Deciding Glucose Lowering Combinations for Type 2 Diabetes Mellitus

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Disclosures

Speaker for Sanofi

Opinion leader for Abbvie

Objectives

To briefly review guidelines for Type 2 Diabetes Mellitus pharmacologic management

To discuss events that lead to changes in guidelines for type 2 Diabetes Mellitus management

To be able to apply guidelines and available evidence in the selection of agents for the therapy optimization in 3 different clinical scenarios

Before 2008 Diabetes Research Was ...

Mostly based on A1c results

Short termed – 8-12 months phase 2 and phase 3 trials

Using healthier and younger populations – Excluded patients with CVD

William T. Cefalu et al. Dia Care 2018;41:14-31

Then …

- A meta-analysis of rosiglitazone pointed to:
  - 43% increased risk of MI (statistically significant)
  - 64% increased risk of CV death versus comparators (non-significant)

Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008)

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.2 Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

Trials on the effects of intensive glycemic control of diabetes

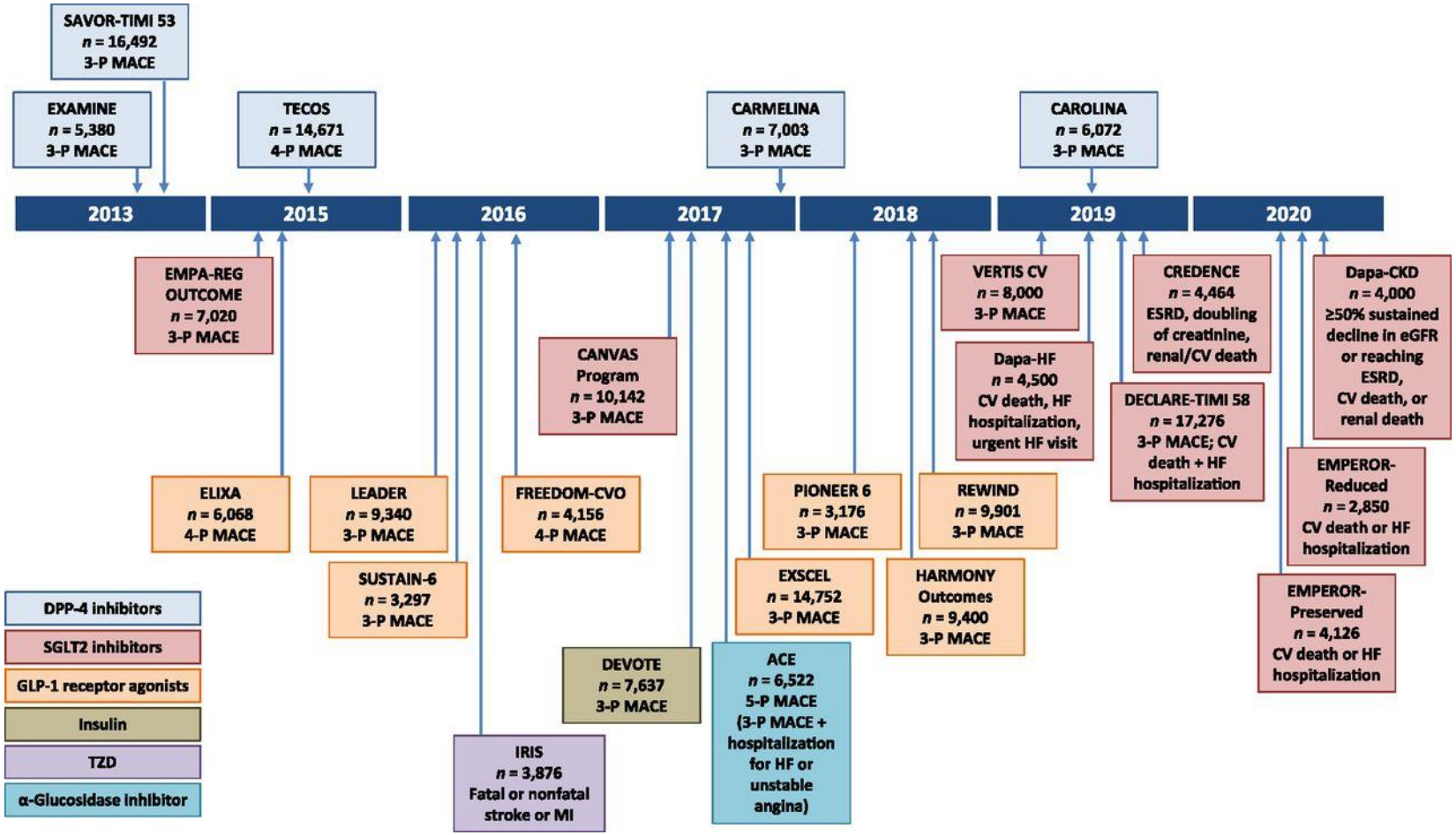
Table 1

Early major trials evaluating the effects of intensive glycemic control of diabetes

Study	Diabetes type	CV composite		MI		CV mortality		All-cause mortality	
DCCT/EDIC (17,26,27)	Type 1	↔	↓	—	—	—	—	↔	↓
UKPDS	Type 2								
Main randomization (SU or insulin vs. conventional therapy) (18,28)		—	—	↔	↓	—	—	↔	↓
Additional randomization of overweight patients (metformin vs. SU vs. conventional therapy) (19,28)		—	—	↓*	↓*	—	—	↓*	↓*
ACCORD (20,30)	Type 2	↔	↔	↓	↔	↑	↑	↑	↔
ADVANCE (21)	Type 2	↔†		↔		↔		↔	
VADT (22,29)	Type 2	↔	↓	↔	↔	↔	↔	↔	↔

- Left columns show initial results; right columns show long-term follow-up. ↔, Neutral effect; ↓, decrease; ↑, increase; —, not assessed/reported; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; SU, sulfonylurea. Adapted from Bergenstal et al. (97).
- *Metformin group only.
- †A decrease was reported in a combined CV/microvascular composite but was found to be mostly attributable to nephropathy.

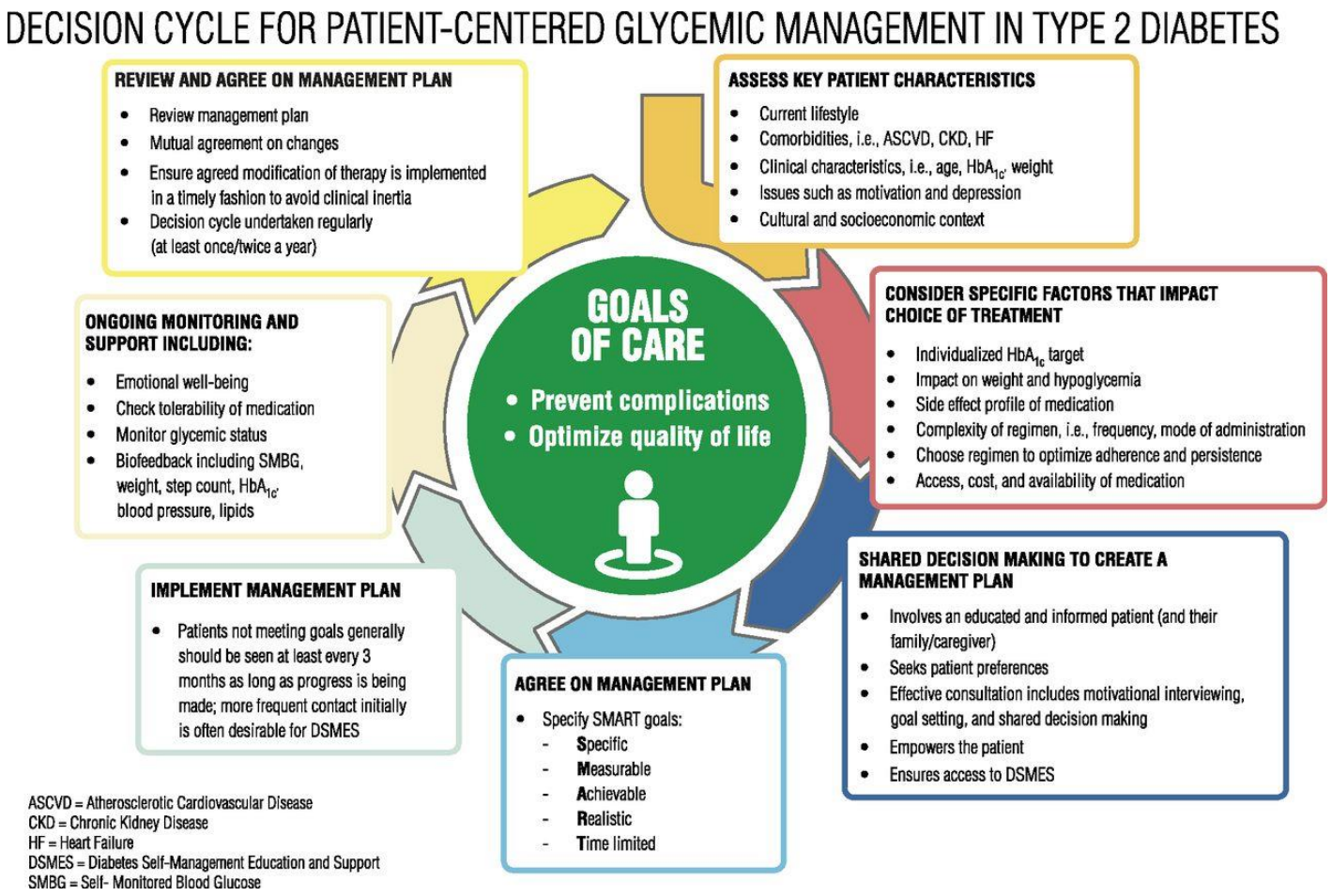
Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.



William T. Cefalu et al. Dia Care 2018;41:14-31

American Diabetes Association.

American Diabetes Association



AMERICAN DIABETES ASSOCIATION

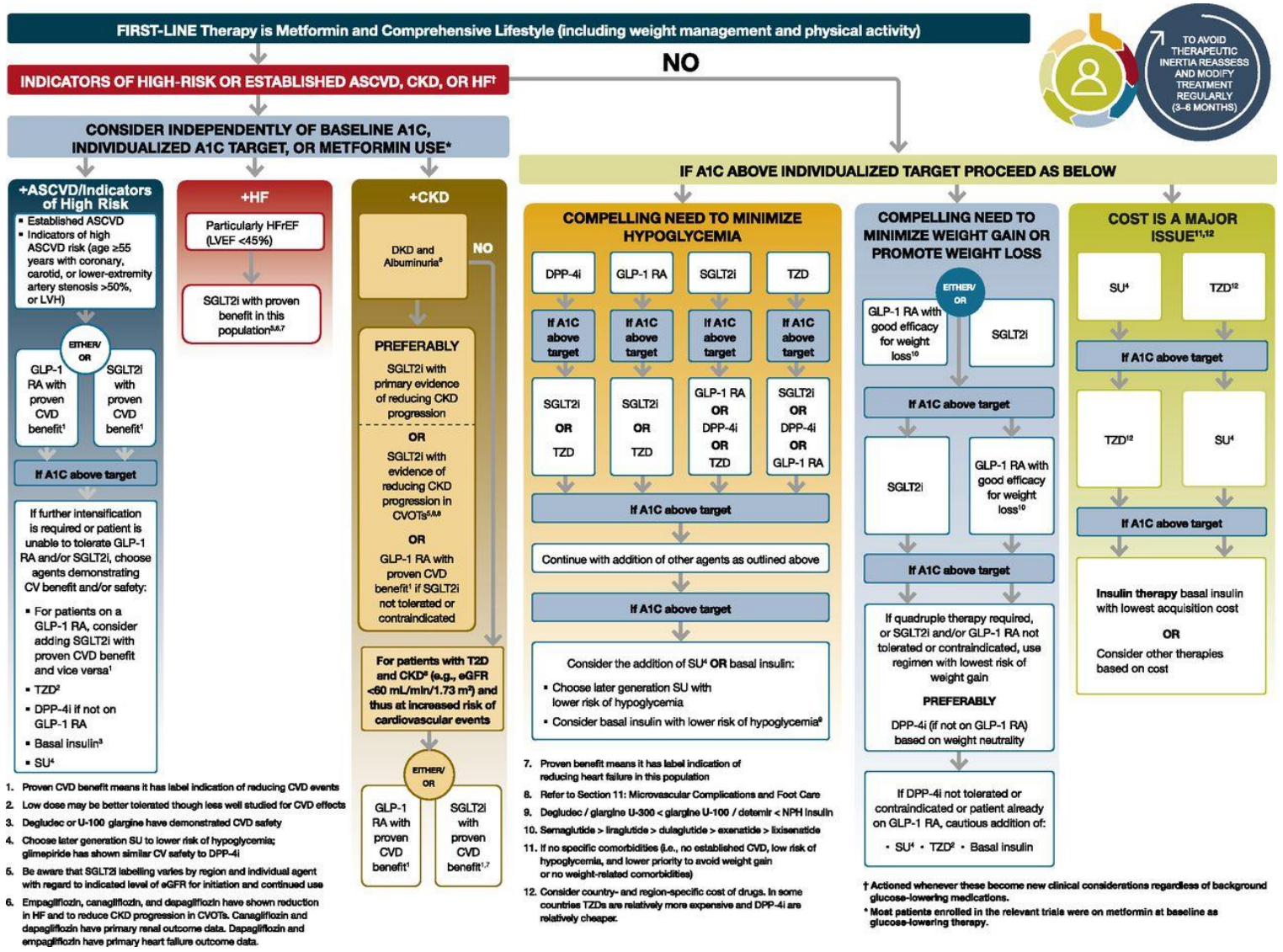
ASSESS KEY PATIENT CHARACTERISTICS

- Current lifestyle
- Comorbidities, i.e., ASCVD, CKD, HF
- Clinical characteristics, i.e., age, HbA_{1c}, weight
- Issues such as motivation and depression
- Cultural and socioeconomic context

CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT

- Individualized HbA_{1c} target
- Impact on weight and hypoglycemia
- Side effect profile of medication
- Complexity of regimen, i.e., frequency, mode of administration
- Choose regimen to optimize adherence and persistence
- Access, cost, and availability of medication

AMERICAN DIABETES ASSOCIATION

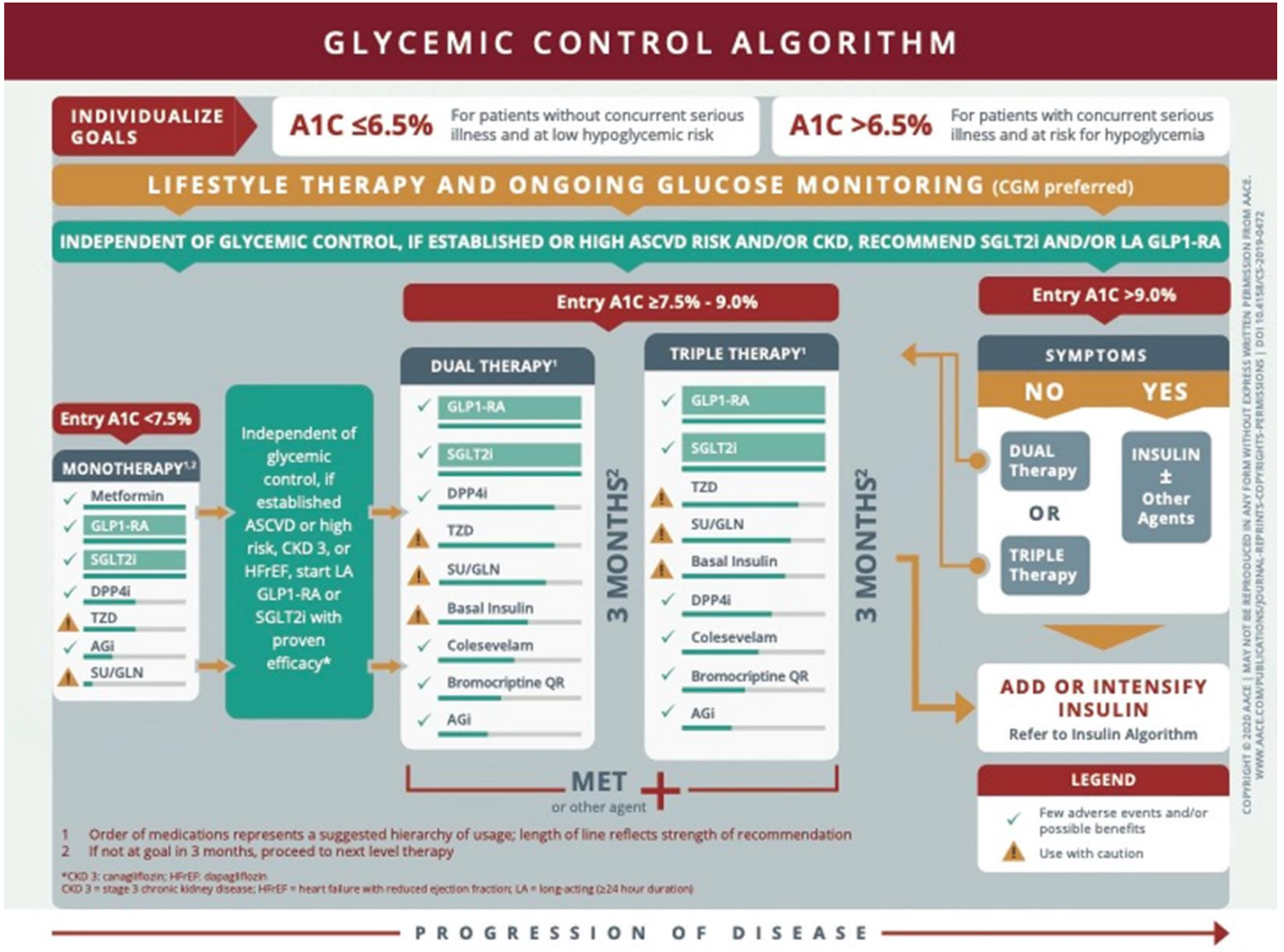


AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGY

PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)
2.	Avoid hypoglycemia
3.	Avoid weight gain
4.	Individualize all glycemic targets (A1C, FPG, PPG)
5.	Optimal A1C is ≤6.5%, or as close to normal as is safe and achievable
6.	Therapy choices are patient centric based on A1C at presentation and shared decision-making
7.	Choice of therapy reflects ASCVD, CHF, and renal status
8.	Comorbidities must be managed for comprehensive care
9.	Get to goal as soon as possible—adjust at ≤3 months until at goal
10.	Choice of therapy includes ease of use and affordability
11.	CGM is highly recommended, as available, to assist patients in reaching goals safely

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGY



CASE # 1

MARCOS

49 –year-old man with Type 2 Diabetes Mellitus, and hypertension. He was diagnosed at 42 years old. No known complications. He was treated by a general practitioner since his diagnoses. His therapy consists of metformin 500 mg bid, and lisinopril 5 mg. He refers: Tiredness and intermittent vague abdominal discomfort. Otherwise, no symptoms.

V/S: BP: 155/88 mmHg HR 85 Wt: 254# Ht: 68”
Abd: 40” BMI 53.52
Physical examination is remarkable for acanthosis nigricans, and a palpable liver below costal margin.

CASE # 1

MARCOS

LABORATORY DATA

Hgb: 14.5 g/dL PLT 215 x 10^3/uL A1c: 8.5% FBS 168 mg/dL BUN 18 CR 0.90 AST 88 U/L ALT 83U/L ALP 124u/L GFR 100 ml/min/1.73m² CHOL 187mg/dL TG 330mg/dL HDL 30 mg/dL LDL 91 mg/dL.

Additional laboratories:

Anti-hepatitis C virus antibody. Hepatitis A IgG, Hepatitis B surface antigen, surface antibody, and core antibody,Plasma iron, ferritin, and total iron binding capacity,AFP Serum gammaglobulin level, antinuclear antibody, antismooth muscle antibody, and anti-liver/kidney microsomal antibody-1 are all wnl.

Imaging data:

Liver ultrasound is remarkable for fatty liver infiltration. Fibroscan, shows stage 1 fibrosis.

CASE # 1

MARCOS

After optimizing antihypertensive therapy, the best therapeutic approach for Marcos, include:

a. **Addition of rosuvastatin 40 mg qd, empagliflozin 10 mg daily and increase metformin to 1000 mg bid in addition to lifestyle changes intervention.**
b. **Addition of pioglitazone 15 mg daily, rosuvastatin 40 mg daily and increase metformin to 1000 mg bid addition to lifestyle changes intervention.**
c. **Addition of rosuvastatin 40 mg qd, semaglutide 0.25 mg to be titrated up, and increase metformin 1000 mg daily in addition to lifestyle changes intervention.**
d. **All alternatives can be considered in this patient when effects of medications in patient's comorbidities are considered.**

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https://doi.org/10.1007/s12325-020-01498-5

ORIGINAL RESEARCH

Effect of Empagliflozin on Liver Steatosis and Fibrosis in Patients With Non-Alcoholic Fatty Liver Disease Without Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial

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Effect of Empagliflozin on Liver Steatosis and Fibrosis in Patients With Non-Alcoholic Fatty Liver Disease Without Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial

- Methods:
  - **Prospective randomized, double-blind, placebo-controlled clinical trial**
  - Inclusion criteria:
    - **20–65 years w/ NAFLD** (evidence of hepatic steatosis in previous ultrasound imaging or liver function test)

Effect of Empagliflozin on Liver Steatosis and Fibrosis in Patients With Non-Alcoholic Fatty Liver Disease Without Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial

- Exclusion criteria:
  - T2DM (FBS ≥ 126 mg/dL or HbA1c) level ≥ 6.5% (48 mmol/mol)
  - alcohol consumption greater than 20 g per day in women or greater than 30 g in men for at least three consecutive months over the past 5 years;
  - Acute or chronic CLD
  - biliary, or cirrhotic diseases
  - heart failure (NYHA class 2–4)
  - renal failure (eGFR < 45 mL/min/1.73 m^2)
  - medications associated with fatty liver such as:
    - NSAIDs, amiodarone, tamoxifen, sodium valproate, corticosteroids, methotrexate;
  - using supplements including:
    - vitamin E, vitamin C, zinc, and selenium or antioxidant agents over the last 3 months
  - history of cardiovascular events within the past 3 months
  - pregnancy or breastfeeding
  - active cancer or history of cancer treatment over the past 2 years
  - untreated thyroid disorder
  - BMI > 40 kg/m^2.

Effect of Empagliflozin on Liver Steatosis and Fibrosis in Patients With Non-Alcoholic Fatty Liver Disease Without Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial

- Randomization:
  - empagliflozin (10 mg/day) (n = 43)
  - placebo (n = 47)
- Duration:
  - 24 weeks
- Primary outcome:
  - Change in controlled attenuation parameter (CAP) score by transient elastography at 24 weeks.
- Secondary outcome:
  - Change in liver stiffness measurement (LSM).

Table 1 Characteristics of the study participants

	Empagliflozin (n = 43)			Placebo (n = 47)			P value[+]
	Enrollment	EOT*	P value	Enrollment	EOT	P value	
Age (years)	43.8 (9.7)			44.1 (9.3)			0.875
Sex (male)	28 (65.1%)			22 (46.8%)			0.081
Weight (kg)	86.5 (12.2)	84.9 (13.7)	0.003	85.3 (12.9)	85.9 (13.3)	0.253	0.003
BMI (kg/m^2)	30.5 (2.3)	29.9 (2.8)	0.002	30.7 (3.5)	30.9 (3.8)	0.201	0.001
WC (cm)	104.9 (6.5)	102.3 (8.3)	0.001	106.0 (9.0)	104.7 (10.6)	0.070	0.181
WHR	0.975 (0.045)	0.971 (0.049)	0.363	0.971 (0.053)	0.960 (0.057)	0.061	0.393
Statin use (yes)	5 (11.6%)			6 (12.8%)			0.869
FBS (mg/dl)	94.0 (9.2)	96.5 (10.0)	0.160	91.4 (7.8)	95.3 (10.7)	0.023	0.543
ALT (Ut/l)	39.1 (23.6)	32.3 (18.2)	0.007	33.4 (20.7)	31.8 (20.0)	0.545	0.151
AST (Ut/l)	25.8 (10.2)	22.4 (7.3)	0.004	24.8 (9.3)	23.6 (9.3)	0.385	0.204
Fasting insulin (mIU/L)	16.2 (7.4)	14.3 (4.8)	0.045	15.5 (8.5)	15.6 (8.8)	0.973	0.182
HOMA2-IR	2.08 (0.91)	1.86 (0.62)	0.067	1.99 (1.07)	2.00 (1.07)	0.901	0.183
Calorie intake (kcal/day)	2087.8 (477.4)	2085.4 (541.5)	0.952	1949 (462.6)	1950 (439.9)	0.977	0.949
Physical activity MET-min/week	2859.6 (3387.5)	2224.7 (2266.1)	0.149	2883.7 (2747.3)	2372.0 (1549.6)	0.199	0.833

Data are the mean ± SD for normally distributed parameters or n (%)

BMI body mass index, *WC* waist circumference, *WHR* waist to hip ratio, *FBS* fasting blood sugar, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *EOT* end of trial

[+] P value for difference between two groups

Control Attenuation Parameter (CAP) SCORE

- Significant decrease in both groups; but:
  - No significant difference was observed between the two groups ($P = 0.396$)

- No significant association between changes in CAP and gender, age, BMI, waist circumference, physical activity, and calorie intake

- In a subgroup analysis in 44 patients (23 patients in the empagliflozin group and 21 in the placebo group) who had significant steatosis at baseline (defined as CAP ≥ 302 dB/m); the percentage of patients with improved steatosis was significantly greater in the empagliflozin group (37.2% vs. 17%, $P = 0.035$).

Liver Stiffness Measure (LSM)

- Significantly decreased after 24 weeks in the empagliflozin group (6.03 ± 1.40 kPa to 5.33 ± 1.08 kPa, $P = 0.001$)
- Non-significant decrease in the placebo group (5.56 ± 1.05 kPa to 5.35 ± 0.96 kPa, $P = 0.139$).
- No significant association between changes in LSM and gender, age, BMI, waist circumference, physical activity, and calorie intake.
- Greater difference in fibrosis score in empagliflozin group ($P = 0.039$).

Visual Fatty Liver Measure

- Significant decrease in grade of fatty liver on visual analysis and grading of ultrasound images (done blindly).
- In the empagliflozin group 44.2% had grade 2 fatty liver at baseline, while it decreased to 18.6% at the end of trial; $P = 0.001$.
- In total, by the end of study, 9.3% of individuals in the empagliflozin group no longer had fatty liver, while no change was observed in the placebo group.

Empagliflozin Improves Liver Steatosis and Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Haleh Chehrehgosha · Masoud Reza Sohrabi · Faramarz Ismail-Beigi · Mojtaba Malek · Mohammad Reza Babaei · Farhad Zamani · Hossein Ajdarkosh · Mahmood Khoonsari · Afshin Eshghi Fallah · Mohammad E. Khamseh

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Empagliflozin Improves Liver Steatosis and Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

- Prospective randomized, double-blind, placebo-controlled trial
- Inclusion criteria: NAFLD (CAP- 238 dB/m) and T2DM, 20 to 65 years-old, with a hemoglobin A1c (HbA1c) of 7–10
- Randomization:
  - Empagliflozin 10 mg (n = 35)
  - Pioglitazone 30 mg (n = 34)
  - Placebo (n = 37) for 24 weeks
- Measurements:
  - Liver fat content and liver stiffness - Fibroscans.
  - Body composition assessment by DXA
- Primary end point was change from baseline in liver steatosis, using the (CAP) score.

Diabetes Ther https://doi.org/10.1007/s13300-021-01011-3

Empagliflozin Improves Liver Steatosis and Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

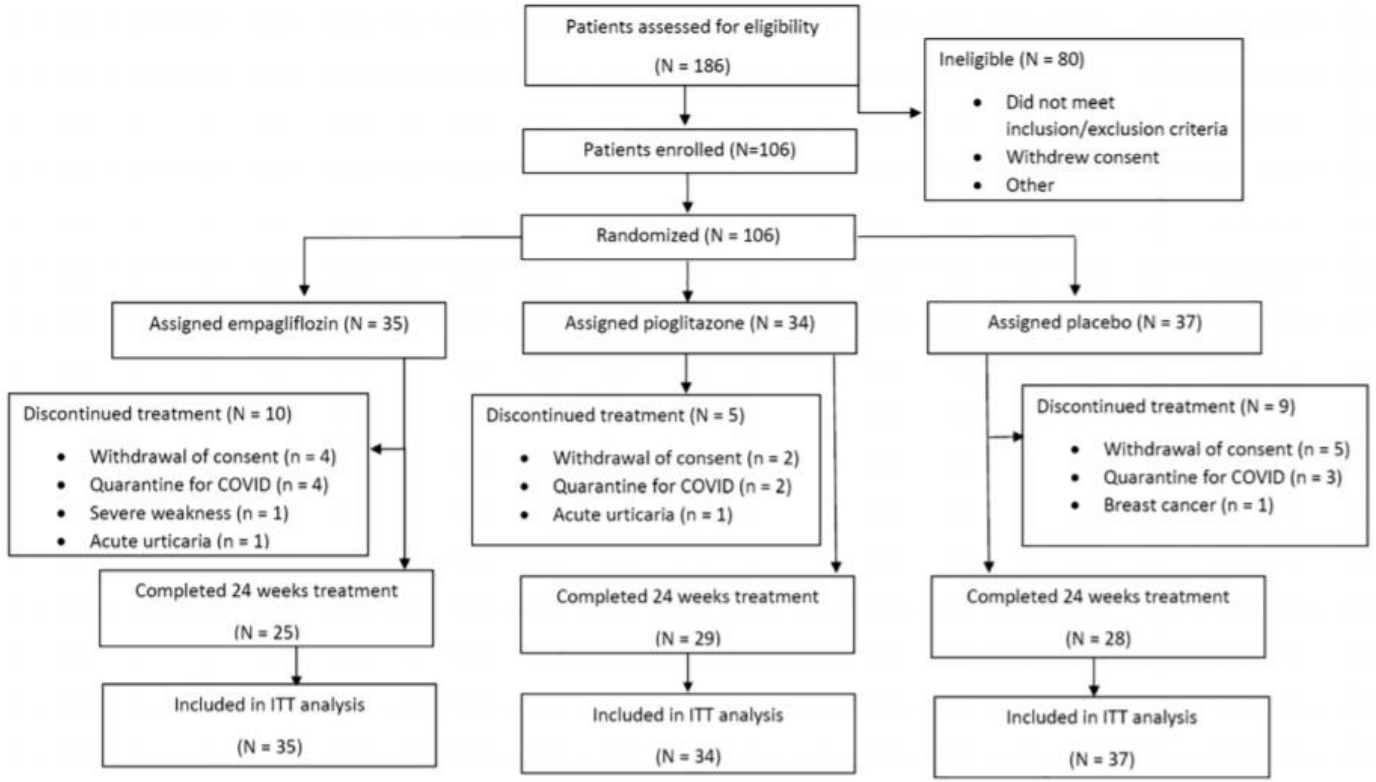


Fig. 1 Patient enrollment flow diagram. *ITT* intention to treat

Results:

- Significant decrease in CAP score with empagliflozin compared to placebo
  - mean difference: - 29.6 dB/m (- 39.5 to - 19.6) versus - 16.4 dB/m (- 25.0 to - 7.8), respectively; p = 0.05.
- Significant reduction in the placebo-corrected change in liver stiffness measurement (LSM) with empagliflozin compared to pioglitazone:
  - - 0.77 kPa (- 1.45, - 0.09), p = 0.02, versus 0.01 kPa (95% CI - 0.70, 0.71, p = 0.98), p for comparison = 0.03.

Results:

- Changes in the following parameters were comparable between treatment groups (pio and empa):
  - serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
  - fasting insulin
  - homeostatic model assessment for insulin resistance (HOMA-IR),
  - fibrosis-4 index (FIB4 index)
  - NAFLD fibrosis score
  - aspartate aminotransferase to platelet ratio index (APRI)

Results

- Body weight and visceral fat
  - Reduction in empagliflozin group ($p = 0.001$ and $p = 0.01$, respectively)
  - Increased in the placebo and pioglitazone groups.
- No serious adverse events in either group.

Conclusion

Treatment for 24 weeks with empagliflozin vs. pioglitazone

- associated with improvement of liver steatosis and fibrosis in patients with NAFLD and T2DM
- Associated with decrease in:
  - body weight and abdominal fat area

Investigation of Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With Non-alcoholic Steatohepatitis.

- **Double-blind randomized phase 2 trial**
- **Subjects**:
  - Patients with **biopsy-confirmed NASH** and **liver fibrosis** of stage F1, F2, or F3.
- **Randomization** (3:3:3:1:1:1 ratio)
  - Subcutaneous semaglutide at a dose of 0.1, 0.2, or 0.4 mg or corresponding placebo.
- **Primary Endpoint**:
  - Resolution of NASH with no worsening of fibrosis.
- **Secondary end point**:
  - Improvement of at least one fibrosis stage with no worsening of NASH.

PN Newsome et al. N Engl J Med 2021;384:1113-1124.

Demographic and Baseline Clinical Characteristics

Table 1. Demographic and Baseline Clinical Characteristics.*

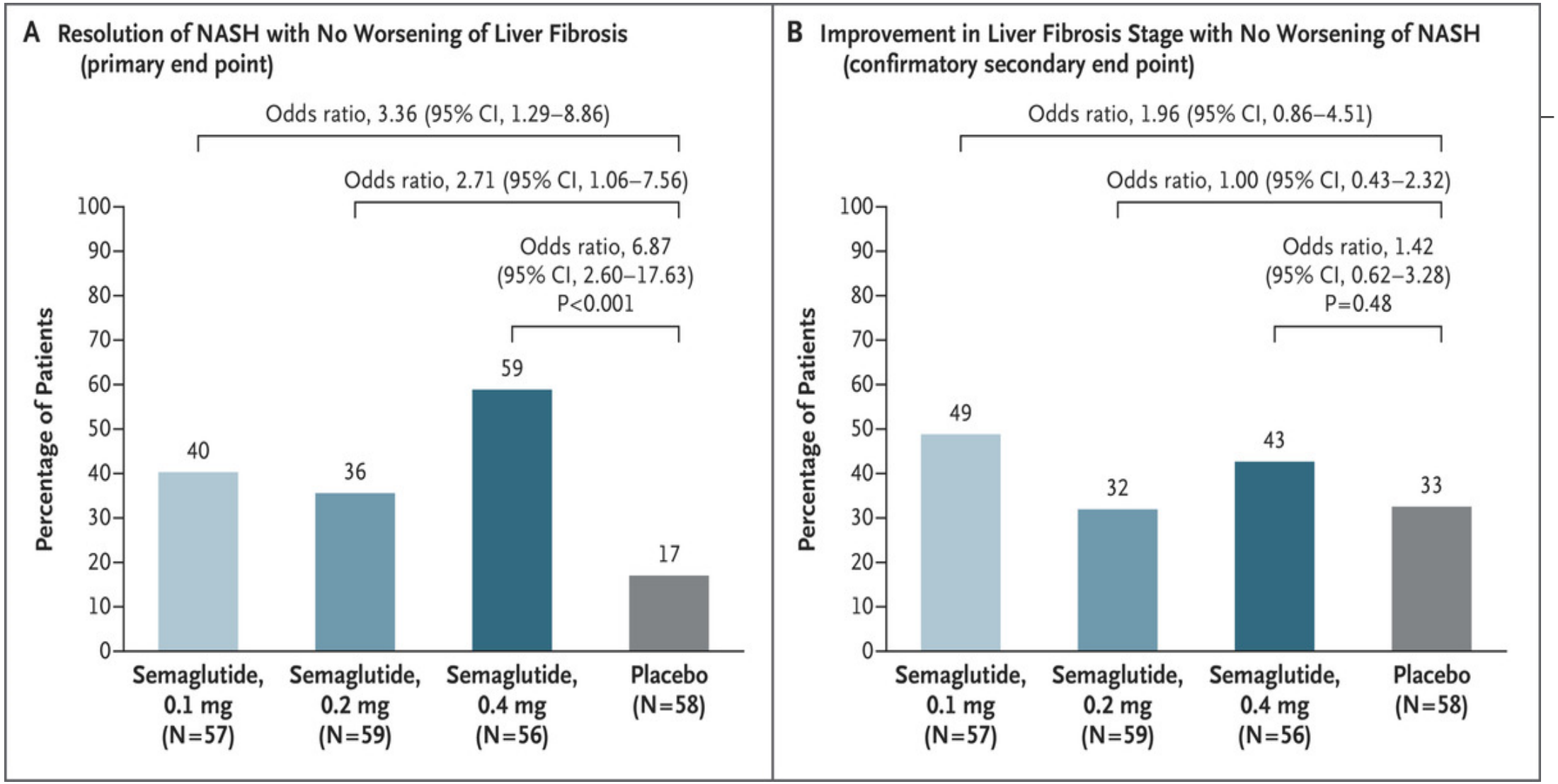
Characteristic	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Age — yr	55.2±10.9	58.1±9.9	54.3±10.2	52.4±10.8
Female sex — no. (%)	51 (64)	52 (67)	47 (57)	44 (55)
Body weight — kg	98.4±21.1	97.1±22.0	96.6±20.1	101.3±23.3
Body-mass index	36.1±6.4	35.6±6.1	35.2±6.6	36.1±6.6
Type 2 diabetes — no. (%)	49 (61)	51 (65)	49 (60)	50 (62)
Glycated hemoglobin level among patients with type 2 diabetes — %†	7.4±1.3	7.2±1.0	7.2±1.2	7.3±1.2
Liver-enzyme levels — U/liter				
Alanine aminotransferase	55±90	53±78	54±84	55±92
Aspartate aminotransferase	44±82	43±73	44±78	42±83
Liver fibrosis stage — no. (%)‡				
F1	23 (29)	19 (24)	26 (32)	22 (28)
F2	18 (22)	18 (23)	14 (17)	22 (28)
F3	39 (49)	41 (53)	42 (51)	36 (45)
Total activity score for nonalcoholic fatty liver disease§	4.9±0.8	4.9±0.9	4.8±0.9	4.9±0.9
Noninvasive measures of liver steatosis and fibrosis				
Liver steatosis, as assessed by FibroScan — dB/m¶	332.0±46.2	347.4±55.0	335.7±55.8	348.6±35.2
Liver stiffness, as assessed by FibroScan — kPa¶	10.4±78.5	12.3±74.0	11.5±87.1	8.7±90.0
Enhanced liver fibrosis test score‖	9.8±1.0	9.8±0.9	9.9±1.0	9.6±0.9

* Plus–minus values are means ±SD, except for body-mass index, liver-enzyme levels, and liver stiffness as assessed by FibroScan, which are geometric means ±coefficient of variation. Percentages may not total 100 because of rounding.
† These values were based on the number of patients with type 2 diabetes in each group (49, 51, 49, and 50 patients in the 0.1-mg, 0.2-mg, 0.4-mg, and placebo groups, respectively).
‡ Stages are defined as follows: F0, no fibrosis; F1, mild-to-moderate zone 3 perisinusoidal fibrosis or portal or periportal fibrosis only; F2, zone 3 perisinusoidal fibrosis and portal or periportal fibrosis; F3, bridging fibrosis; and F4, cirrhosis.
§ Scores range from 0 to 8 (unweighted sum of the scores for steatosis [assessed on a scale of 0 to 3], lobular inflammation [assessed on a scale of 0 to 3], and hepatocyte ballooning [assessed on a scale of 0 to 2]), with higher scores indicating an increased likelihood of nonalcoholic steatohepatitis.[19]
¶ This assessment was performed only at sites at which FibroScan equipment was available. Liver steatosis was assessed in 161 patients and liver stiffness in 212 patients.
‖ The enhanced liver fibrosis test provides an algorithmic liver fibrosis score that is based on the serum levels of hyaluronic acid, procollagen type III N-terminal peptide, and tissue inhibitor of metalloproteinase 1. A score of greater than 9.8 indicates a moderate risk of advanced fibrosis, and a score of greater than 11.3 denotes a high risk of advanced fibrosis.

Investigation of Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With Non-alcoholic Steatohepatitis.

Arm/Group Title	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Arm/Group Description	Participants were to receive once daily subcutaneous (s.c.) injection of semaglutide for 72 weeks. Participants initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).	Participants were to receive once daily s.c. injection of semaglutide for 72 weeks. Participants initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).	Participants were to receive once daily s.c. injection of semaglutide for 72 weeks. Participants initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).	Participants were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) fo

Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*



Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

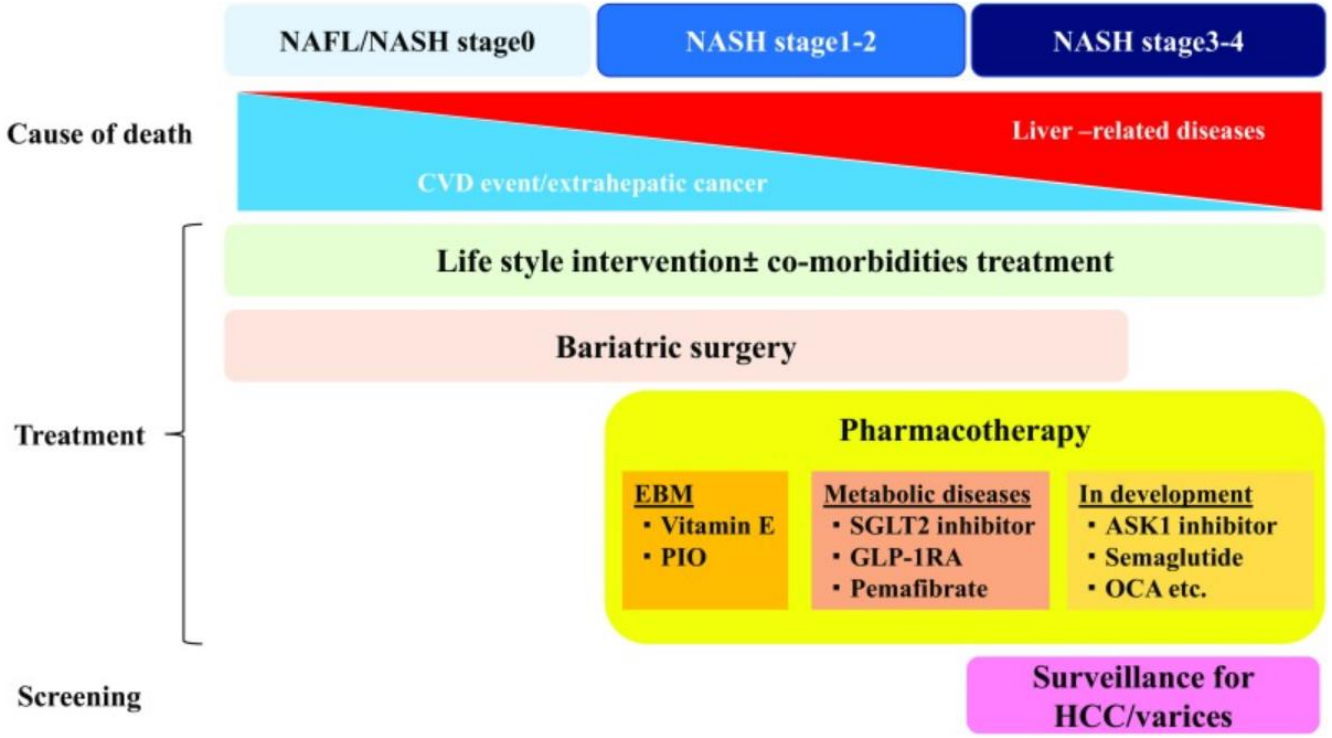
Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

End Point	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment M30†	0.55	0.50	0.47	0.78
Caspase-cleaved cytokeratin-18 fragment M65†	0.53	0.52	0.42	0.71
Total cholesterol	0.97	1.00	0.93	0.94
Triglycerides	0.88	0.90	0.73	0.97
Liver stiffness, as assessed by FibroScan‡	0.76	0.71	0.72	1.02
Change from baseline to wk 72				
Enhanced liver fibrosis test score	–0.34	–0.39	–0.56	0.01
Body weight — %	–4.84	–8.91	–12.51	–0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	–0.63	–1.07	–1.15	–0.01

* Data are from all the patients during the in-trial observation period (from randomization until the last study-related procedure). A lower ratio of the value at week 72 to the value at baseline indicates a larger reduction.
† Higher levels of cytokeratin-18 fragments are a biomarker of hepatocyte apoptosis.
‡ This assessment was performed only at sites at which FibroScan equipment was available. Changes in liver steatosis were assessed in 161 patients, and changes in liver stiffness were assessed in 212 patients.
§ These values were based on the number of patients with type 2 diabetes in each group (49, 51, 49, and 50 patients in the 0.1-mg, 0.2-mg, 0.4-mg, and placebo groups, respectively).

Current and future pharmacological therapies for NAFL/NASH

J Gastroenterol. 2018 Mar;53(3):362-376.



Current and future pharmacological therapies for NAFL/NASH

- Pioglitazone – Randomized studies
  - Patients with NASH and diabetes mellitus
    - Reduced steatosis and necroinflammation compared to placebo
      - *N Engl J Med. 2006 Nov 30; 355(22):2297-307.*
      - *Gastroenterology.* 2008;135:1176–1184
  - Patients with NASH and prediabetes/type 2 Diabetes Mellitus
    - Confirmed long term safety and efficacy
    - 18 months RCT – 18 month open-label phase (pioglitazone)
      - *Ann Intern Med. 2016 Sep 6; 165(5):305-15.*

J Gastroenterol. 2018 Mar;53(3):362-376.

CASE # 2

Isabel

56–year-old woman with Type 2 Diabetes Mellitus and hypertension comes for initial evaluation. Hx. of gestational diabetes. Diagnosed at 41 years. She is currently on treatment with liraglutide 1.8 mg qd, metformin 1000 mg bid, atorvastatin 40 mg and losartan 25 mg daily. No known complications. She is a teacher and is currently supervising her grandchildren in virtual classes. Refers that she barely has time to take care of her health and has not been following her dietary or exercise recommendations.

V/S: BP: 128/79 mmHg HR 85 Wt: 175# Ht: 64” Abd: 36” BMI 30.0 kg/m2
Physical examination is remarkable for abdominal obesity, otherwise no pertinent findings.

CASE # 2

ISABEL

LABORATORY DATA

Hgb: 13.2 g/dL PLT 215 x 10^3/uL A1c: 8.9% FBS 168 mg/dL BUN 13 CR 0.72 AST 32 U/L ALT 33U/L ALP 120 u/L GFR 100 ml/min/1.73m^2 LDL 72 mg/dL.

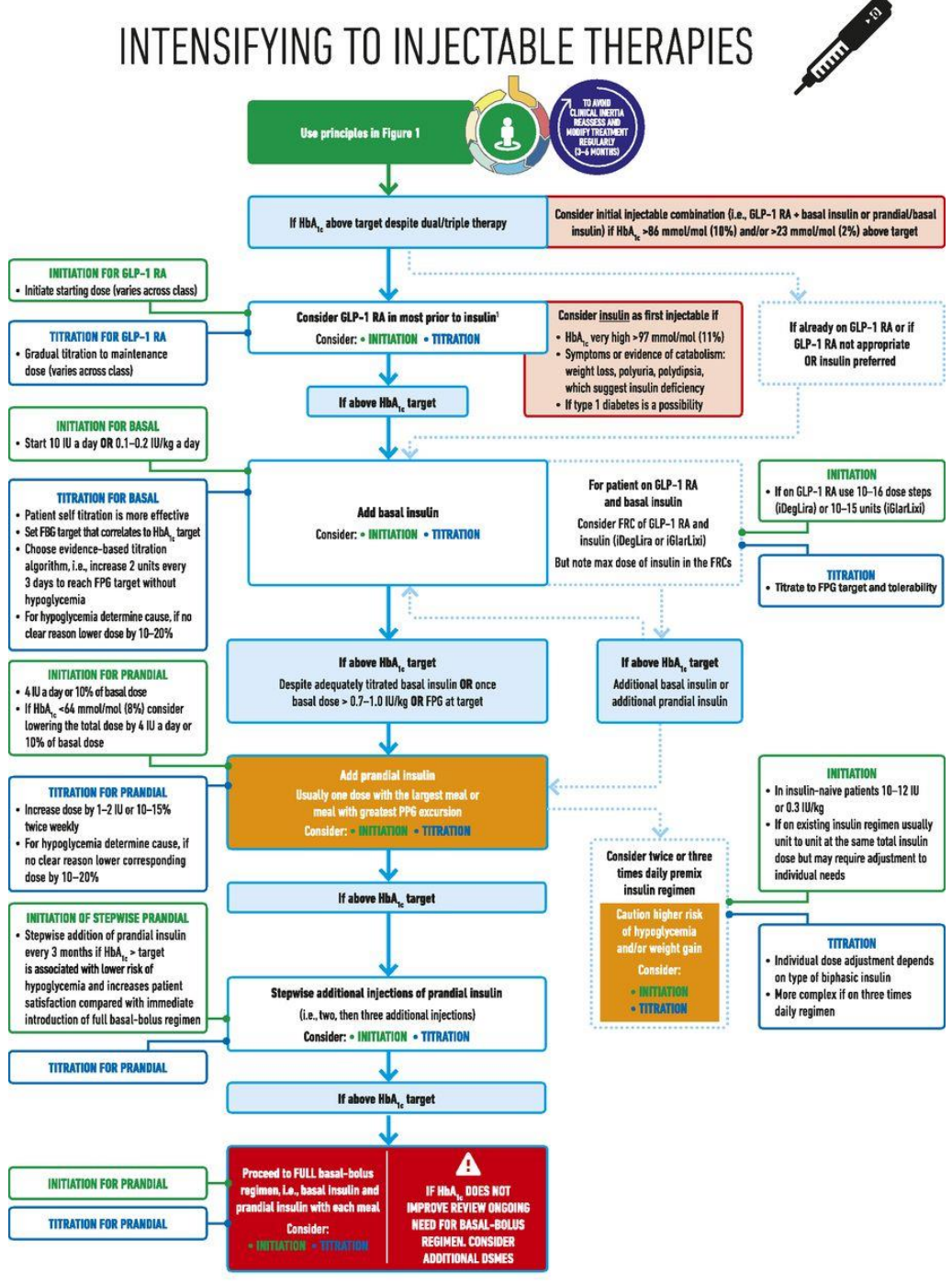
CASE # 2

ISABEL

In addition to lifestyle changes: What therapy recommendations would you offer to Isabel?

a. Addition of a basal insulin.
b. Addition of an SGLT-2.
c. Change to a combination insulin/GLP-1 RA.
d. All of the above options can be considered for her treatment.
e. A and C are the best options.

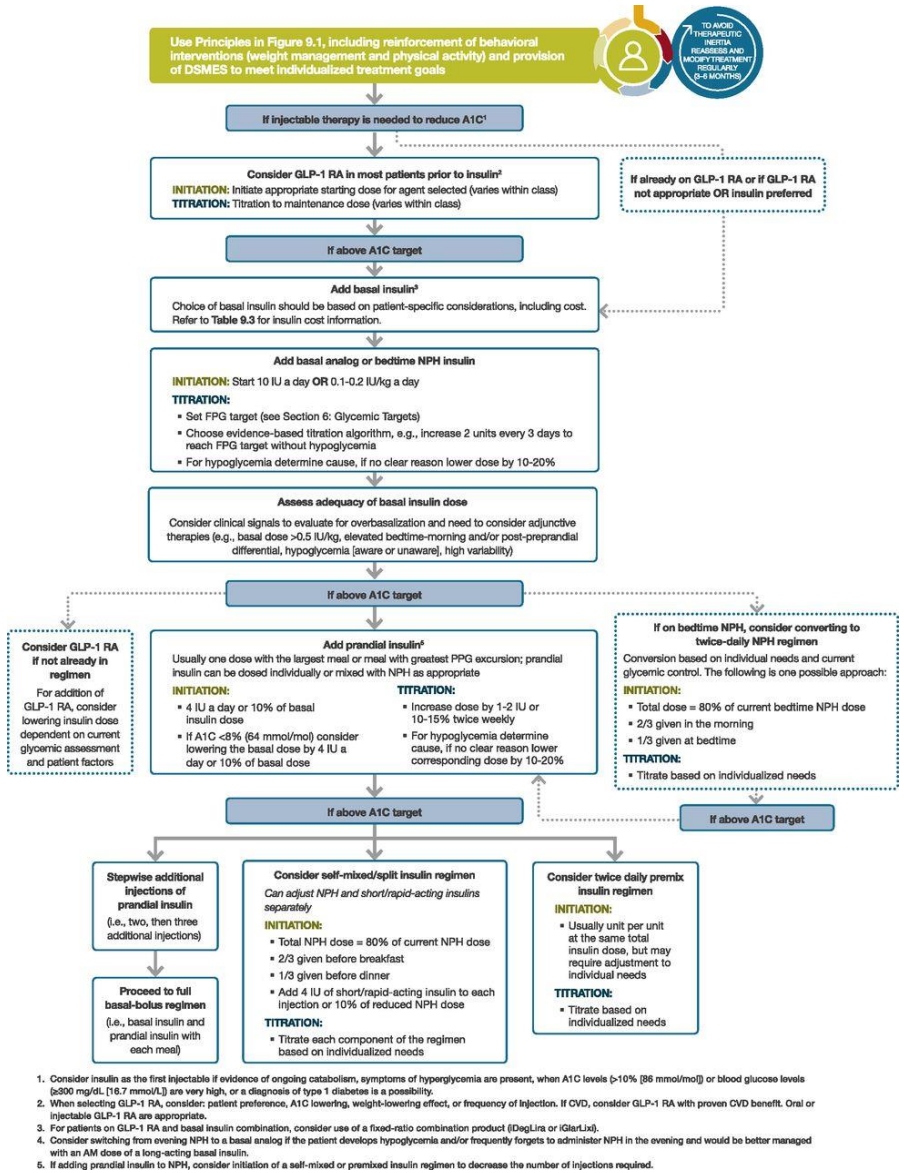
INTENSIFYING TO INJECTABLE THERAPIES



1. Consider choice of GLP-1 RA considering: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

Intensifying to injectable therapies.



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

TABLE 1 Overview of the DUAL I, III, V, VII, VIII, and IX Clinical Trials of IDegLira in Patients With Type 2 Diabetes

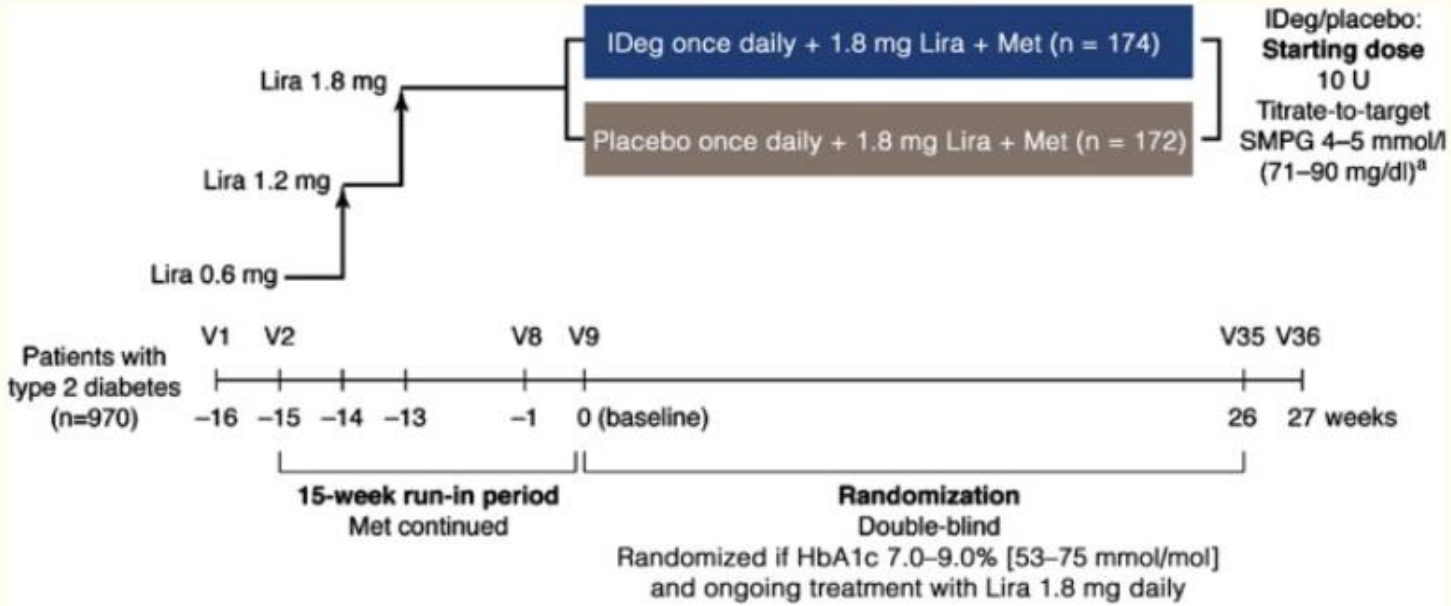
Study	Treatment Duration (weeks)	Patients	Comparator	Change in A1C, %: ETD IDegLira – Comparator (95% CI), *P*	Confirmed Hypoglycemia: ERR IDegLira/Comparator (95% CI), *P*	Change in Body Weight, kg:ETD IDegLira – Comparator (95% CI), *P*	EOT Insulin Dose, units: ETD IDegLira – Comparator (95% CI), *P*
DUAL I (10)	26	Uncontrolled on metformin ± pioglitazone (*n* = 1,663)	Insulin degludec (no dose cap)	−0.47 (−0.58 to −0.36), <0.0001*	0.68 (0.53-0.87), 0.0023	−2.2 (−2.64 to −1.80), <0.0001	−14.9 (−17.14 to −12.66), <0.0001
			Liraglutide 1.8 mg	−0.64 (−0.75 to −0.53), <0.0001†	7.61 (5.17-11.21), <0.0001	2.4 (2.02-2.86), <0.0001	NA
DUAL I extension (37)	52	Uncontrolled on metformin ± pioglitazone (*n* = 1,311)	Insulin degludec (no dose cap)	−0.46 (−0.57 to −0.34), <0.0001	0.63 (0.50-0.79), <0.0001	−2.8 (NR), <0.0001	−23.4 (−26.4 to −20.3), <0.0001
			Liraglutide 1.8 mg	−0.65 (−0.76 to −0.53), <0.0001	8.52 (6.09- 11.93), <0.0001	2.7 (NR), <0.0001	NA
DUAL III (12)	26	Uncontrolled on GLP-1RA + metformin ± SU ± pioglitazone (*n* = 438)	GLP-1RA	−0.94 (−1.11 to −0.78), <0.001†	25.36 (10.6-60.5), <0.001	2.9 (2.17-3.62), <0.001	NA
DUAL V (14)	26	Uncontrolled on metformin + IGlar U100 20-50 units (*n* = 557)	IGlar U100	−0.59 (−0.74 to −0.45), <0.001†	0.43 (0.30-0.61), <0.001	−3.2 (-3.77 to -2.64), <0.001	−25.5 (−28.90 to −22.05), <0.001
DUAL VII (15)	26	Uncontrolled on metformin + IGlar U100 20-50 units (*n* = 506)	IGlar U100 + insulin aspart	−0.02 (−0.16 to 0.12), <0.0001*	0.39 (0.29-0.51), <0.0001	−3.6 (−4.2 to −2.9), <0.0001	−44.5 (−48.3 to −40.7), <0.0001
DUAL VIII (36)	104	Uncontrolled on metformin, SU, glinide, pioglitazone, or DPP-4i (*n* = 1,012)	IGlar U100	NA‡	0.44 (0.33-0.60), <0.0001	−1.7 (−2.47 to −0.93), <0.0001	−14.9 (−17.41 to −12.47), <0.0001
DUAL VIII, prespecified 26-week analysis (38)	26	Uncontrolled on metformin, SU, glinide, pioglitazone, or DPP-4i (*n* = 1,012)	IGlar U100	−0.47 (−0.58 to −0.36), <0.0001	0.56 (0.39-0.82), 0.0023	−1.6 (−2.00 to −1.13), <0.0001	−13.0 (−15.03 to −10.99), <0.0001
DUAL IX (32)	26	Uncontrolled on SGLT2i (*n* = 420)	IGlar U100	−0.36 (−0.50 to −0.21), <0.0001†	0.42 (0.23-0.75), 0.0035	−1.9 (−2.64 to −1.19), <0.0001	−15.4 (−19.60 to −11.13), <0.0001

*Confirmed noninferiority of IDegLira. †Confirmed superiority of IDegLira. ‡This end point was not analyzed at week 104 in DUAL VIII. DPP-4i, DPP-4 inhibitor; ERR, estimated rate ratio; ETD, estimated treatment difference; GLP-1RA, GLP-1 receptor agonist; NA, not applicable; NR, not reported; OR, odds ratio; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 Study)

- Randomized (1 : 1), parallel-group, double-blind, multinational, controlled trial
  - 15-week run-in phase
  - 26-week core phase
- Inclusion criteria:
  - aged ≥18 years with T2DM
  - Insulin naïve
  - (BMI) ≤45 kg/m^2.
  - On tx with metformin ± a sulfonylurea, glinide, a dipeptidyl peptidase-4 inhibitor or exenatide bid
  - HbA1c level of 7.5–10.0% in patients on monotx with metformin
  - Run in period – tx other than metformin d/c
  - if patient still poorly controlled after increasing liraglutide to 1.8 mg with met > 1500 mg/day, randomized to degludec vs placebo.

Diabetes Obes Metab. 2016 Jul; 18(7): 663–670



[a]Titration guideline – insulin degludec and placebo dummy insulin units.

Pre-breakfast plasma glucose measurements*		Adjustment
mmol/l	mg/dl	U
<3.1	<56	–4 (if dose >45 U, reduce by 10%)
3.1–3.9	56–70	–2 (if dose >45 U, reduce by 5%)
4.0–5.0	71–90	0
5.1–7.0	91–126	+2
7.1–8.0	127–144	+4
8.1–9.0	145–162	+6
>9.0	>162	+8

*Based on the average pre-breakfast self-measured plasma glucose (SMPG) values measured on three successive days.

Figure 1

Trial design. FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IDeg, insulin degludec; Lira, liraglutide; Met, metformin; SMPG, self-measured plasma glucose; V, visit.

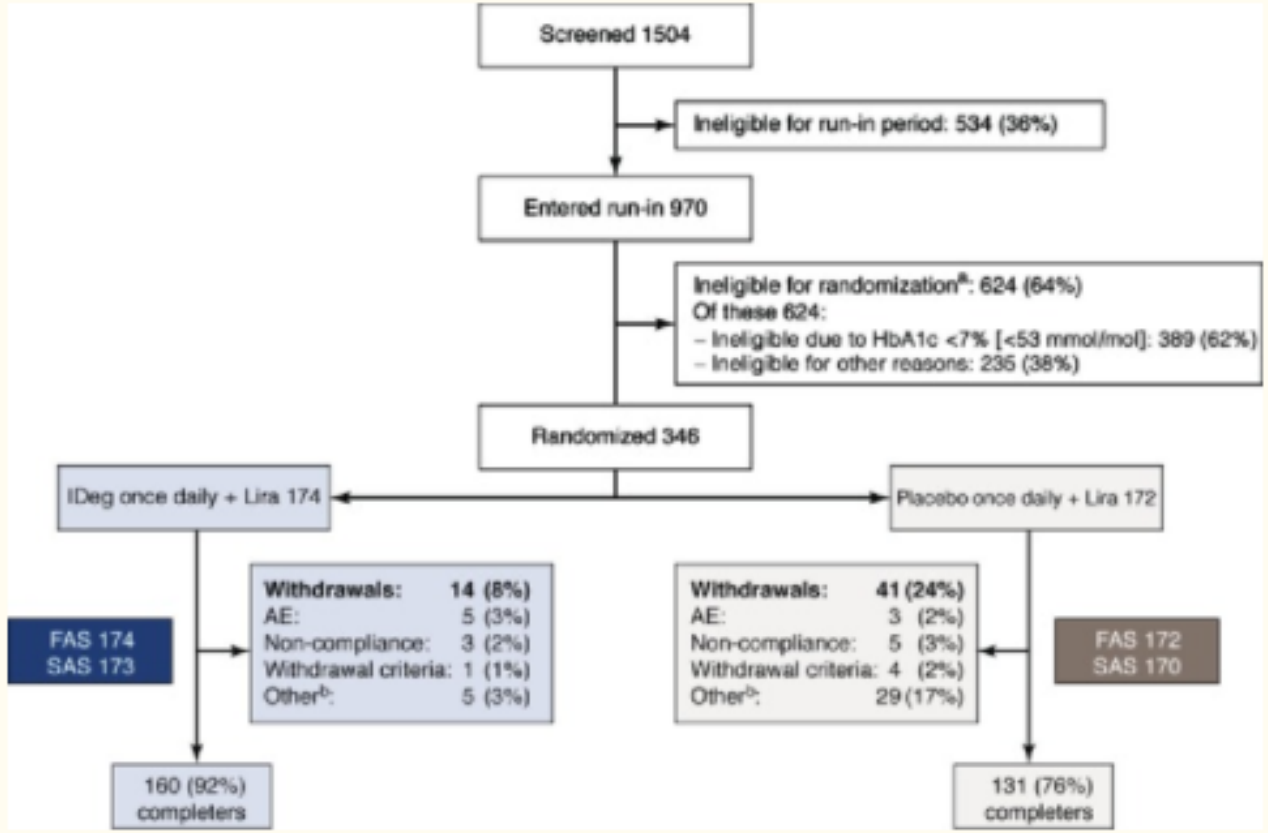


Figure 2

Patient disposition. AE, adverse event; FAS, full analysis set; HbA1c, glycated haemoglobin; IDeg, insulin degludec; Lira, liraglutide; SAS, safety analysis set. FAS: all randomized patients. SAS, all patients receiving at least one dose of study drug. [a]During the run-in period patients were ineligible for randomization for the following reasons: AE, n = 76; non-compliance with protocol, n = 29; randomization criteria (including HbA1c <7.0% [<53 mmol/mol]), n = 426; withdrawal criteria, n = 2; other, n = 91. [b]During the treatment phase: withdrawals due to 'other' reasons were caused by erroneous randomization, inefficient therapy (only in placebo + liraglutide group) and personal reasons such as patient not able to attend visits or unspecified withdrawn consent.

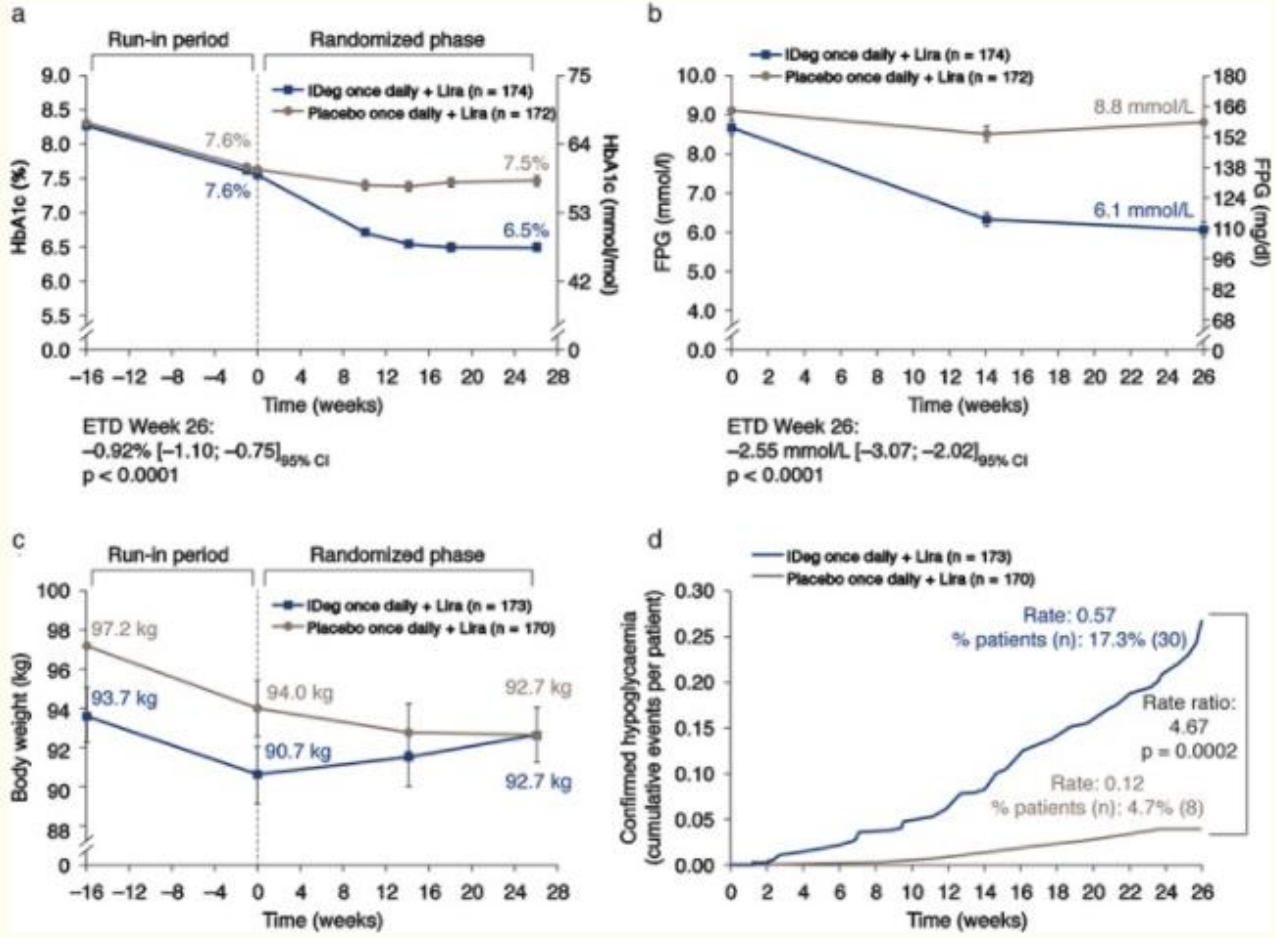


Figure 3

(a) Glycated haemoglobin (HbA1c), (b) fasting plasma glucose (FPG), (c) body weight and (d) hypoglycaemia over time. (FPG values were not available for week −16.) CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose; IDeg, insulin degludec; Lira, liraglutide; n, number of patients with events; Rate, number of events per patient-year of exposure; % patients, proportion of patients with events. HbA1c and FPG are mean values ± standard error (s.e.). Full analysis set: last observation carried forward. Comparisons: estimates adjusted for multiple covariates. Body weight (mean values ± s.e.) and hypoglycaemia are safety analysis set. The statistical comparisons for hypoglycaemia are based on the full analysis set.

Results

- Mean change in A1c
  - > on IDeg add-on to liraglutide arm (−1.04%) than in the placebo add-on to liraglutide arm (−0.16%; $p < 0.0001$).
- Mean FBS reduction was greater, and self-measured plasma glucose values were lower at all eight time points, with IDeg add-on versus placebo add-on (both $p < 0.0001$)
- At 26 weeks, the IDeg dose was 51 U (0.54 U/kg)
- Mean weight change
  - +2.0 kg (IDeg add-on to liraglutide)
  - −1.3 kg (placebo add-on to liraglutide)
- Confirmed hypoglycaemia
  - Higher with IDeg than with placebo (0.57 vs. 0.12 episodes/patient-years of exposure; $p = 0.0002$).
  - No episodes of severe hypoglycaemia
  - No marked differences in adverse events with either treatment approach.

The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial

Sultan Linjawi · Bruce W. Bode · Louis B. Chaykin · Jean-Pierre Courrèges · Yehuda Handelsman · Lucine M. Lehmann · Abhishek Mishra · Richard W. Simpson

Received: August 22, 2016 / Published online: December 10, 2016

The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial

- 26-week, multi-center, randomized, open-label, two-group parallel, treat-to-target trial conducted at 81 sites in five countries (Australia, France, Hungary, Slovakia, and the United States) between August 2012 and March 2014

- Inclusion criteria:
  - T2DM, ≥18 y/o
  - On maximum-dose GLP-1RA therapy (liraglutide qd or exenatide bid) with metformin alone or with pioglitazone and/or sulfonylurea
  - Insulin naïve
  - BMI ≤ 40 kg/ m2

- Randomized 2:1 to IDegLira once daily (n = 292) or to unchanged GLP-1RA therapy (n = 146), continuing OADs at the pre-trial dose.

Diabetes Ther (2017) 8:101–114

Table 1 Baseline characteristics

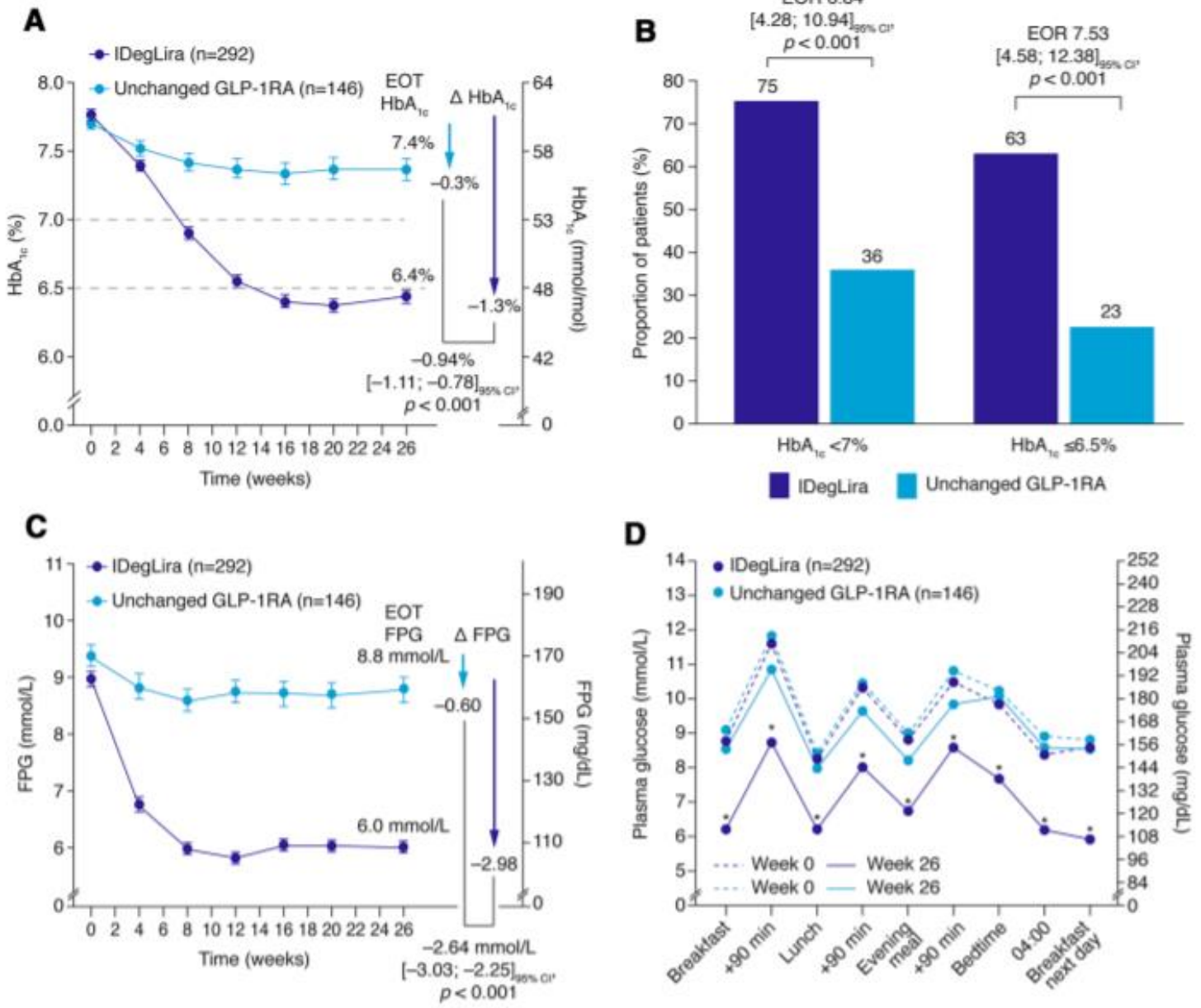
Characteristic	IDegLira	Unchanged GLP-1RA
Full analysis set (FAS), *n*	292	146
Female/male, %	47.6/52.4	51.4/48.6
Race: white/black/Asian/American Indian (or Alaska native)/other, %	92.1/5.1/2.1/0.3/0.3	89.7/8.2/1.4/0.0/0.7
Ethnicity: Hispanic or Latin American, %	8.9	10.3
Age, years	58.3 ± 9.9	58.4 ± 8.8
Weight, kg	95.6 ± 16.6	95.5 ± 17.3
BMI, kg/m^2	32.9 ± 4.4	33.0 ± 4.1
Duration of diabetes, years	10.4 ± 5.8	10.4 ± 5.8
HbA_{1c}, %	7.8 ± 0.6	7.7 ± 0.6
mmol/mol[a]	61.5 ± 6.2	60.8 ± 6.7
FPG, mmol/L	9.0 ± 2.1	9.4 ± 2.3
mg/dL	161.7 ± 38.2	169.1 ± 41.7
Pretrial OADs, %		
Metformin	74.3	74.0
Metformin + sulfonylurea	20.9	21.9
Metformin + pioglitazone	2.4	2.7
Metformin + sulfonylurea + pioglitazone	2.4	1.4
Duration of treatment with GLP-1RA prior to randomization, days	468.1 ± 616.0	498.6 ± 525.1

Values are the mean ± SD unless otherwise stated

GLP-1RA glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *OAD* oral antidiabetic drug, *SD* standard deviation

[a] Calculated not measured

Results


A
IDegLira (n=292)
Unchanged GLP-1RA (n=146)
EOT HbA1c
Δ HbA1c
7.4%
−0.3%
6.4%
−1.3%
−0.94%
[−1.11; −0.78]95% CI*
p < 0.001
HbA1c (%)
HbA1c (mmol/mol)
Time (weeks)
B
EOR 6.84
[4.28; 10.94]95% CI*
p < 0.001
EOR 7.53
[4.58; 12.38]95% CI*
p < 0.001
75
36
63
23
Proportion of patients (%)
HbA1c <7%
HbA1c ≤6.5%
IDegLira
Unchanged GLP-1RA
C
IDegLira (n=292)
Unchanged GLP-1RA (n=146)
EOT FPG
Δ FPG
8.8 mmol/L
−0.60
6.0 mmol/L
−2.98
−2.64 mmol/L
[−3.03; −2.25]95% CI*
p < 0.001
FPG (mmol/L)
FPG (mg/dL)
Time (weeks)
D
IDegLira (n=292)
Unchanged GLP-1RA (n=146)
Week 0
Week 26
Week 0
Week 26
Plasma glucose (mmol/L)
Plasma glucose (mg/dL)
Breakfast
+90 min
Lunch
+90 min
Evening meal
+90 min
Bedtime
04:00
Breakfast next day

LixiLan-G: A Randomized Trial Assessing Switching to iGlarLixi vs. Continuation of Daily or Weekly GLP-1RA in T2D Inadequately Controlled by a GLP-1RA and OAD(s)

LAWRENCE BLONDE, JULIO ROSENSTOCK, STEFANO DEL PRATO, ROBERT R. HENRY, NAIM SHEHADEH, ELISABETH NIEMOELLER, ELISABETH SOUHAMI, JUNLONG WU, XIANGLING WANG, CHEN JI, VANITA R. ARODA

Diabetes Jun 2019, 68 (Supplement 1) 149-OR

Design

- Randomized, open-label, active-controlled, parallel-group, phase 3 study
- Duration:
  - 26-weeks
  - followed by a single-arm, 26-week extension for iGlarLixi
- Inclusion criteria
  - T2DM dagnosed for at least 1 year
  - HbA1c $7% to #9%
  - On maximum tolerated dose of a GLP-1 RA – metformin =/- pio or SGLT-2 inh
    - >4 months of tx w/
      - liraglutide once daily or exenatide twice daily,
    - >6 months of tx
      - exenatide extended release once weekly, albiglutide once weekly, or dulaglutide once weekly

Design

- Exclusion criteria:
  - BMI ≤20 or >40 kg/m2 at screening
  - Hx hypoglycemia unawareness
  - Previous tx w/ insulin in the year before the screening visit (with the exception of short-term treatment
  - tx with other antidiabetes drugs within 3 months
  - Laboratory exclusion criteria:
    - amylase and/or lipase levels more than three times the upper limit of normal
    - calcitonin ≥20 pg/mL

Design

- Randomization 1:1
  - Stratified by:
    - A1c $\leq$8%, and > 8%
    - GLP-1 subtype

Table 1—Demographics and baseline disease characteristics at screening or baseline

	Participants randomized to initial 26-week treatment period		Participants who entered 26-week extension period
	GLP-1 RA (n = 257)	iGlarLixi (n = 257)	iGlarLixi (n = 206)
Age (years)	60.0 ± 10.3	59.2 ± 9.6	59.8 ± 9.1
Female	113 (44.0)	131 (51.0)	106 (51.5)
BMI (kg/m^2)	33.0 ± 4.4	32.8 ± 4.4	32.9 ± 4.4
Duration of diabetes (years)	11.0 ± 6.1	11.2 ± 7.4	11.5 ± 7.7
Duration of GLP-1 RA treatment (years)	1.9 ± 1.9	1.9 ± 1.8	1.9 ± 1.8
HbA_{1c} at screening			
%	7.9 ± 0.5	7.9 ± 0.6	7.8 ± 0.5
mmol/mol	63 ± 5	63 ± 7	62 ± 5
GLP-1 RA use by type at screening			
Once-daily/twice-daily formulation	154 (59.9)	153 (59.5)	126 (61.2)
Liraglutide once daily	145 (56.4)	135 (52.5)	112 (54.4)
Exenatide twice daily	9 (3.5)	18 (7.0)	14 (6.8)
Once-weekly formulation	103 (40.1)	104 (40.5)	80 (38.8)
Dulaglutide	51 (19.8)	54 (21.0)	43 (20.9)
Exenatide ER	48 (18.7)	45 (17.5)	33 (16.0)
Albiglutide	4 (1.6)	5 (1.9)	4 (1.9)
Pioglitazone use at screening	22 (8.6)	12 (4.7)	10 (4.9)
SGLT2 inhibitor use at screening	26 (10.1)	26 (10.1)	19 (9.2)

Data are mean ± SD or n (%). ER, extended release; SGLT2, sodium–glucose cotransporter 2.

CASE # 3

Amalia

58–year-old woman with Type 2 Diabetes Mellitus and hypertension. She is on treatment with metformin 1000 bid and a combination of SGLT-2/DPP-4. Her current A1c is 6.2%. She discloses to you that she will no longer has a medical insurance after her company filed for bankrupcy due to pandemic. She is asking you to change her medications since she can no longer afford her current therapy.

What would be your therapeutic approach?

Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m^2	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin†	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2D) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m^2 • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

Medicines for Treatment Intensification in Type 2 Diabetes and Type of Insulin in Type 1 and Type 2 Diabetes in Low-Resource Settings: Synopsis of the World Health Organization Guidelines on Second- and Third-Line Medicines and Type of Insulin for the Control of Blood Glucose Levels in Nonpregnant Adults With Diabetes Mellitus

Godja Roglic, MD,MSc, Susan L. Norris, MD, MPH

Ann Intern Med. 2018 Sep 18;169(6):394-397

Summary of Recommendations

- #1
  - Use a sulfonyl urea to patients not controlled on metformin or with contraindication to metformin (strong recommendation)
    - Similar and and SS improvement in A1c when added to metformin

- #2
  - Introduce human insulin to patients who do not achieve glycemic control with metformin and a sulfonylurea

Summary of Recommendations

- #3
  - If insulin unsuitable a DPP-4 inhibitor, an SGLT-2 inhibitor or TZD may be added (weak recommendation, very-low quality evidence)
    - Ex. People who live alone and depend on others to administer tx.
      - Only insulin and TZDs offer a statistically significant decrease in A1c when compared to placebo.

- #4
  - Use human insulin to manage blood glucose in adults with type 1 and type 2 DM with insulin indication (Strong recommendation, low quality evidence).

- #5
  - Consider long-acting insulin analogues to magage blood glucose in adults with type 1 or type 2 diabetes with frequent severe hypoglycemia.

Conclusions:

- We now have a broad range of pharmacologic agents for optimization of therapy in patients with type 2 Diabetes Mellitus.
  - Therapeutic decisions should take in consideration the individual taking in consideration clinical, social and psychological aspects.
  - All medications have an ideal patient, and all patients have an ideal medication, but sometimes they travel in different roads.

Special thanks to …

- Mrs. Cynthia Alvarez
- Dr. Miguel Lob
- Dr. Michelle Mangual
- Dr. Carlos Vera

And thanks to all of you for being here!
I really missed you all!