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ORIGINAL ARTICLE

A Decision Support Tool for Appropriate Glucose-Lowering Therapy in Patients with Type 2 Diabetes

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Abstract

Background: Optimal glucose-lowering therapy in type 2 diabetes mellitus requires a patient-specific approach. Although a good framework, current guidelines are insufficiently detailed to address the different phenotypes and individual needs of patients seen in daily practice. We developed a patient-specific decision support tool based on a systematic analysis of expert opinion.

Materials and Methods: Based on the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) 2012 position statement, a panel of 12 European experts rated the appropriateness (RAND/UCLA Appropriateness Method) of treatment strategies for 930 clinical scenarios, which were permutations of clinical variables considered relevant to treatment choice. These included current treatment, hemoglobin A1c difference from individualized target, risk of hypoglycemia, body mass index, life expectancy, and comorbidities. Treatment options included addition of a second or third agent, drug switches, and replacement by monotherapies if the patient was metformin-intolerant. Treatment costs were not considered. Appropriateness (appropriate, inappropriate, uncertain) was based on the median score and expert agreement. The panel recommendations were embedded in an online decision support tool (DiaScope®; Novo Nordisk Health Care AG, Zürich, Switzerland).

Results: Treatment appropriateness was associated with (combinations of) the patient variables mentioned above. As second-line agents, dipeptidyl peptidase-4 inhibitors were considered appropriate in all scenarios, followed by glucagon-like peptide-1 receptor agonists (50%), insulins (33%), and sulfonylureas (25%), but not pioglitazone (0%). Ratings of third-line combinations followed a similar pattern. Disagreement was highest for regimens including pioglitazone, sulfonylureas, or insulins and was partly due to differences in panelists' opinions and in drug availability and reimbursement across European countries (although costs were disregarded in the rating process).

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Conclusions: A novel decision support tool based on the ADA/EASD 2012 position statement and a systematic analysis of expert opinion has been developed to help healthcare professionals to individualize glucose-lowering therapy in daily clinical situations.

Introduction

THE COMPLEXITY OF GLYCEMIC management in type 2 diabetes mellitus (T2DM) has increased dramatically over the past 20 years. In 1995, the drugs available for treatment of T2DM in Europe were insulin, metformin, and sulfonylureas (SU). In 2012, nine glucose-lowering drug (GLD) classes were available, significantly increasing the number of treatment options.[1] Therefore, new combinations of agents with complementary mechanisms of action are possible, facilitating individualized, patient-centered care as proposed in the latest position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[1] Besides lifestyle modification measures, the statement recommends setting individual glycemic targets and treatment selection based on patient characteristics and properties of the glucose-lowering agents. However, phenotypes in T2DM vary widely, with substantial heterogeneity in clinical outcomes. Therefore, healthcare professionals now have many pharmacological approaches available to tailor treatment to individual patient needs. However, the expansion in clinical options is accompanied by a general lack of long-term comparative effectiveness studies to inform clinical decision-making, as well as new uncertainties regarding the long-term benefits of new drugs, for example, on macrovascular complications.[2–4] Consequently, many clinicians are uncertain when faced with the task of finding the most suitable strategy for any given clinical scenario.

Despite the wide range of glucose-lowering options and the availability of treatment guidelines, observational studies in T2DM consistently report clinical inertia, defined as failure to initiate or intensify therapy according to evidence-based guidelines, along with poor hemoglobin A1c (HbA1c) levels.[5] A retrospective cohort study based on 81,573 people with T2DM in the United Kingdom between 2004 and 2011 showed significant delays in intensifying treatment, with patients remaining in poor glycemic control for more than 7 years before intensification with insulin.[6] In patients taking one, two, or three oral GLDs, median time from initiation of treatment to intensification with an additional GLD or insulin exceeded 7.2 years. The mean HbA1c level at intensification with an GLD or insulin for people taking one, two, or three GLDs was 8.7%, 9.1%, and 9.7%, respectively.[6] In another retrospective database study in primary care in Germany and the United Kingdom, the time to insulin therapy significantly increased in T2DM patients from 2005 to 2010.[7] The last HbA1c values before insulin initiation were high and slightly increased during the study period (Germany, from 8.2% in 2005 to 8.4% in 2010; United Kingdom, from 9.5% to 9.8%, respectively).[7]

One reason for clinical inertia includes treatment complexity. Therefore, there is a need for better translating scientific knowledge to everyday practice decisions.[8] The use of clinical decision support systems (CDSSs) may be one solution because they can provide patient-specific recommendations at the point of care, through the input of patient data in an electronic or nonelectronic system with a use of algorithms that can match pieces of information from a knowledge database.

In order to simplify decision-making for glucose-lowering therapy in T2DM for primary care physicians and nonspecialists, we conducted a European expert panel study to translate the ADA/EASD position statement into recommendations at the patient-specific level, combining the evidence from clinical trials and expert opinion. The study focused on treatment choice for patients insufficiently controlled by or intolerant to metformin.

Materials and Methods

The study followed a systematic methodology with well-defined steps, previously used to develop decision support tools in other disease areas.[9–11]

RAND/UCLA Appropriateness Method

The appropriateness of treatment for a variety of clinical scenarios was studied using the RAND/UCLA Appropriateness Method (RUAM).[12] The RUAM, a modified Delphi method, encompasses a highly structured approach to develop patient-specific treatment recommendations, based on the best available evidence from clinical studies and practice experience.[12,13] A treatment is considered appropriate if its expected benefits exceed its potential negative consequences by a sufficient margin. Studies on reliability, internal consistency, and (predictive) validity of the RUAM have shown favorable results.[14]

Literature review

An extensive literature review was conducted to shape the research question and study design and to ensure that panel members had access to the same body of evidence during the rating process. For details, see supporting information at http://diascope.org/sites/default/files/RAND-DM_Literature.pdf

Panel composition and process

Based on their scientific and clinical expertise in the field of diabetes, 12 experts from eight European countries were selected: 11 diabetologists and one general practitioner with special expertise in diabetes. The panel met in November 2012 to discuss the literature review and starting points of the study. These included criteria for the patient population to be considered (T2DM, insufficient glycemic control with metformin mono-/dual therapy or intolerance to metformin, age ≥ 18 years, and absence of specific conditions such as pregnancy and severe renal impairment), as well as selection of seven clinical variables that formed the basis for developing a comprehensive set of clinical scenarios or patient profiles (current treatment, disease duration, HbA1c difference from individual target, risk of hypoglycemia, body mass index [BMI], life expectancy, and comorbidities relevant to antidiabetes treatment). Treatment options consisted of the addition of a second or a third drug (SU, pioglitazone,

dipeptidyl peptidase-4 inhibitors [DPP-4i], glucagon-like peptide-1 receptor agonists [GLP-1 RA], or insulins) and drug switches. Insulin intensification was not considered in this initial phase of the study, and sodium/glucose co-transporter 2 inhibitors were not included, as they were not widely available in Europe at the time of this project. Using an electronic program, panelists individually performed 1,398 appropriateness ratings on a 9-point scale (reference values: 1 = very inappropriate; 5 = uncertain; 9 = very appropriate). Panelists were instructed to take only the clinical perspective into consideration and to disregard costs and other potential constraints.

After the first rating round, the panel convened to discuss the results (January 2013). Panelists received feedback on their own ratings in comparison with the anonymous results of their colleagues. The discussion revealed that the variable ''disease duration'' was not discriminative for treatment choice and could therefore be removed from the model. Furthermore, the panel made several refinements to the definitions of criteria, variables, and treatment options. Thereafter, a second individual rating round, including 930 assessments, was conducted (May 2013). An overview of clinical variables and treatment options used in the second round is given in Table 1.

Statistical analysis

For calculating the appropriateness of treatments, the mathematical rules that are typically applied in RUAM studies were used.[12] The outcome was appropriate if the median panel score was between 7 and 9 and inappropriate if the median was between 1 and 3, both without disagree-

ment between panelists. Disagreement was defined when at least four out of 12 panelists scored in each of the sections 1–3 and 7–9. All other situations were deemed uncertain. Frequency tables and cross-tabulations were used to describe and analyze the appropriateness of treatments by clinical variables.

Electronic decision tool

The results of the second round were embedded in an electronic decision support tool (DiaScope®; Novo Nordisk Health Care AG, Zürich, Switzerland), which shows the appropriateness of treatments for any given patient profile. Where applicable, the results of separate conditions were combined with overall panel recommendations using the principle that the final outcome is determined by the lowest appropriateness category of the separate conditions.

Results

Insufficient glycemic control with metformin monotherapy

For patients insufficiently controlled with metformin monotherapy, second-line regimens with DPP-4i were rated appropriate for all scenarios (Fig. 1), followed by those with GLP-1 RA (50%), insulins (33%), and SU (25%). Analysis of appropriateness by clinical variables showed that the appropriateness of GLP-1 RA decreased if life expectancy was < 2 years and BMI was < 25 kg/m^2 (Fig. 2). In contrast, the appropriateness of GLP-1 RA was high if the difference from the individualized HbA1c target was ≥ 1% and the BMI was ≥ 25 kg/m^2. Regarding insulin, the dominant factor driving its

TABLE 1. OVERVIEW OF CLINICAL VARIABLES AND TREATMENT OPTIONS USED IN THE SECOND RATING ROUND DURING THE DEVELOPMENT OF A CLINICAL DECISION SUPPORT SYSTEM FOR THE MANAGEMENT OF HYPERGLYCEMIA IN TYPE 2 DIABETES MELLITUS

Variable	Number of categories	Description
Previous treatment	5	Metformin monotherapy or dual therapy with SU, PIO, DPP-4i, or GLP-1 RA
Difference from individualized HbA1c target	2	< 1%; ≥ 1%
Risk of hypoglycemia	2	Low; moderate–high
Body mass index	3	25; 25–29.9; ≥ 30 kg/m^2
Life expectancy	2	≥ 2 years; < 2 years
Comorbidities	6	Coronary heart disease, heart failure, advanced microvascular complications, renal impairment, liver dysfunction, dementia

Decision areas	Number of treatment options	Description
Insufficient control of metformin monotherapy	5	Two-drug regimen including SU, PIO, DPP-4i, GLP-1 RA, or insulins
Insufficient control of dual therapy with metformin	27	Addition of third drug or replacement by other two-drug regimen including metformin
Intolerance to metformin	5	Replacement by another monotherapy (SU, PIO, DPP-4i, GLP-1 RA, or insulins)
Comorbidities	6	Metformin, SU, PIO, DPP-4i, GLP-1 RA, insulins

DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; PIO, pioglitazone; SU, sulfonylureas.
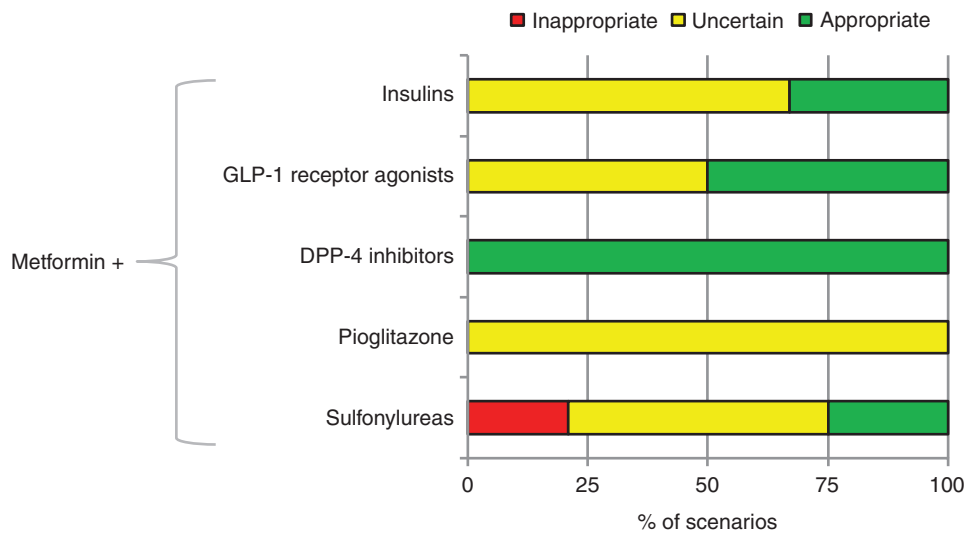
FIG. 1. Appropriateness of second-line regimens with metformin (percentage of clinical scenarios). A treatment is considered appropriate if its expected benefits exceed its potential negative consequences by a sufficient margin. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
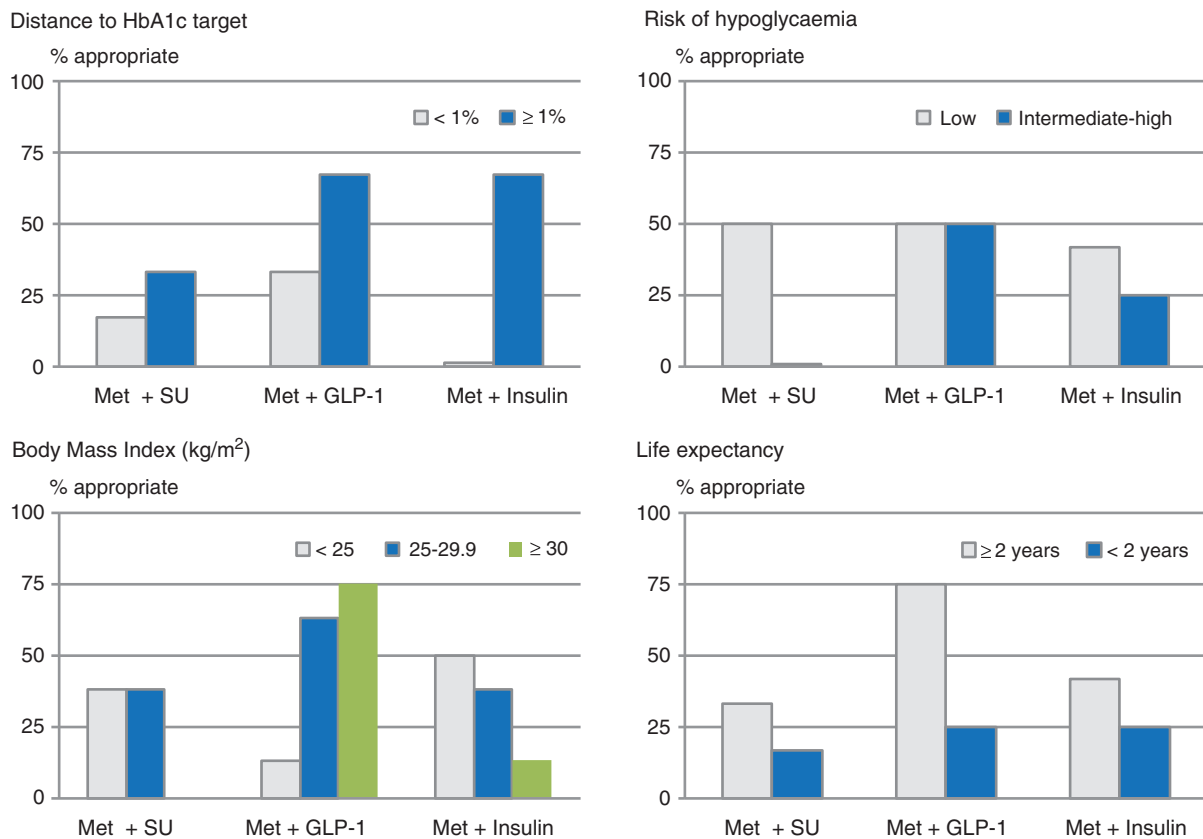

FIG. 2. Appropriateness of second-line treatments (sulfonylureas [SU], glucagon-like peptide-1 receptor agonists [GLP-1 RA], and insulins, all with metformin [Met]) by clinical variables: distance to hemoglobin A1c (HbA1c) target, risk of hypoglycemia; body mass index, and life expectancy. Data are percentages of scenarios considered appropriate. Met + dipeptidyl peptidase-4 inhibitors was always considered appropriate, and Met + pioglitazone was never considered appropriate; therefore these combinations are not shown here.

appropriateness was also the difference from HbA1c target, whereas other variables (hypoglycemia risk, BMI, life expectancy) showed a negative association with appropriateness. The only class for which inappropriate outcomes were seen was SU. These apply exclusively to patients with difference from HbA1c target of <1% and moderate/high risk of hypoglycemia (details not shown). The outcomes for pioglitazone were always uncertain, predominantly because of disagreement between panelists.

Insufficient control with metformin dual therapy

Addition of a third drug in patients insufficiently controlled by dual therapy showed a hierarchy of appropriateness that was comparable to dual therapies (Table 2). Replacement by another two-drug regimen (switch) was in general less often considered appropriate than addition of a third drug (Table 2). The few situations in which a switch was perceived more relevant than addition was for GLP-1 RA after dual therapy with DPP-4i and for initiation of insulin after dual therapy with pioglitazone. Analysis of appropriateness of triple therapies in relation to clinical variables (data not shown) revealed similar underlying patterns as described for second-line treatments.

Intolerance to metformin

For patients displaying intolerance to metformin monotherapy, the appropriateness of replacement by other monotherapies was rated separately. For SU, pioglitazone, and DPP-4i, the results were identical to those of adding the same drug when metformin alone was insufficient. For GLP-1 RA and insulin monotherapies, the appropriateness was somewhat lower (GLP-1 RA, 33% monotherapy vs. 50% dual therapy; insulins, 17% vs. 33%, respectively).

Comorbidities

Appropriateness of treatment in relation to comorbidities (see Table 1) was rated separately from other conditions. The panel considered pioglitazone to be inappropriate (absolute contraindication) in patients with heart failure. Relative contraindications (''use with caution'') were reported for coronary heart disease and stroke (SU, pioglitazone), stable heart failure and moderate renal impairment (metformin, SU), liver dysfunction (metformin, SU, pioglitazone), and dementia (SU, insulin).

Uncertainty and disagreement

The outcomes were uncertain for 60% of scenarios if all ratings were taken together. Out of these uncertain cases, 59% were due to ratings in the middle of the 9-point scale, reflecting either equilibrium of potential benefits and risks or uncertainty of the experts. For the remaining 41%, uncertainty was ascribed to disagreement among the 12 panelists. Disagreement was highest for regimens including pioglitazone (39%), SU (31%), and insulins (27%). Discussions during face-to-face meetings revealed that this was partly due to different personal experiences and opinions and to differences in drug availability and reimbursement conditions across European countries (although costs were supposed to be disregarded in the rating process).

Electronic decision support tool

The results of the second rating round were embedded in an electronic decision support tool, called DiaScope. The heart of this decision tool is an interface that allows the user to create a patient profile and to see the appropriateness of the various treatment options (Fig. 3). Clicking through on a treatment shows the considerations behind the panel recommendation and provides detailed additional information on, for example, comorbidities. The tool is available in both online and offline formats and is accessible for physicians after registration (http://diascope.org).

Discussion

Adequate glucose-lowering therapy in subjects with T2DM requires repeated follow-up, with frequent adjustments of goals and treatment as the disease progresses. Real-

TABLE 2. APPROPRIATENESS OF TREATMENT REGIMENS IN CASES OF INSUFFICIENT CONTROL BY DUAL THERAPY WITH METFORMIN (PERCENTAGE OF CLINICAL SCENARIOS)

	Current (failing) dual therapy (%)			
	Met + SU	Met + PIO	Met + DPP-4i	Met + GLP-1 RA
Change to three-drug regimen				
Add SU	NA	13	17	33
Add PIO	0	NA	0	0
Add DPP-4i	83	100	NA	NA
Add GLP-1 RA	42	54	NA	NA
Add insulin	33	8	38	42
Replace by other two-drug regimen				
Metformin + SU	NA	0	0	NA
Metformin + PIO	0	NA	0	NA
Metformin + DPP-4i	0	46	NA	NA
Metformin + GLP-1 RA	33	33	33	NA
Metformin + insulin	38	50	25	38

DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; NA, not applicable; PIO, pioglitazone; SU, sulfonylureas.

FIG. 3. User interface of the DiaScope: patient profile and display of treatment recommendations and additional information. DPP-4-i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; INS, insulins; MET, metformin; SU, sulfonylureas; TZD, thiazolidinediones.

life audits show that approximately 40% of patients in Europe do not have good glycemic control despite a large therapeutic armamentarium and numerous guidelines.[15]

The ADA/EASD 2012 position statement[1] was used as the starting point for our discussions. It was assumed that lifestyle changes and diet should be recommended throughout the disease duration and that all patients should start with metformin monotherapy. In line with the RAND/UCLA method, patient variables were selected on their relevance to treatment decisions, and clinical scenarios had to be mutually exclusive. In accordance with the ADA/EASD statement, our model included different HbA1c targets, hypoglycemia risk, life expectancy, important comorbidities, and the presence of established vascular complications. However, BMI was preferred over weight in order to differentiate lean, overweight, and obese groups. In addition, life expectancy was considered a highly important variable for clinical decision-making. Finding an appropriate cutoff point separating short

and long life expectancies in diabetes was not possible because of a lack of clinical evidence and of the difficulty in predicting life expectancy with confidence. However, it is generally easier to identify patients with a very short life expectancy (e.g., in the case of advanced and progressive cancer) and for whom treatment is primarily aimed at preserving patient comfort and avoiding aggressive strategies. The final consensus was a cutoff point of 2 years, as anything beyond is more difficult to predict.

Regarding comorbidities relevant to clinical decision-making, we added dementia to the list recommended by ADA/EASD. Dementia limits the patient in managing complex regimens or even injections, and cognitive dysfunction may also delay the recognition of symptoms of hypoglycemia and increase the risk in falls and fractures.[16]

In contrast, some other variables from the ADA/EASD statement were not included after detailed discussions. ''Disease duration'' proved not to be a differentiating

criterion in the ratings, and we agreed that reaching an individualized HbA1c target in an effective and safe manner was more important than diabetes duration by itself. Moreover, T2DM is often diagnosed incidentally (e.g., after a check-up or diagnosis in a family relative), and the actual disease duration is unknown. Risks associated with ''older age'' in the position statement are reflected in the variables used in our model (higher atherosclerotic disease burden, reduced renal function, other comorbidities, hypoglycemia). Therefore, age was not retained as a separate variable as we considered that life expectancy and absence/presence of comorbidities were more important than age per se and that these variables are good proxies of a patient's overall functional status. Some drug classes were not included because they are used less in Europe (glinides, α-glucosidase inhibitors) or had only recently been approved (sodium/glucose cotransporter 2 inhibitors) so that real-life experience was too limited at the time of this study. Sodium/glucose cotransporter 2 inhibitors will be included in the next update of DiaScope.

Regimens with DPP-4i were considered appropriate in all scenarios because of their low side effect profile and oral administration, followed by those with GLP-1 RA and with insulins. However, these figures apply to a theoretical set of scenarios, and their distribution in real-life practice is yet to be determined. Sixty percent of all treatment options were labeled as uncertain, of which 41% were deemed as such because they received opposite (rather than equivocal) ratings. These opposite ratings reflect differences in expert opinions and experiences and hence the complexity of GLD management.

Similar to most other RAND/UCLA studies, we took the clinical perspective as a starting point, disregarding costs and other potential constraints to treatment choice. Despite extensive discussions, we were unable to totally eliminate the influence of country-specific perspectives on the ratings, resulting in disagreement for a substantial number of scenarios. As this reflects the ''personal'' character of the ratings, it may be questioned whether another panel, with another (geographic) composition or of different size, would have reached the same conclusions. Results from other RAND/UCLA studies comparing different panels for one same topic have shown that interpanel agreement is generally very satisfactory[14] and is highest in panels composed of the same medical specialty.[17–19]

DiaScope is the first CDSS for the management of T2DM developed using the RAND/UCLA method. Treatment recommendations are displayed at a patient-specific level, based on published evidence and the collective judgment of a panel of 12 European experts in diabetes. Appropriateness levels reflect both the median value of the individual ratings and the extent of agreement between the experts. In addition, pop-ups provide detailed clarification on the key clinical variables (e.g., comorbidities) and show the considerations behind the panel recommendations. Other advantages include the display of all common treatment options for each patient profile (not only those considered appropriate), the gradation (median score) of the recommendations as opposed to categories only, and the inclusion of educational comments. The strength of DiaScope is the overview of a wide range of treatment options for multiple clinical presentations that physicians face in

daily practice. The recommendations reflect the expert panel's opinion on their efficacy, tolerability, and ease of use, for given patient profiles, and are never in contradiction with the ADA/EASD position statement.

This tool may offer individual healthcare professionals an opportunity to assess a relevant clinical situation, draw their own conclusions, and then compare them with the panel recommendation. Although the panelists were almost all diabetologists, they took the RAND/UCLA perspective, ''an average patient presenting to an average physician in an average care-providing facility,''[13] as the starting point for their considerations, making the tool applicable for decision-making in most common healthcare settings. By providing a ''second opinion'' directly at the point of care, DiaScope should be viewed as an educational tool that could help promote the adoption and utilization of the ADA/EASD statements by presenting them in the context of interactive clinical scenarios.

Each time a CDSS is developed, the inevitable question is whether it will affect clinical care. Several CDSSs for the management of T2D for healthcare providers already exist, with large differences in terms of development methods, algorithms, content and sophistication level.[20–24] In-depth literature reviews of CDSSs, one of which is in primary T2DM care, found that these tools can indeed be effective in improving the process of care, although few have shown improvements in patient outcomes.[25,26] However, as many factors may influence health outcomes, measuring the effectiveness of CDSSs on these end points is difficult.

On the other hand, there is a risk that CDSSs could generate erroneous advice or misinterpretations. DiaScope is a simple and user-friendly tool that displays experts' opinions for all common treatment options instead of a single solution. Likewise, patient treatment preference was not retained to avoid excluding prematurely valuable options, as preference may be managed by physician–patient discussion or patient education as a subsequent step.

Most important is that a decision support system is only as effective as its underlying knowledge base, which changes rapidly as medical science evolves.[27–29] Therefore we plan annual updates of DiaScope to reflect knowledge progression, changing guidelines, and increased expertise, making the tool as ''evidence-adaptive'' as possible.

Conclusions

Using the RAND/UCLA approach, an expert panel formulated patient-specific recommendations for glucose-lowering therapy in T2DM across numerous clinical scenarios, all embedded in an electronic tool. With the evolving complexity of T2DM management and the increasingly important role of general practitioners in managing these patients, the DiaScope tool may facilitate decision-making and eventually help to reduce clinical inertia. Further research will evaluate its applicability in primary care practice.

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Author disclosure statement

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