetologists, four cardiologists), identified as key opinion leaders (KOLs) in their respective fields in Italy. The KOLs met to fully analyze the published literature and

discuss the unmet needs about the topic. Hence, they identified 30 statements with a major need of clarification and debate, focused on the definition of “early T2DM patient”, early treatment, CV risk, treat-to-benefit approach, and therapeutic strategies as an add-on to metformin. The panel also chose four Italian expert diabetologists to serve as external validators of the questionnaire, to test its understandability and clarity. After approval by the external validators, the questionnaire was distributed to 80 expert diabetologists via an online platform with anonymized results. The panelists were clinicians with solid experience in the field of diabetes (at least 10 years of clinical experience in diabetology), selected throughout the country mainly among regional presidents or vice presidents of the principal scientific societies in the field (Italian Diabetes Society, Association of Medical Diabetologists, Italian Society of Endocrinology, and Italian Society of Gerontology and Geriatrics) and members of the aforementioned Italian scientific societies. Furthermore, the size of the panel of Italian experts was determined by involving expert diabetologists from all Italian regions (from at least 1–12 diabetologists) to have a representative sample of the whole national territory and a homogeneous distribution between Northern, Central, and Southern Italy.

Panelists were invited to express their level of agreement or disagreement on each statement using a 5-point Likert scale, scored from 1 to 5 (1, strongly disagree; 2, disagree; 3, agree; 4, mostly agree; and 5, strongly agree). Results were expressed as a percentage of respondents who scored each item as 1 or 2 (disagreement) or as 3, 4, or 5 (agreement) (see electronic supplementary material). A positive consensus was reached in case of more than 66% agreement, a negative consensus in case of more than 66% disagreement, consensus was not reached when the sum for disagreement or agreement was below 66% [26, 27].

For the statements on which consensus had not been achieved, panelists were asked to re-rate in a second round their agreement/disagreement, after being provided with relevant literature on the topic selected by the KOLs in a dedicated meeting.

**Table 1** Characteristics of responders in the Delphi survey

Characteristic	% or mean $\pm$ SD
Gender (female)	64%
Mean age	52.74 $\pm$ 9.85
Age	
$\leq$ 45 years	27%
46–55 years	27%
$>$ 55 years	45%
Italian region	
Northern Italy	33%
Central Italy	33%
Southern Italy	35%

Descriptive analysis was performed to summarize the results.

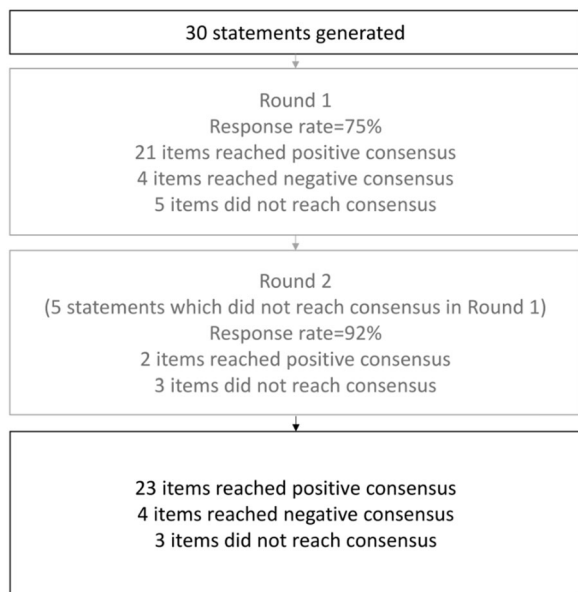
### Compliance with Ethics Guidelines

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. All experts involved in the Delphi survey were informed of the study’s objectives and the possibility of publishing the results in a peer-reviewed article. The participation was voluntary. They expressed their consent to participate in the survey after logging into the secure online survey platform via credentials, by actively clicking on the appropriate box.

## RESULTS

### Degree of Consensus in the Delphi Process

In the first round of the Delphi survey, there were 60 respondents out of 80 invited panelists.



**Fig. 1** Delphi survey flowchart

Round 2 was completed by the 55 panelists who responded to round 1. Overall, the response rate was 69%: 64% of the respondents were female and the mean age was 53 years with a nationwide homogeneous distribution (Table 1). In round 1, consensus was reached for 25/30 statements (83%) (Fig. 1). In the second round, performed on the five statements for which consensus had not been reached, consensus was reached for 2/5 statements. Overall, 27 statements of the Delphi survey reached consensus (90%), while no consensus was reached for 3 statements (Fig. 1).

Table 2 summarizes the statements and presents the percentage of agreement/disagreement for each one based on the responses of the 55 panelists.

Major statements, grouped for macro-areas, are reported below.

#### **“Early T2DM Patient”**

The panelists strongly agreed that a patient is defined as “early” according to the short duration of disease (91%). Experts also agreed that the definition of the “early patient” is based on the absence of organ damage (73%); patients naïve to glucose-lowering therapy or treated with metformin alone were also considered “early” (73%).

#### **Early Treatment**

A consensus was reached regarding the importance to reach the lowest possible level of HbA1c, soon after the clinical diagnosis (95%). Furthermore, HbA1c targets should be reached using several glucose-lowering agents with at least one able to also reduce CV risk (75%). There was consensus that the reduction in CV risk is not strictly related to the reduction of HbA1c levels (82%), but the choice to use GLP-1RAs or SGLT2 inhibitors is not strictly related to the need to normalize HbA1c values (80%).

#### **Definition of Cardiovascular Risk in T2DM**

As for the distinction between primary and secondary CV prevention, there was consensus on the distinction based on a previous CV event (84%). Furthermore, panelists strongly disagreed that the definition of CV risk is based only on established CVD (i.e., a prior myocardial infarction) (98%). No consensus was reached on whether the distinction should be based on the level of CV risk or if the definition of CV risk is based on the presence of obliterating arteriopathy of the lower limbs.

Consensus on the CV risk of patients with T2DM was almost unanimous. Panelists agreed that patients may have different levels of CV risk (91%) and that the definition of a high-risk diabetic patient may be independent of the duration of the disease (100%).

A consensus was also reached on the statement that urinary albumin/creatinine ratio, a well-known marker of diabetic kidney disease, is a strong predictor of CVD (91%).

#### **Treat-to-Benefit Approach**

When the treat-to-benefit approach was considered, there was a strong consensus for the early addition of a second glucose-lowering agent with proven CV benefits (98%). Panelists unanimously agreed that the choice of GLP-1RAs and SGLT2 inhibitors represents a key strategy in this approach (100%).

Furthermore, treatment with metformin could not be necessarily considered the first choice in a patient with newly diagnosed T2DM and with concomitant CVD (76%). Besides, panelists agreed that sulfonylureas have a

**Table 2** Delphi survey results

	<b>Statement</b>	<b>Disagreement (score 1–2)</b>	<b>Agreement (score 3–5)</b>	<b>Reasoning behind consensus</b>
1	A patient is defined “early” when the short duration of disease is known	9%	91%	Pathophysiological approach to define a condition with preserved beta cell function
2	A patient is defined “early” when he/she is still naïve to glucose-lowering therapy or is treated with metformin alone	27%	73%	Clinical approach to define a condition adequately controlled with metformin
3	A patient is defined “early” when there is no evidence of organ damage	27%	73%	Pathophysiological approach from a cardiovascular point of view to define a condition without organ damage
4	It is necessary to reach the lowest possible level of HbA1c since diagnosis, as long as there is no risk of hypoglycemia	5%	95%	According to guidelines in the management of “early patients”
5	It is necessary from the diagnosis using several agents in combination to reduce both HbA1c levels and cardiovascular risk	25%	75%	According to guidelines to support an approach based on both glycemic and cardiovascular targets
6	The reduction of cardiovascular risk is not strictly related to the reduction of HbA1c levels	18%	82%	HbA1c is not the only CV risk factor in T2DM
7	The choice to use GLP-1 receptor agonists or SGLT2 inhibitors is not related to the need to normalize HbA1c values	20%	80%	The choice of these glucose-lowering drugs is also based on the need to reduce CV risk
8	The distinction between primary and secondary cardiovascular prevention is commonly established based on a previous cardiovascular event	16%	84%	The definition reflects the common classification of cardiovascular prevention
9	The distinction between primary and secondary cardiovascular prevention is established based on the level of cardiovascular risk (low, intermediate, high)	64%	36%	The patients with T2DM can be at high risk despite no prior CV events
10	The definition of cardiovascular risk is based on the presence of coronary artery disease alone	98%	2%	The definition of cardiovascular risk is not only based on the presence of coronary artery disease
11	The definition of cardiovascular risk is based on the presence of obliterating arteriopathy of the lower limbs	49%	51%	The definition of cardiovascular risk is not necessarily limited to the peripheral vascular district

**Table 2** continued

Statement	Disagreement (score 1–2)	Agreement (score 3–5)	Reasoning behind consensus
12 Patients with T2DM may have different levels of cardiovascular risk	9%	91%	According to ESC 2019 guidelines patients with T2DM can be classified as at moderate, high, and very high CV risk
13 The definition of a high-risk diabetic patient may be independent of the duration of the disease	0%	100%	Duration of T2DM is usually unknown and CV events may even precede the diagnosis of T2DM
14 An increased urinary albumin/creatinine ratio is a stronger predictor of cardiovascular disease than of progression of kidney damage	9%	91%	Albumin/creatinine ratio is a strong predictor of CVD
15 A treat-to-benefit approach involves the addition of a second glucose-lowering agent with proven cardiovascular benefits to metformin since diagnosis or in any case in an early stage of diabetes	2%	98%	According to available literature, a treat-to-benefit approach, aiming at reducing CV risk, suggests the addition of drugs with proven CV benefits, even at early stages
16 Treatment with metformin is not always the first choice in a patient with newly diagnosed T2DM and with concomitant cardiovascular disease	24%	76%	In accordance with ESC/EASD guidelines
17 GLP-1 receptor agonists and SGLT2 inhibitors represent a key strategy in the treat-to-benefit approach	0%	100%	Same as statement 15
18 The decision to prescribe a glucose-lowering agent in add-on to metformin is based on the presence of a previous cardiovascular event	42%	58%	CVOT, ESC, and EASD/ADA consensus endorse the use of either GLP-1RA and SGLT2 inhibitors simultaneously to metformin in patients with new-onset type 2 diabetes with CVD, heart failure, and CKD, but these comorbidities are not the only determinant of the diabetologists' therapeutic decision
19 The decision to prescribe a glucose-lowering agent in add-on to metformin is based on the level of cardiovascular risk (low, intermediate, high)	15%	85%	Therapeutic strategies are based on a global assessment of the CV risk of the patient

**Table 2** continued

	<b>Statement</b>	<b>Disagreement (score 1–2)</b>	<b>Agreement (score 3–5)</b>	<b>Reasoning behind consensus</b>
20	The decision to prescribe a glucose-lowering agent in add-on to metformin is based on the presence of microangiopathy	24%	76%	Therapeutic hypoglycemic strategies should be based on several aspects including the presence of complications not limited to microangiopathy
21	Sulfonylureas no longer have a place in the therapeutic algorithm for the treatment of T2DM	24%	76%	Although sulfonylureas are increasingly replaced by other drugs, current guidelines still allow their use as third- or fourth-line choice
22	The benefits of GLP-1 receptor agonists and SGLT2 inhibitors are limited to patients with T2DM and cardiovascular disease	95%	5%	Efficacy of GLP-1RAs and SGLT2 inhibitors was shown in patients with T2DM irrespective of the presence of previous CVD
23	In patients with high levels of HbA1c, the use of GLP-1 receptor agonists is more indicated	24%	76%	Higher potency demonstrated by GLP-1RAs in reducing HbA1c with respect to SGLT2 inhibitors
24	In order to prevent atherosclerotic disease, GLP-1 receptor agonists should be used at an earlier stage than SGLT2 inhibitors	24%	76%	According to available literature demonstrating anti-atherosclerotic properties of GLP-1RAs
25	In order to prevent heart failure, GLP-1 receptor agonists should be used at an earlier stage than SGLT2 inhibitors	84%	16%	According to available literature demonstrating a reduction of HF hospitalization with the use of SGLT2 inhibitors
26	Based on the data available to date, in patients with evidence of subclinical atherosclerotic disease, the use of GLP-1 receptor agonists is a first choice over SGLT2 inhibitors	4%	96%	Same as statement 24
27	GLP-1 receptor agonists and SGLT2 inhibitors should only be used in patients who have been shown to have subclinical atherosclerotic disease	96%	4%	Same as statements 22 and 24
28	In patients with T2DM the prevalence of atherosclerotic cardiovascular disease is higher than the prevalence of heart failure	31%	69%	Atherosclerotic cardiovascular disease is the leading comorbidity in patients with T2DM



**Table 2** continued

Statement	Disagreement (score 1–2)	Agreement (score 3–5)	Reasoning behind consensus
29 In patients with T2DM the risk of atherosclerotic cardiovascular disease is greater than that of heart failure	29%	71%	The CVOT showed that the incidence rate of MACE is about threefold higher than that of HF
30 Regardless of their hypoglycemic efficacy, GLP-1 receptor agonists and SGLT2 inhibitors have a beneficial effect on multiple cardiovascular risk factors (weight, blood pressure, hyperlipidemia, hyperuricemia, inflammation) although the mechanisms and extent of effect on individual risk factors differ between the two drug classes	0%	100%	SGLT2 inhibitors and GLP-1RAs have well-documented effects on multiple CV risk factors

*ADA* American Diabetes Association, *CVD* cardiovascular disease, *CVOT* cardiovascular outcomes trial, *EASD* European Association for the Study of Diabetes, *ESC* European Society of Cardiology, *GLP-1* glucagon-like peptide 1, *HbA1c* glycated haemoglobin, *HF* heart failure, *MACE* major adverse cardiovascular event, *SGLT2* sodium-glucose co-transporter 2, *T2DM* type 2 diabetes mellitus

relatively small place in the therapeutic algorithm for the treatment of T2DM (76%), specifically in high-risk patients.

When criteria to prescribe a glucose-lowering agent in add-on to metformin were investigated, there was positive consensus that the choice should be made on the level of CV risk (85%), and on the presence of microangiopathy (76%). No consensus was obtained on the decision to prescribe a glucose-lowering agent in add-on to metformin based only on the presence of a previous CV event.

### **Indications for GLP-1RAs and SGLT2 Inhibitors**

The expert panel agreed that the benefits of GLP-1RAs and SGLT2 inhibitors are not limited to patients with T2DM and CVD (95%) and that GLP-1RAs are more indicated in patients with high levels of HbA1c (76%). Furthermore, panelists agreed to use GLP-1RAs at an earlier stage than SGLT2 inhibitors to prevent atherosclerotic disease (76%) but not HF (84%). There was also a strong consensus on the use of GLP-1RAs as the first choice over SGLT2 inhibitors in

patients with evidence of subclinical atherosclerotic disease (96%). Panelists disagreed that GLP-1RAs and SGLT2 inhibitors should be used only in patients with a subclinical atherosclerotic disease (96%). There was consensus that the prevalence (69%) and the risk (71%) of atherosclerotic CVD are higher than those of HF in patients with T2DM. Finally, consensus on the beneficial effects of GLP-1RAs and SGLT2 inhibitors on multiple CV risk factors was unanimous (100%).

## **DISCUSSION**

The purpose of the study was to perform a Delphi survey among a panel of Italian diabetes specialists to gather an expert consensus on the treatment of patients with newly diagnosed T2DM, as well as to generate clinical recommendations on the optimal management of CV risk immediately after the clinical diagnosis. After two rounds of Delphi survey, a consensus was reached on 27/30 statements.

Overall, panelists agreed that patients with newly diagnosed T2DM, without long-term complications, and with a preserved beta cell function may be considered “early” subjects. In this population the normalization of HbA1c should be sought aggressively, also by a combination therapy with agents with complementary mechanisms of action. To implement a treat-to-benefit approach, i.e., to reach an HbA1c at target and to decrease the CV risk, the early use of GLP-1RAs and SGLT2 inhibitors either as first- or second-line treatment in “early T2DM subjects” reached a broad consensus. The preference for one over the other of these classes of drugs is based on specific evidence-based characteristics, including the results of CVOTs and the recommendations of current consensus and guidelines in T2DM [6–15, 24].

Panelists also agreed on the distinction between primary and secondary CV prevention based on prior CV event and not on the level of CV risk. The Delphi consensus suggested that the glucose-lowering approach either for high CV risk or for very high-risk patients should be similar. The presence of microangiopathy, and in particular of diabetic kidney disease, was also unanimously considered an important risk factor for the definition of CVD risk.

These statements opened up several further considerations on the definition of the target patient to be considered “early”, the best pharmacological approach to treat this patient, and how to fill the gap in current recommendations.

According to Italian diabetes experts, a patient is defined as “early” according to different interpretations: pathophysiological and clinical aspects, and/or according to the timing of the diagnosis. These definitions identify a patient with newly diagnosed T2DM, drug naïve, or already treated with metformin alone, with no evidence of organ damage and, possibly, in an early stage of the disease, in which beta cell insulin secretion still sufficiently copes with insulin resistance.

However, T2DM may be diagnosed soon after the occurrence of the first CV event. Thus, the UKPDS, enrolling newly diagnosed patients with T2DM, highlighted that more than 50% of patients already had complications at diagnosis [28]. The presence of CVD at diagnosis was

already documented in observational studies [29], in patients with diabetes or prediabetes [30].

The unanimous consensus on the need to reach the lowest possible level of HbA1c and normalize HbA1c is supported by several pieces of evidence. The results of the observational long-term follow-up of the UKPDS demonstrated that intensive glucose control starting at the time of diabetes diagnosis could be associated with a significantly decreased risk of myocardial infarction and death from any cause [31]. Also, the meta-analysis of CVOTs revealed that intensive glycemic control was associated with a 9% reduction in the risk of MACE [32], but not of all-cause or CV death.

The normalization of HbA1c at an early stage of the disease leads to a reduction in CV events [5, 31]. A population-based study on patients with newly diagnosed T2DM showed that a 1-year delay in treatment intensification in conjunction with poor glycemic control significantly increased the risks of HF, stroke, and composite CV events in patients with and without a history of CVD before diabetes diagnosis [33]. Furthermore, the achievement of an HbA1c less than 6.5% within 6 months after metformin initiation translated into a lower risk of CV events and death [34]. Thus, early glycemic control, particularly during the first year following diagnosis, may be crucial for the prevention of disease progression and of later complications [31, 35]. Furthermore, the legacy effect of early blood glucose control can extend up to almost 20 years after the clinical diagnosis of diabetes [36].

Panelists also agreed on the early use of a combination therapy to reach HbA1c targets and prevent CV risk. The concept of using multiple drugs immediately after the diagnosis of diabetes is relatively new in diabetology and diabetes guidelines have recently introduced, in the therapeutic algorithm, the possibility of initial combination therapy for newly diagnosed patients with HbA1c levels more than 1.5% above their target [7].

The VERIFY study demonstrated the potential of early combination therapy in providing greater and durable long-term benefits: time to loss of glycemic control was nearly doubled,

and more than twice the number of patients experienced extended glycemic control, with a vildagliptin–metformin combination therapy versus metformin alone [37]. Similarly, a meta-analysis of 36 studies on the efficacy of initial combination therapy in drug-naïve patients with T2DM demonstrated that all initial combination therapies resulted in significant HbA1c reductions compared with metformin monotherapy [38].

Furthermore, early combination therapy using agents targeting different physiological abnormalities could provide longer periods with stable HbA1c levels, delaying the need for therapy intensification and reducing the risk of chronic complications [20]. The incoming GRADE (Glycemia Reduction Approaches in Diabetes: a Comparative Effectiveness) study will additionally clarify the clinical effectiveness of the addition of four classes of glucose-lowering agents to metformin [39].

Recent guidelines recommend routinely perform a CV risk assessment in T2DM [40] since diagnosis. ESC guidelines classified patients with T2DM in different CV risk classes, independent of baseline HbA1c, considering only patients aged less than 50 years with diabetes duration less than 10 years and no additional risk factors, at moderate risk. The presence of CVD, or target organ damage, or multiple major risk factors classifies the subject as very high risk [41]. This classification is in line with the consensus obtained on the independence of the definition of high-risk patients with T2DM from diabetes duration when CV events, organ damage, or multiple major risk factors are present.

Conversely, the statement that the definition of CV risk is based on the presence of peripheral artery disease (PAD) did not reach a consensus, because CV risk is multifactorial, and the presence of PAD is just one of the multiple criteria.

The perception of the importance of the evaluation of urinary albumin/creatinine ratio is also underlined by the ESC/EASD guidelines: there is a strong recommendation to routinely assess microalbuminuria to identify patients at risk of developing renal dysfunction or at high risk of CVD [24].

Notably, panelists strongly agreed on adopting a treat-to-benefit approach, a consensus that is in line with current guidelines that recommend glucose-lowering agents with proven CV benefit in people with T2DM and established CVD or at high/very high CV risk [7, 24]. The unanimous consensus on the use of GLP-1RAs and SGLT2 inhibitors in the treat-to-benefit approach reflects the awareness and knowledge of the multiple supporting evidence of these two agents in the reduction of CV events or kidney disease, associated with low risk of hypoglycemia.

Thus, the results of this Delphi consensus suggest early use of these classes of drugs, further extending the indications of current ESC/EASD guidelines that recommend GLP-1RAs or SGLT2 inhibitors in drug-naïve patients with established atherosclerotic CVD or those at high or very high risk (diabetes duration at least 10 years without target organ damage plus any other additional risk factors) [24].

However, despite these recommendations, only 15.3% of Italian patients with T2DM are currently treated with a glucose-lowering agent with an approved CV indication, irrespective of CV status [42]. This is a very low percentage when compared with the data from a diabetes register in Scotland, showing that more than 70% of naïve or metformin-treated patients with T2DM were at high or very high risk according to these guidelines [43].

The lack of consensus on the addition of a glucose-lowering-agent in add-on to metformin according to a previous CV event could be explained as diabetes specialists decide on the addition of another agent as an add-on to metformin mainly on the basis of glycemic control, considering several clinical aspects, including CV risk and kidney function.

Conversely, Italian real-world data from the ARNO Observatory showed that sulfonylureas are still used in 22% of patients with T2DM [44], a therapeutic approach that received a negative consensus in the Delphi survey in 76% of cases. The partially discordant agreement on this statement may stem from current guidelines that still allow use of sulfonylureas as third-line therapy [7].

In this regard, the lack of consensus on the addition of a glucose-lowering-agent in add-on to metformin according to a previous CV event was expected, and it is likely related to the complex clinical reasoning on the choice of second hypoglycemic agents after metformin that takes into account several clinical and non-clinical variables, including glucose control, diabetes duration, comorbidities, age, life expectancy, family support, etc.

The consensus reached on the choice of timing for introduction of GLP-1RA or SGLT2 inhibitors in the history of the disease reflects the acknowledgment of their demonstrated mechanisms of action and the results of clinical trials, including CVOTs. Thus, SGLT2 inhibitors, by acting through diuretic and natriuretic effects, decrease HF hospitalization, reduce CV mortality, and mitigate the progression of diabetic kidney disease [45], whereas GLP-1RAs contribute to risk reduction by both correcting multiple CV risk factors and by acting directly on the pathophysiology of atherosclerotic plaque [46]. The reduction of CV events obtained with SGLT2 inhibitors or GLP-1RAs is most likely independent of their glucose-lowering properties [47, 48].

The agreement on the use of SGLT2 inhibitors earlier than GLP-1RAs to prevent HF is supported by cumulative evidence from randomized controlled trials that demonstrated the efficacy of this class of drugs in reducing hospitalizations for HF by 23% and the risk of progression of renal disease by 45%. These effects were observed consistently across a range of estimated glomerular filtration rates (eGFRs) and irrespective of the presence of ischemic heart disease or HF at baseline [49, 50]. Although the mechanisms of the beneficial effects of SGLT2 inhibitors in cardiorenal complications are not fully understood [51], recent studies indicate that the renoprotective effects related to the natriuresis are involved in the improvement in hospitalization for HF [52, 53].

Recent data from the DAPA-HF [54] and EMPEROR-reduced [55] trials in patients with HF and a reduced ejection fraction with or without diabetes showed that patients treated with SGLT2 inhibitors had a lower risk of worsening HF or CV death than those on

placebo, suggesting that SGLT2 inhibition is beneficial even in the absence of diabetes. On the other hand, GLP-1RAs showed no clear benefit on HF hospitalization reduction and there is uncertainty on GLP-1RA efficacy in patients with HF with reduced ejection fraction. Preliminary hypotheses suggest that these agents may be efficacious in patients with HF with preserved ejection fraction [56].

The results of the REWIND trial [12], which included a greater proportion of patients with T2DM without established CVD and with high CV risk, highlighted the efficacy of dulaglutide in the reduction of major CV events also in patients without a history of CVD. On the other hand, a clear benefit was not documented with dapagliflozin in the DECLARE-TIMI 58 study [14] for the same outcome. In this regard, the consensus obtained in the preference for GLP-1RAs in patients with the subclinical atherosclerotic disease may reflect these results from the CV outcomes trials as well as the documented mechanisms of action of the two classes of drugs from experimental and pre-clinical studies [57, 58].

The beneficial effects of GLP-1RAs and SGLT2 inhibitors on multiple CV risk factors have been well documented including advantages with respect to body weight, blood pressure, lipids, uric acid, and inflammatory markers, with some differences between the two classes in terms of efficacy on selected risk factors [58, 59]; accordingly, these beneficial effects were acknowledged by the Delphi panelists.

Notably, since this Delphi-driven consensus aimed to define the optimal early antidiabetic treatment for CVD prevention in patients with T2DM, only glucose-lowering agents with proven CVD benefits, i.e., GLP-1RAs and SGLT2i, were included; other classes of glucose-lowering agents with proven efficacy on glucose control, such as DPP4i, glitazones, and acarbose, were not taken into account.

There are some limitations to our study. Thus, even if consensus is reached results are dependent on the composition of the respondents. However, to minimize the potential for selection bias, panelists were identified

according to their long-term experience in diabetes fields and to their nationwide distribution.

Moreover, the statements suggested by KOLs were further validated by four external expert validators, but the clarity of some of the statements might have been missed. The attrition rates over the two rounds were low, thereby ensuring that the range of expert opinion was adequately represented, and the level of consensus was specified a priori.

## CONCLUSIONS

The results of the Delphi survey suggest that Italian diabetologists recognized the pivotal importance of adopting a tailored approach for patients with T2DM and CV risk factors; moreover, they emphasized the strategic role of the early treatment with GLP-1RAs and SGLT2 inhibitors in the treat-to-benefit approach.

A paradigm shift to enhance treatment adherence should therefore be implemented by focusing the attention not only on metabolic control but also on the long-term benefits of glucose-lowering agents with proven CV efficacy.

There are still some aspects where consensus was not achieved, reflecting open issues yet to be addressed.

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

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