CEDA diabetes
Zentraleuropäische Diabetesgesellschaft
Central European Diabetes Association
Föderation der Internationalen Donau-Symposia über Diabetes mellitus
Federation of International Danube-Symposia on Diabetes mellitus

De-escalation of complex insulin regimens in well controlled patients with type 2 diabetes mellitus in everyday clinical practice

Z. Taybani[1], B. Bótyik[1], M. Katkó[2], A. Gyimesi[1†], T. Várkonyi[3], P. Kempler[4]

Importance of insulin therapy

Currently 425 million people are living with diabetes in the world and the International Diabetes Federation (IDF) estimates that in 2045 this number will be 629 million [International Diabetes Federation 2017]. Insulin was first used in the treatment of diabetes on 11 January 1922. Although novel glucose lowering agents were introduced in the last decade (glucagon-like peptide-1 receptor agonists [GLP-1 RAs] or sodium-glucose cotransporter-2 inhibitors [SGLT2Is]), insulin used in complex regimens still remained the cornerstone of antidiabetic therapy after nearly 100 years of its discovery in 1921. The major advantage of insulin over other glucose-lowering medications is that it lowers glucose in a dose-dependent manner over a wide range to almost any glycaemic target, but it can increase the risk of hypoglycaemia, promote weight gain and cause significant treatment burden for the patients.

Treat-to-target in type 2 diabetes (intensification vs. simplification)

Actual clinical practice guidelines about the antihyperglycaemic treatment of type 2 diabetes mellitus (T2D) are focusing on intensifying therapy to achieve target HbA_{1c} levels soon after diagnosis. Treatment intensification is generally the stepwise addition of a new glucose-lowering agent or the switching to more complex insulin regimens. As it is clearly proven that long-term intensive glucose control reduces the risk of diabetes-associated micro- and macrovascular complications, the failure to intensify treatment may have a negative impact on patients' outcomes.

However, in the last couple of years it has been recognised that in certain clinical situations there is a need for de-escalation of complex glucose-lowering regimens, and the delay in simplifying the treatment can also have detrimental consequences for the patients. De-escalation of the treatment is reasonable in T2D patients 1) after bariatric surgery, 2) with significant weight loss, 3) with continuously worsening renal function, 4) among older patients with comorbidities, 5) in patients who used multiple daily insulin injections (MDI) for a transient reason (surgery, intercurrent illness etc.) but restitution of the former therapy was missed, 6) in social deprivation, 7) and also in patients who are overtreated [Jermendy 2019].

CEDA Science

Unter CEDA Science veröffentlicht die Zentraleuropäische Diabetes-Gesellschaft (CEDA/FID) wissenschaftliche Artikel ihrer Mitglieder.

Overtreatment of patients with type 2 diabetes

In general, overtreatment is defined as the use of a treatment even when the potential harms exceed the possible benefits [Chassin 1998]. T2D patients who are treated with hypoglycaemic agents too aggressively and have HbA_{1c} values permanently lower than individually recommended are considered overtreated and overcontrolled. Overtreatment of T2D with hypoglycaemic agents especially in older individuals with several associated comorbidities is potentially harmful because it increases the risk of adverse events like hypoglycaemia and weight gain, poses unnecessary treatment burden to them and worsens their quality of life. Another form of overtreatment is when well-controlled T2D patients are treated with unnecessarily complex regimens instead of simpler alternatives ensuring the same glycaemic control with less treatment burden and side effects. Many recent studies demonstrated that overtreatment is a common and generally unrecognised problem in patients with T2D [Lipska 2015, McAlister 2016, Tseng 2014]. The latest guidelines nowadays recommend de-escalation of treatment regimens in

1) 1st Department of Endocrinology, Békés County Central Hospital – Dr. Réthy Pál Member Hospital, Békéscsaba, Hungary
2) Department of Internal Medicine – Division of Endocrinology, University of Debrecen, Debrecen, Hungary
3) 1st Department of Internal Medicine, University of Szeged, Szeged, Hungary
4) 1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary

older adults but it is generally accepted that overtreatment can happen in any age group [American Diabetes Association 2019b].

De-escalation of complex insulin regimens

It is well-documented that overtreatment is common among patients with T2D but medication de-intensification is still infrequent in everyday clinical practice [Hart 2018, Maciejewski 2018, McAlister 2017, Sussman 2015]. Insulin as initial therapy is definitely recommended when blood glucose is ≥ 16.7 mmol/l or HbA_{1c} is ≥ 10 % or if symptoms of hyperglycaemia are present [American Diabetes Association 2019a]. T2D patients presenting with severe hyperglycaemia are often put on multiple daily injections (MDI). If glucose toxicity resolves, the complex insulin regimen may potentially be simplified, but there are no specific guidelines regarding this and a lot of patients are left on MDI for years meanwhile a significant proportion of them become overtreated [American Diabetes Association 2018, Gaál 2017, Inzucchi 2015]. In general the means of treatment de-intensification or de-escalation in T2D are dosage reduction, discontinuation of a medication and simplification of complex regimens.

Very few studies enrolling small numbers of older T2D patients treated with glucose-lowering medication reported the outcome of treatment de-intensification and there are even less published data about the process of simplifying complex insulin regimens in well-controlled people with diabetes [Abdelhafiz 2018].

Fixed ratio combinations for de-escalation?

A single-arm intervention study was conducted enrolling elderly MDI treated T2D patients (n = 65, baseline HbA_{1c} 7.7 %) with 1 or more episodes of hypoglycaemia detected with continuous glucose monitoring (CGM) [Munshi 2016]. Switching MDI to a single dose of a first-generation basal insulin analogue (insulin glargine U100) combined with non-insulin glucose-lowering agents resulted in less hypoglycaemia and better disease-related distress scores. HbA_{1c} improved in patients whose baseline HbA_{1c} levels were above 8 %, no change was noted in those with HbA_{1c} levels between 7 % and 8 %, while there was a small worsening in those with baseline HbA_{1c} levels below 7 %. Based on these data the ADA recommends de-intensification for older T2D patients with declining self-management ability on complex insulin regimens to reduce hypoglycaemia and disease-related distress [American Diabetes Association 2019b].

IDegLira and IGlarLixi are titratable fixed-ratio combinations (FRCs) of a basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1 RA). IDegLira consists of the second-generation ultra-long acting basal insulin analogue insulin degludec and the GLP-1 RA liraglutide. IGlarLixi is the combination of insulin glargine U100 and lixisenatide. The rationale for combining these agents is the complementary mechanism of their glucose-lowering effect. Basal insulins provide control of fasting glucose, while GLP-1 RAs have an effect on fasting and/or postprandial glucose and reduce food intake by

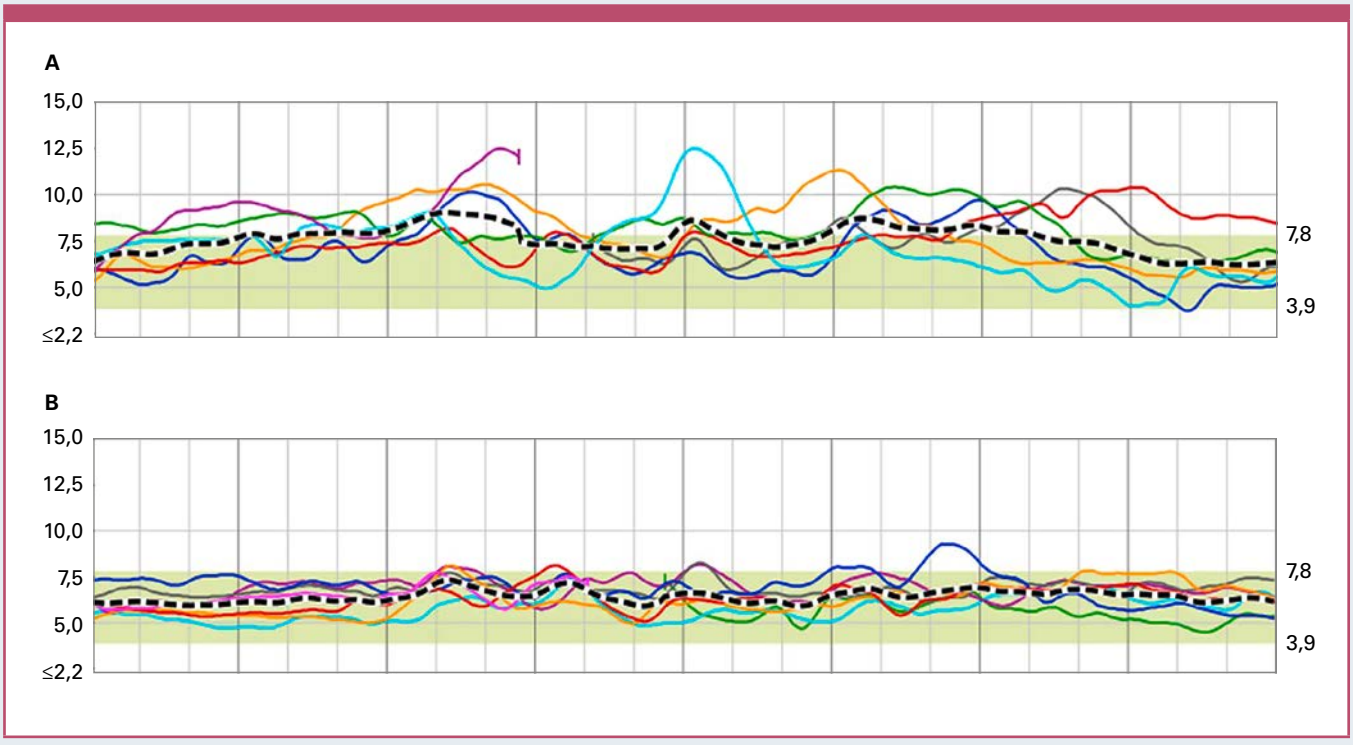

Fig. 1: A: CGM data (mmol/l) of a 67 year-old man with type 2 diabetes treated with 3 doses of human regular and 1 dose of NPH insulin plus 500 mg metformin XR at baseline (HbA_{1c}: 6.4 %, body weight: 78 kg, body mass index [BMI]: 27.9 kg/m², total daily dose [TDD] 44 U/d [0.58 U/kg]); 24-h SD of the glucose readings is 1.5. B: CGM data of the same patient 3 months after simplifying MDI with IDegLira (HbA_{1c} 5.8 %, body weight: 70.3 kg, BMI: 25.2 kg/m², TDD 24 units of IDegLira [0.34 units/kg]); metformin XR was uptitrated to 1500 mg, 24-h SD of the glucose reading decreased to 0.8.

stimulating glucose-dependent insulin secretion, suppressing glucagon secretion, delaying gastric emptying and decreasing appetite.

The placebo-controlled LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial confirmed the cardiovascular (CV) benefits of liraglutide and the DEVOTE trial supported the similar CV safety of insulin degludec with insulin glargine U100 among patients with T2D at high risk for CV events [Marso 2016, Marso 2017]. The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial confirmed the CV safety of insulin glargine U100, while ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) demonstrated the safety of lixisenatide in patients with T2D and a recent acute coronary syndrome [ORIGIN Trial Investigators 2012, Pfeffer 2015].

In T2D patients insulin degludec results in significantly less overall and nocturnal symptomatic hypoglycaemia compared to other basal insulins, while liraglutide, besides its potent glucose-lowering effect, reduces food intake and promotes weight loss [Wysham 2017].

Treatment with IDegLira can provide greater improvement in overall glycaemic control associated with lower hypoglycaemia risk and a more favourable effect on body weight compared with a basal insulin due to the fasting and prandial glucose lowering effects of liraglutide [Gough 2014, Gough 2015, Lingvay 2016]. Compared to insulin glargine U100, IGlarLixi produces greater improvements in HbA_{1c} with beneficial effects on body weight and no additional risk of hypoglycaemia in T2D patients inadequately controlled with a basal insulin or oral glucose-lowering agents [Aroda 2016, Rosenstock 2016].

In patients with uncontrolled T2D on insulin glargine U100 plus metformin IDegLira provides comparable glycaemic effects to MDI, with less hypoglycaemia and weight loss versus weight gain [Billings 2018]. There are also data suggesting that IGlarLixi can offer an effective alternative to MDI, with lower rates of hypoglycaemia and weight gain in patients with T2D inadequately controlled with a basal insulin [Meier 2018].

FRCs can induce significantly greater improvement in overall glycaemic control than a basal insulin due to the additional effect of the GLP-1 RA component with similar or better safety profile regarding hypoglycaemia and body weight, and may achieve HbA_{1c} reductions comparable to basal-bolus therapy, thus it is reasonable to consider that an FRC could be a better alternative for de-intensification of MDI regimens than a single basal insulin.

Real-world use of IDegLira for simplifying complex insulin regimens

In our real-world setting, prospective, one-arm clinical trial the safety and efficacy of switching from MDI to once daily IDegLira in relatively well controlled subjects with T2D using low total daily dose (TDD) of insulin was evaluated [Taybani 2019].

Adult patients with detectable random, non-fasting serum C-peptide levels (≥ 1.1 ng/ml; normal range 1.1 – 4.1 ng/ml) and an HbA_{1c} < 7.5 % treated with MDI plus metformin using relatively low TDD entered the study. At baseline 49 (79%) patients were on a basal-bolus regimen using 1 dose of basal and 3 doses of prandial insulins (38 used human and 11 used analogue insulins), 13 (21 %) patients were treated with 2 or 3 doses of human or analogue premix insulins. TDD was defined as TDD < 70 U/d and TDD < 0.6 U/kg/d at the same time. Overinsulinised patients having severe or repeated symptomatic hypoglycaemia during the month before baseline visit using TDD < 70 U/d and 0.8 > TDD > 0.6 U/kg/d could also be enrolled.

62 adults with T2D (baseline age 64.06 ± 10.24 years, HbA_{1c} 6.42 ± 0.68 %, body mass index (BMI) 33.53 ± 6.90 kg/m², body weight 93.81 ± 19.26 kg, TDD 43.31 ± 10.99 U/d, insulin requirement 0.47 ± 0.13 U/kg, duration of diabetes 10.84 ± 7.50 years; mean ± SD) treated with MDI with/without metformin participated in the study. Previous insulins were stopped and once daily IDegLira was started, administered usually in the morning. IDegLira was titrated by the patients to achieve a self-measured pre-breakfast blood glucose concentration of < 6.0 mmol/l. Metformin was initiated or continued and titrated up with 500 mg weekly dose to the maximal tolerated dose.

After 99.2 days of a mean follow-up mean HbA_{1c} decreased by 0.30 % to 6.12 ± 0.65 % ($p < 0.0001$), body weight decreased by 3.11 kg to 90.70 ± 19.12 kg ($p < 0.0001$), and BMI decreased from 33.53 ± 6.90 kg/m² to 32.39 ± 6.71 kg/m² ($p < 0.0001$). After 3 months of treatment the mean dose of IDegLira was 20.76 + 6.60 units, while mean insulin requirement decreased from 0.47 ± 0.13 U/kg to 0.23 ± 0.08 U/kg. Proportion of patients reaching an HbA_{1c} < 7.0% and an HbA_{1c} < 6.5 % without weight gain and without hypoglycaemia was 72.58 % and 46.77 %, respectively. Mean daily number of injections changed from 3.69 to 1. IDegLira plus metformin combination therapy was safe and generally well tolerated. During the month before the baseline visit 28 patients (45 %) had at least one documented or symptomatic hypoglycaemia, while during the follow-up only 6 (9.67 %) patients reported 13 mild documented episodes. Transient gastrointestinal side effects (lack of appetite, nausea or diarrhoea) were reported by 14 patients (22.5 %) and 1 patient had transient dysthymia.

It was hypothesised that relatively well-controlled T2D patients with normal random C-peptide using low-dose MDI could be the best candidates for de-escalation as they might have some residual endogenous insulin secretion which is required for the effect of liraglutide, while their moderate daily insulin need could be safely ensured with IDegLira, as its maximal daily dose is 50 units.

This study showed that in everyday clinical practice switching from low-dose MDI to IDegLira in patients with well-controlled T2D was safe, was associated with weight loss, resulted in similar or better glycaemic control with less hypoglycaemia. Moreover, it substantially reduced insulin requirement and decreased treatment burden.

Conclusions

Clinical practice guidelines are focusing on intensifying therapy for patients with T2D to reach individual treatment goals without any delay to prevent diabetes-associated complications. At the same time, in selected clinical situations like overtreatment glucose-lowering treatment should be de-escalated.

One form of overtreatment is when T2D patients are treated too aggressively and their HbA_{1c} is permanently lower than recommended. The other form of overtreatment is when well-controlled T2D patients are using unnecessarily complex regimens instead of simpler alternatives which would ensure the same glycaemic control with less side effects and treatment burden. Fix-ratio combinations consisting of a basal insulin and a GLP-1 RA are potentially suitable tools for de-escalation of complex insulin regimens.

Our real-world setting trial data suggest that in everyday clinical practice simplifying complex insulin regimens with IDegLira in well-controlled T2D patients using low dose MDI is feasible, safe and ensures the same or better glycaemic control [Taybani 2019]. The de-escalated medication causes less treatment-associated burden to the patients and may improve adherence and quality of life, because mean daily number of injections changed from 3.69 to 1, and the patients could substantially decrease the daily number of blood glucose tests.

The most important side effect of treatment with insulin is hypoglycaemia which is associated with cardiovascular events and mortality. According to mechanistic studies hypoglycaemia probably affects cardiovascular risk by triggering inflammation, inducing increased platelet and neutrophil activation, and activating the sympathoadrenal response which may induce arrhythmias and increase cardiac workload [Desouza 2010, International Hypoglycaemia Study Group 2019].

Since patients treated with IDegLira were able to achieve excellent glycaemic control but experienced significantly less hypoglycaemia compared to the previously used MDI regimens, IDegLira may confer a safer way of glucose lowering treatment from the cardiovascular point of view. De-escalation of MDI with IDegLira is accompanied by weight loss which is favourable for the patients on the long term as weight loss is associated with improved cardiovascular risk factors in overweight and obese individuals with T2D [Wing 2011].

The mean insulin requirement decreased by 50 % after simplifying treatment with IDegLira. The achievement of a better glycaemic state with less daily insulin is definitely also beneficial for the patients, as it is proven that over-insulinisation predisposes to atherosclerosis [Herman 2017].

Glycaemic variability, the degree to which a patient's blood glucose level fluctuates between high and low levels, may be an HbA_{1c}-independent risk factor for diabetes complications and greater glycaemic variability may be associated with lower quality of life and negative moods [Hirsch 2015, Penckofer 2012, Selvin 2014]. Our clinical experience suggests that de-escalation of MDI with IDegLira can decrease glycaemic variability measured by CGM (Fig. 1).

Our real-world setting trial of simplifying complex insulin regimens with FRCs is still ongoing to confirm the results in a larger group of patients with longer follow-up data, and a CGM substudy was also initiated to analyse changes in glycaemic variability.

References

1. Abdelhafiz AH, Sinclair AJ: Deintensification of hypoglycaemic medications – use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. J Diabetes Complications 2018; 32: 444-450
2. American Diabetes Association: 11. Older adults: standards of medical care in diabetes – 2018. Diabetes Care 2018; 41 (Suppl 1): S119-S125
3. American Diabetes Association: 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes – 2019. Diabetes Care 2019a; 42 (Suppl 1): S90-S102
4. American Diabetes Association: 12. Older adults: standards of medical care in diabetes – 2019. Diabetes Care 2019b; 42 (Suppl 1): S139–S147
5. Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G, Takami A, Guo H, Niemoeller E, Souhami E, Bergenstal RM; LixiLan-L Trial Investigators: Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. Diabetes Care 2016; 39: 1972-1980
6. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, Grøn R, Halladin N, Jodar E: Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. Diabetes Care 2018; 41: 1009-1016
7. Chassin MR, Galvin RW: The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. JAMA 1998; 280: 1000-1005
8. Desouza CV, Bolli GB, Fonseca V: Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010; 33: 1389-1394
9. Gaál Z, Gerö L, Hidvégi T, Jermendy G, Kempler P, Winkler G, Wittmann I: Clinical practice guideline – diagnosis, antihyperglycemic treatment and care of patients with diabetes in adulthood. Diabetologia Hungarica 2017; 25: 3-77
10. Gough SC, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, Damgaard LH, Buse JB: Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol 2014; 2: 885-893
11. Gough SC, Bode BW, Woo VC, Rodbard HW, Linjawi S, Zacho M, Reiter PD, Buse JB: One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. Diabetes Obes Metab 2015; 17: 965-973
12. Hart HE, Rutten GE, Bontje KN, Vos RC: Overtreatment of older patients with type 2 diabetes mellitus in primary care. Diabetes Obes Metab 2018; 20: 1066-1069
13. Herman ME, O'Keefe JH, Bell DSH, Schwartz SS: Insulin therapy increases cardiovascular risk in type 2 diabetes. Prog Cardiovasc Dis 2017; 60: 422-434
14. Hirsch IB: Glycemic variability and diabetes complications: Does it matter? Of course it does! Diabetes Care 2015; 38: 1610-1614
15. International Diabetes Federation: IDF Diabetes Atlas – 8th edition. 2017. https://www.diabetesatlas.org/across-the-globe.html (access: 3 August 2019)
16. International Hypoglycaemia Study Group: Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. Lancet Diabetes Endocrinol 2019; 7: 385-396
17. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR: Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140-149
18. Jermendy Gy: De-escalation of antihyperglycemic treatment in patients with type 2 diabetes – when less is more. Orv Hetil 2019; 160: 1207-1215
19. Lingvay I, Pérez Manghi F, García-Hernández P, Norwood P, Lehmann L, Tarp-Johansen MJ, Buse JB, DUAL V Investigators: Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated he-

moglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. JAMA 2016; 315: 898-907
20. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA: Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med 2015; 175: 356-362
21. Maciejewski ML, Mi X, Sussman J, Greiner M, Curtis LH, Ng J, Haffer SC, Kerr EA: Overtreatment and deintensification of diabetic therapy among medicare beneficiaries. J Gen Intern Med 2018; 33: 34-41
22. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poultr NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB: Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375: 311-322
23. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB: Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017; 377: 723-732
24. McAlister FA, Youngson E, Eurich DT: Treated glycosylated hemoglobin levels in individuals with diabetes mellitus vary little by health status: a retrospective cohort study. Medicine (Baltimore) 2016; 95: e3894
25. McAlister FA, Youngson E, Eurich DT: Treatment deintensification is uncommon in adults with type 2 diabetes mellitus: a retrospective cohort study. Circ Cardiovasc Qual Outcomes 2017; 10: e003514
26. Meier J, Anderson J, Wysham C, Tinahones FJ, Saremi A, Stella P, Liu M, Tabak AG: Propensity-matched patient-level comparison of iGlarLixi and basal-bolus regimen in patients with type 2 diabetes. Diabetologia 2018; 61 (Suppl 1): S385-S386
27. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K: Simplification of insulin regimen in older adults and risk of hypoglycemia. JAMA Intern Med 2016; 176: 1023-1025
28. ORIGIN Trial Investigators, Gerstein HC, Bosch J Dagenais GR, Díaz R, Jung H, Maggioni AP Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S: Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; 367: 319-328
29. Penckofer S, Quinn L, Byrn M, Ferrans C, Miller M, Strange P: Does glycemic variability impact mood and quality of life? Diabetes Technol Ther 2012; 14: 303-310
30. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, Ping L, Wei X, Lewis EF Maggioni AP, McMurray JJ, Probstfield JL Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators: Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373: 2247-2257
31. Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, Cheng X, Zhou T, Niemoeller E, Souhami E, Davies M; LixiLan-O Trial Investigators: Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care 2016; 39: 2026-2035
32. Selvin E, Rawlings AM, Grams M, Klein R, Steffes M, Coresh J: Association of 1,5-anhydroglucitol with diabetes and microvascular conditions. Clin Chem 2014; 60: 1409-1418
33. Sussman JB, Kerr EA, Saini SD, Holleman RG, Klamerus ML, Min LC, Vijan S, Hofer TP: Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. JAMA Intern Med 2015; 175: 1942-1949
34. Taybani Z, Bótyik B, Katkó M, Gyimesi A, Várkonyi T: Simplifying complex insulin regimens while preserving good glycemic control in type 2 diabetes. Diabetes Ther 2019 Jul 25. doi: 10.1007/s13300-019-0673-8 [Epub ahead of print]
35. Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM: Assessing potential glycemic overtreatment in persons at hypoglycemic risk. JAMA Intern Med 2014; 174: 259-268
36. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L; Look AHEAD Research Group: Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011; 34: 1481-1486
37. Wysham C, Bhargava A,Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, Kvist K, Norwood P: Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA 2017; 318: 45-56

Address for correspondence
Dr. Zoltán Taybani
Békés County Central Hospital – Dr. Réthy Pál Member Hospital
1st Department of Endocrinology
Gyulai street 18
5600, Békéscsaba
Hungary
E-mail: taybanizoltan@gmail.com

Conflict of interest
Zoltán Taybani, Balázs Bótyik, András Gyimesi, Mónika Katkó, Tamás Várkonyi and Péter Kempler declare no conflict of interest relevant to this article.