Insulin Therapy 2021

PostADA 16.09.2021

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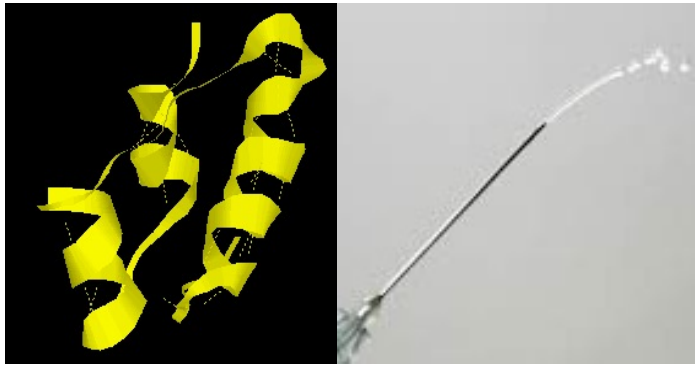
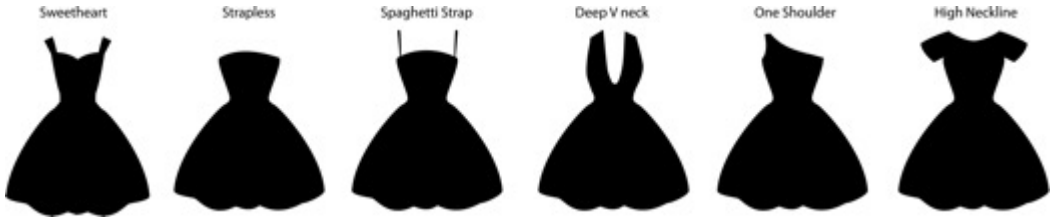


Insulin's Role in Diabetes Management: After 90 Years, Still Considered the Essential "Black Dress"

William T. Cefalu,[1] Julio Rosenstock,[2] Derek LeRoith,[3] and Matthew C. Riddle[4]

Diabetes Care 2015;38:2200–2203 | DOI: 10.2337/dci15-0023



Never WRONG

Efficacy

Wathever eGFR

Physiologic

More patient care

Fit with all

What about after 100 YEARS

PLAN

- **Living with diabetes**
- New insulins on the market
- Recent data about insulin initiation, use and adverse events
- Clinical practice : what will change in 2021

Insulin Indications

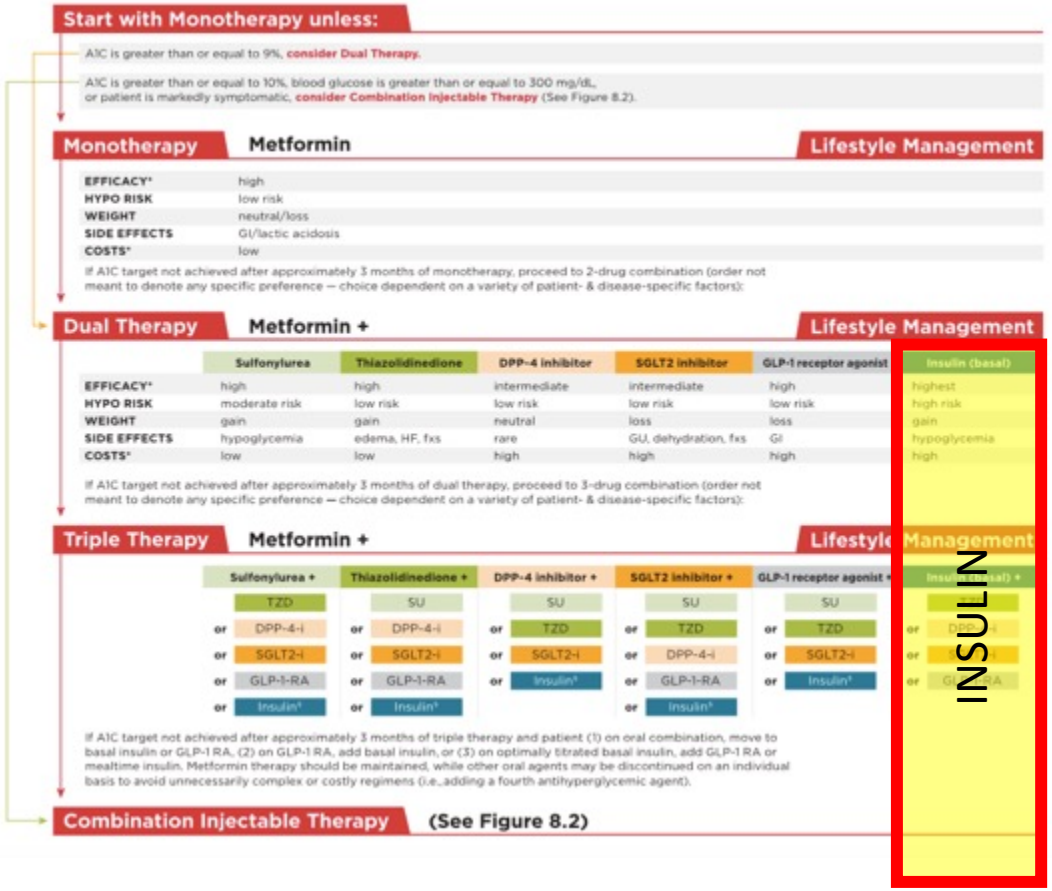
TYPE of DM	% on insuline	Nb of Swiss people	Incidence
• Type 1 diabetes	(100%)	**T1D ≈ 30’000**	**12.5 per 100’000**
• Type 3c diabetes	(40%)	**T3cDM ≈ 10’000**	**7.9 per 100’000**
Pancreatogenic DM			
• Type 2 diabetes	(25%)	**T2D ≈ 100’000**	

- Therapeutic failure
- Diabetic decompensation
- Corticosteroid therapy
- Non-adherence
- Intra-hospital

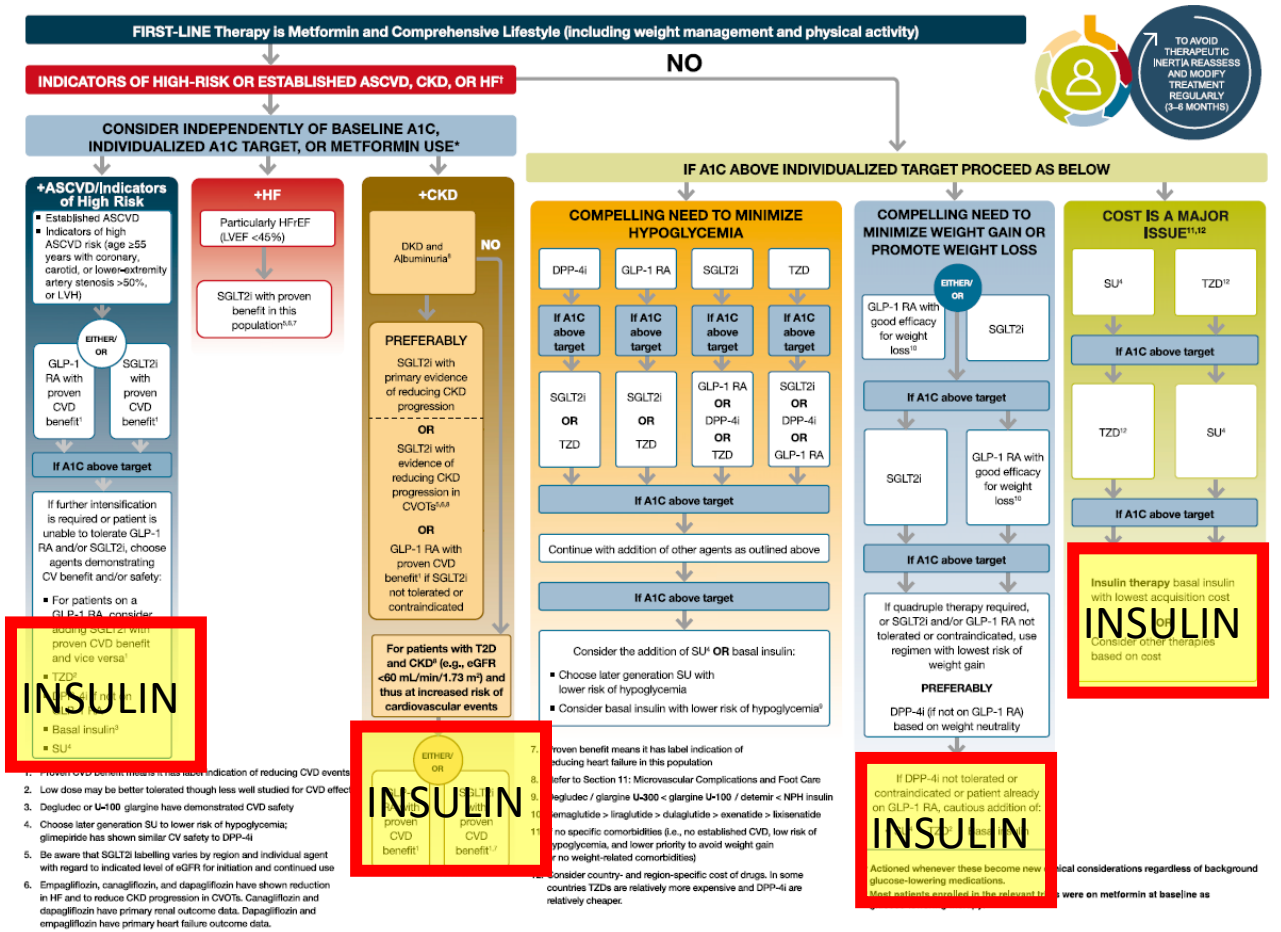
American Diabetes A. 2. Classification and diagnosis of diabetes. Diabetes Care. 2021
Hardt PD et al. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care. 2008

Place of insulin

If HbA1c >10%
If glycemia > 16.7 mmol/l
If symptomatic
→ **Consider insulin**



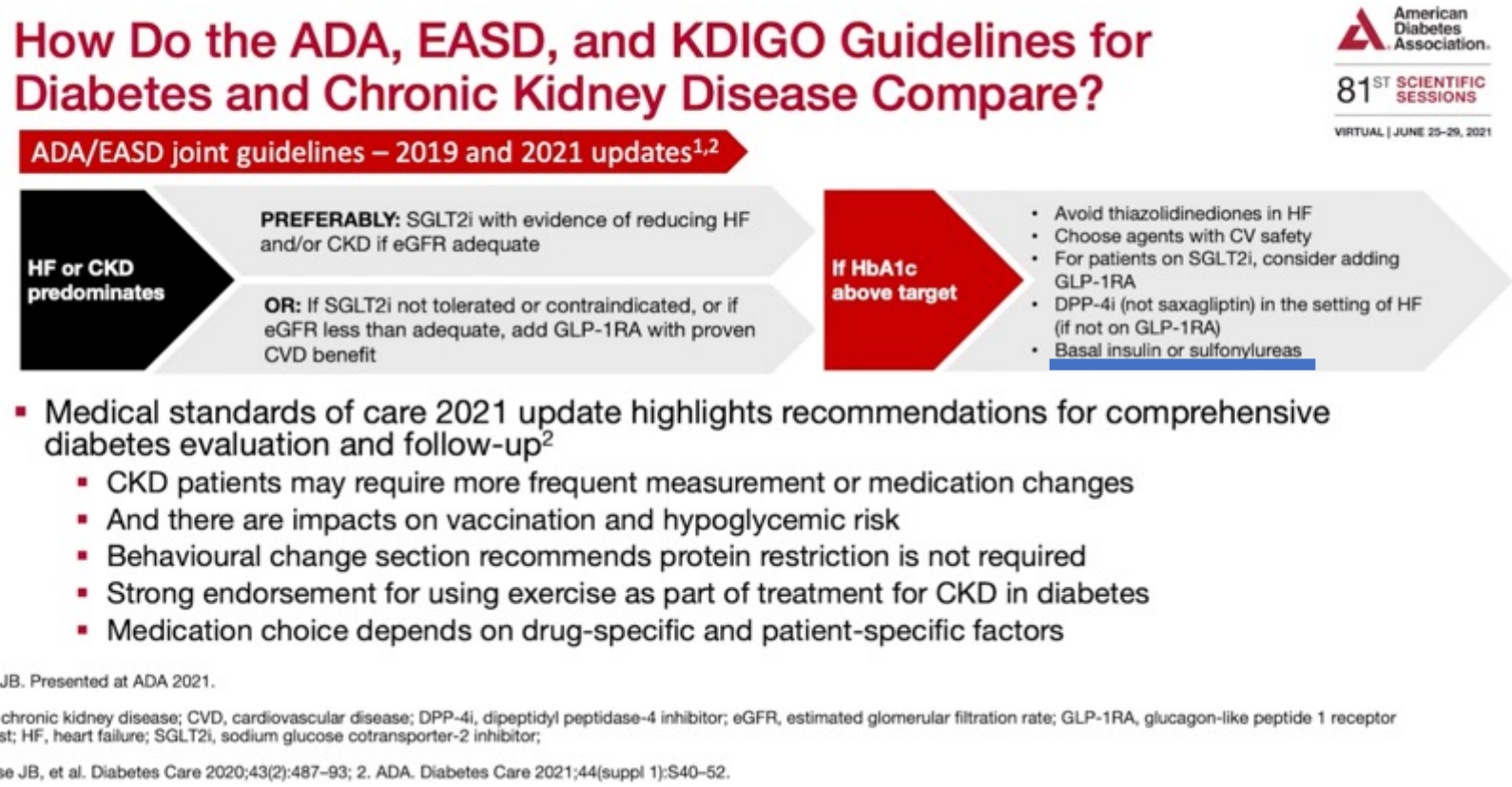
ADA 2017



ADA 2021

Insulin place in case of Diabetes and CKD

→ 1 SGLT2/GLP-1RA → CV safety, DPP-4 → insulin last choice



Living with diabetes (Type 1 or Type 2)

Phase of living with diabetes		Continuum of psychosocial issues and behavioral health disorders in people with diabetes	
		Nonclinical (normative) symptoms/behaviors	Clinical symptoms/diagnosis
	Behavioral health disorder prior to diabetes diagnosis	None	• Mood and anxiety disorders • Psychotic disorders • Intellectual disabilities
	Diabetes diagnosis	Normal course of adjustment reactions, including distress, fear, grief, anger, initial changes in activities, conduct, or personality	• Adjustment disorders*
	Learning diabetes self-management	Issues of autonomy, independence, and empowerment. Initial challenges with self-management demonstrate improvement with further training and support	• Adjustment disorders* • Psychological factors affecting medical condition**
	Maintenance of self-management and coping skills	Periods of waning self-management behaviors, responsive to booster educational or supportive interventions	• Maladaptive eating behaviors • Psychological factors** affecting medical condition
	Life transitions impacting disease self-management	Distress and/or changes in self-management during times of life transition***	• Adjustment disorders* • Psychological factors ** affecting medical condition
	Disease progression and onset of complications	Distress, coping difficulties with progression of diabetes/onset of diabetes complications impacting function, quality of life, sense of self, roles, interpersonal relationships	• Adjustment disorders* • Psychological factors ** affecting medical condition
	Aging and its impact on disease and self-management	Normal, age-related forgetfulness, slowed information processing and physical skills potentially impacting diabetes self-management and coping	• Mild cognitive impairment • Alzheimer or vascular dementia
		All health care team members (e.g., physicians, nurses, diabetes educators, dieticians) as well as behavioral providers	Behavioral or mental health providers (e.g., psychologists, psychiatrists, clinical social workers, certified counselors or therapists)
		Providers for psychosocial and behavioral health intervention	

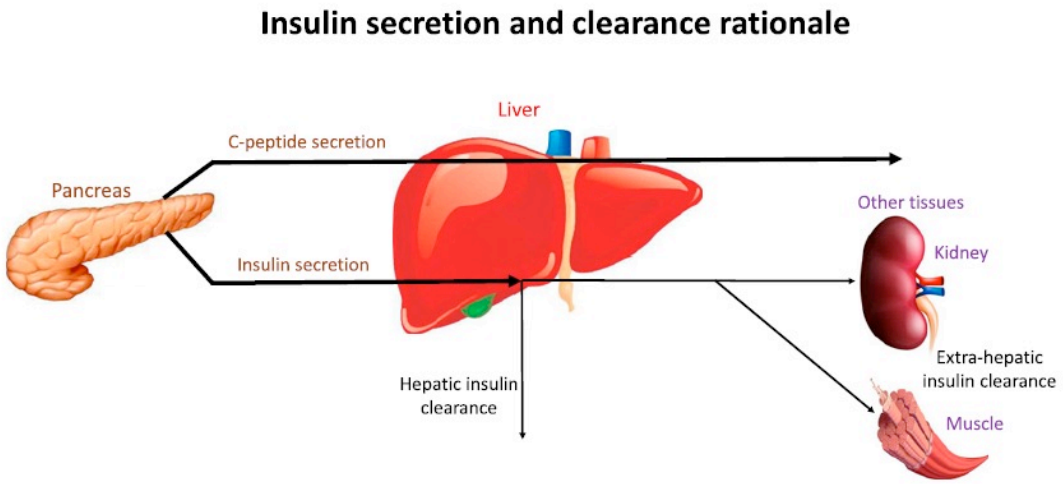
Affective phenomena is a term regrouping emotions, moods, preferences, attitudes, affect dispositions or interpersonal stances. They are highly present in diabetes management. There is a need to separate affect from psychiatric disease in diabetes (ADA 2021).

Powers et al. Diabetes Care 2020;43: 1636–1649
Scherer, 2005

PLAN

- Living with diabetes
- **New insulins on the market**
- Recent data about insulin initiation, use and adverse events
- Clinical practice : what will change in 2021

Insulin clearance Quiz



FSIGT ?
Time for endogenous Insulin clearance ?
% Hepatic insulin clearance ?
Insulin extraction ?

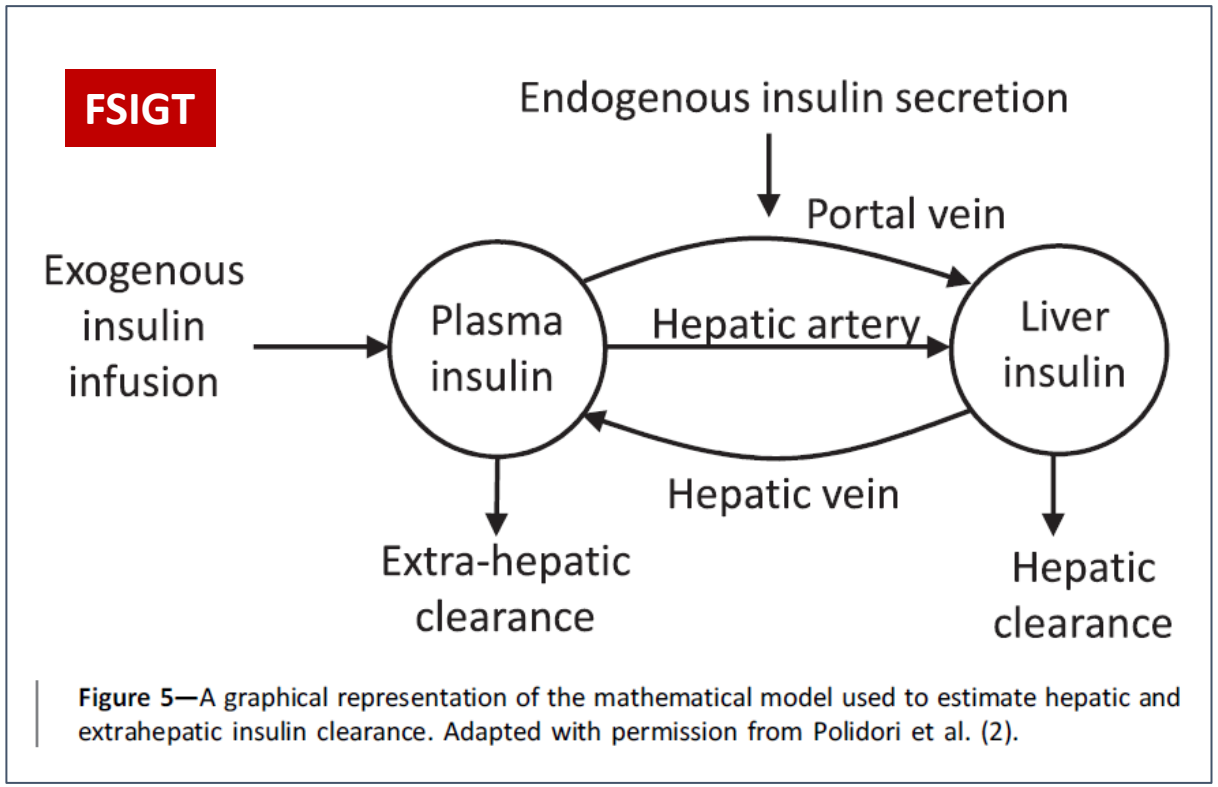


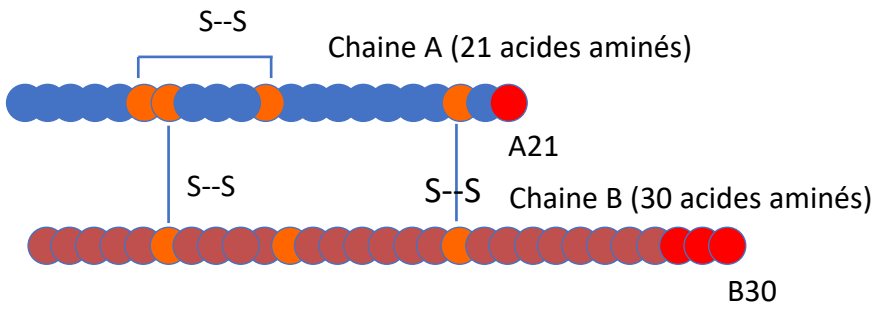
Figure 5—A graphical representation of the mathematical model used to estimate hepatic and extrahepatic insulin clearance. Adapted with permission from Polidori et al. (2).

Postulates for futur research that lower clearance and higher ambient insulin levels could be a risk factors for :

- T2D
- Alzheimer dx
- Cancers

Piccinini P et al. Diabetes Care 2020;43:2296-2302
Bergman R. et al Am. J. Physiol 1979; 236

History



Asparte (B28Asp human insulin)
Lispro (B28Lys,B29Pro human insulin)
Glulisine (Lys B29 par Glu et Asn A3 par Lys)
URLi (pro B28 et B29 par Lys)
Detemir [B29Lys-tetradecanoyl),desB30 human insulin]
Glargine (A21Gly,B31Arg,B32Arg human insulin)
Glargine U300 (A21Gly,B31Arg,B32Arg human insulin)
Degludec (LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin)

- *Iletin* 1922
- Protamine/zinc 1936
- *Isophane* (NPH) 1946
- *Lente* insulin 1951
- *Lantus* 2000
- *Levemir* 2000
- *Tresiba* 2011
- *Toujeo* 2015
- *Fiasp* 2017
- Lyjumej 2021

long acting insulin

Nom	DCI	Nom du stylo (ml et nb Ui)		Prix boite et nb stylo		Prix de 10Ui	Indication
Insulatard®	NPH	FlexPen	3 ml: 300	CHF 53.80	5	0.36 .-	Since 2 years old
Huminsulin®	NPH	KwikPen	3 ml: 300	CHF 52.55	5	0.37 .-	Since 3 years old
Levemir®	detemir	FlexPen	3 ml: 300	CHF 81.90	5	0.61 .-	Since 2 years old
Abasaglar®	glargine	KwikPen	3 ml: 300	CHF 68.40	5	0.46 .-	Since 2 years old
Lantus®	glargine	Solostar	3 ml: 300	CHF 83.70	5	0.57 .-	Since 2 years old
Toujeo®	glargine 300	Solostar	1.5 ml: 450	CHF 69.35	3	0.57.-	Since 6 years old
Tresiba®	degludec	Flextouch	3 ml: 300	CHF 110.05	5	0.73 .-	Since 1 years old
Tresiba 200 ®	degludec 200	Flextouch	3 ml: 600	CHF: 128.80	3	0.72 .-	Since 1 years old

Insulin icodec* (icodec) is a novel once-weekly basal insulin analog in development

Rosenstock J. et al. N Engl J Med 2020

Loading dose Icodec

an initial 100% loading dose
2x [icodec LD] vs (icodec NLD]
To glargine

Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial

Harpreet S. Bajaj, Richard M. Bergenstal, Andreas Christoffersen, Melanie J. Davies, Amoolya Gowda, Joakim Isendahl, Ildiko Lingvay, Peter A. Senior, Robert J. Silver, Roberto Trevisan, Julio Rosenstock

Diabetes Care 2021 Apr; dc202877.
https://doi.org/10.2337/dc20-2877

Check for updates

Similar Hypoglycemia Duration with Once-Weekly Insulin Icodec vs. Insulin Glargine U100 in Insulin Naïve or Experienced Patients with T2D

Post hoc analysis explored hypoglycemia duration using double-blinded CGM (Dexcom G6®) data from 2 phase 2, randomized, open-label, treat-to-target 16-week trials.

- One trial compared 3 titration algorithms of icodec vs. insulin glargine U100 (IGlar U100) in 205 insulin-naïve patients with T2D (NCT03951805)
- Other trial assessed 154 basal insulin-treated patients with T2D switching from any daily basal insulin to icodec with or without a 100% loading dose vs. IGlar U100 (NCT03922750).

Median overall hypoglycemic episode duration (IQR) was
40.0 (20.0, 75.0) min for icodecLD
40.0 (25.0, 80.0) min for icodec NLD
35.0 (20.0, 60.0) min for IGlar U100.

In conclusion, CGM-derived hypoglycemic episode duration was similar with icodec vs. IGlar U100 in insulin-naïve and insulin-experienced patients with T2D, regardless of titration algorithm or initial loading dose use.

Ultra rapid acting – rapid acting

Nom	DCI	Nom du stylo (ml et nb Ui)		Prix boite et nb stylo		Prix de 10Ui	Aux USA
NovoRapid	**asparte**	FlexPen	3 ml: 300 (U-100)	CHF 54.60	5	0.36 .-	179$
Humalog	**lispro**	KwikPen Junior (0.5U)	3 ml: 300 (U-100)	CHF 54.75	5	0.37 .-	212$
Apidra	**glulisine**		3 ml: 300 (U-100)	CHF 92.10	5	0.61 .-	350$
Fiasp	**Fast acting asparte**	FlexPen	3 ml: 300 (U-100)	CHF 68.40	5	0.46 .-	356$
Lyumjev	**Lispro-aabc**	KwikPen Junior (0.5U)	3ml: 300 (U-100) U-200	CHF 66.05	5	0.44.-	424$

US price compared to Switzerland : 3-7 fold

Faster Recovery from Hyperglycemia with Ultrarapid Lispro (URLi) vs. Humalog in Patients with Type 1 Diabetes (T1D) on Continuous Subcutaneous Insulin Infusion (CSII)

Randomized, double-blind, 2-period, crossover study compared pharmacokinetics and glucodynamics of URLi vs. Humalog during recovery from hyperglycemia (plasma glucose [PG] >240 mg/dL) due to missed meal bolus or basal insulin suspension in 32 adults with T1D on CSII.

1.3 mmol/l/H
23 min. earlier

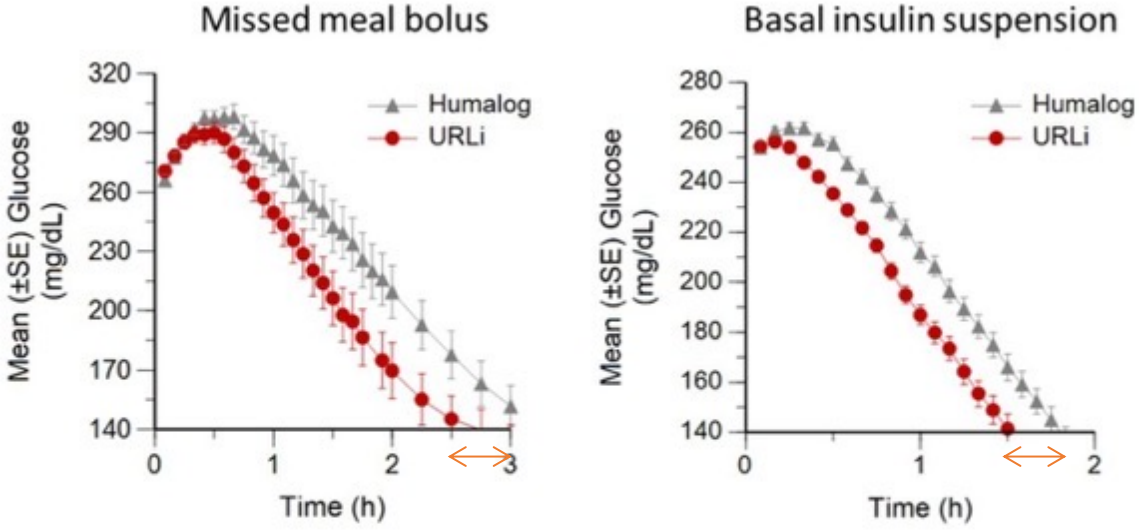


Figure: Mean plasma glucose concentration (± standard error [SE]) vs time after correction bolus of Ultra Rapid Lispro (URLi) or Humalog® for hyperglycemia due to a missed meal bolus (left) or due to basal suspension (right) in patients with type 1 diabetes.

1.3 mmol/l/H
16 min. earlier

JENNIFER LEOHR et al. Diabetes 2021;70:190-OR

Results and conclusions

Following a missed meal bolus, a correction dose of URLi reduced maximum PG (-13 mg/dL; p=0.02), produced more rapid decline in PG (23 mg/dL/hr; p=0.07), and achieved recovery (PG 140 mg/dL) 23 min earlier (p=0.1) vs. Humalog.

Similar results were observed during recovery of hyperglycemia due to basal suspension: a correction dose of URLi reduced maximum PG (-6 mg/dL; p=0.02), produced faster PG decline (24 mg/dL/hr; p<0.001), and achieved recovery 16 min earlier (p=0.001) vs. Humalog.

The early 50% tmax for insulin lispro occurred sooner (-6 or -12 min; p<0.001), and early insulin exposure was greater (2.5 or 4.3 fold, $AUC_{0\text{-}15min}$; 1.7 or 2.5 fold $AUC_{0\text{-}30min}$; both p<0.001), with URLi vs. Humalog after correction bolus for a missed meal bolus or basal insulin suspension, respectively.

During episodes of hyperglycemia commonly experienced by patients with T1D, a correction dose of URLi provided faster recovery vs. Humalog, reflective of the faster insulin absorption.

Ultra rapid acting – rapid acting – short acting insulins

Nom	DCI	Onset	Peak	Duration		Indications
		Minutes		hours		
Ultra-rapid acting						
Fiasp	**Fast acting asparte**	16-20	63	5-7		CSII, Child
Lyumjev	**Lispro-aabc**	15-17	57	4.6-7.3		CSII
Afrezza	Inhaled	12	35-55	1.5-4.5		
Rapid-acting						
NovoRapid	**asparte**	10-20	30-90	3-5		CSII, Child, Pregnancy
Humalog	**lispro**	10-20	30-90	3-5		CSII, Child, Pregnancy
Apidra	**glulisine**	10-20	30-90	3-5		CSII, Child
Short acting insulin						
Humulin R	HUMAN	30-60	120-240	5-8		
Novolin R	HUMAN	30	80-120	Up to 8		

PLAN

- Living with diabetes
- New Insulins on the market
- **Recent data about insulin initiation, use and adverse events**
- Clinical practice : what will change in 2021

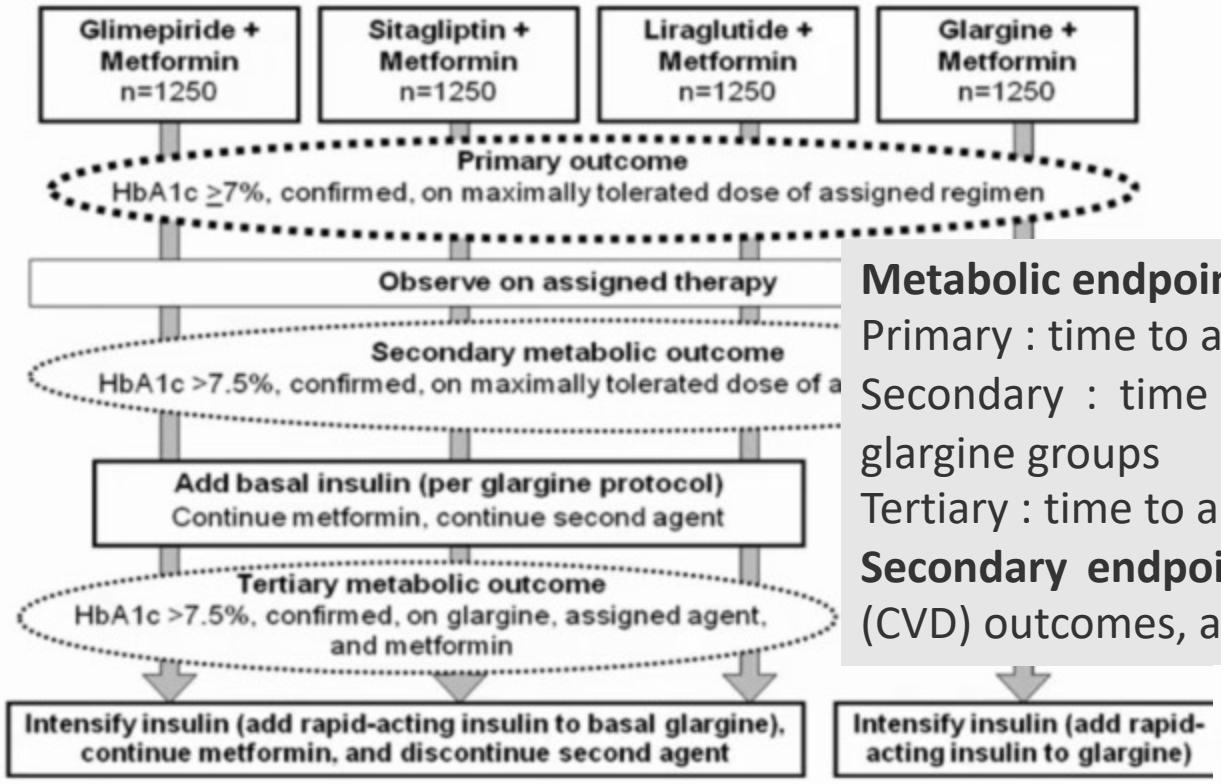
- Academic trial (NHS funded)

- Interventional, randomized, parallel-assigned, open-label clinical trial that recruited 5000 participants on metformin with a mean age of 57.2 years in order to compare the effectiveness of multiple medications in patients with type 2 diabetes long-term in 4 intervention groups of 1250 subjects.
  - Glimepiride/Sitagliptin/Liraglutide/Insulin glargine

- The study consisted of a diverse population, including white (n=3314), black (n=1000), Asian (n=182), and Hispanic/ Latino ethnicity patients (n=929), among others.

- Baseline HbA1c 6.8-8.5% (7.5% mean)

Design



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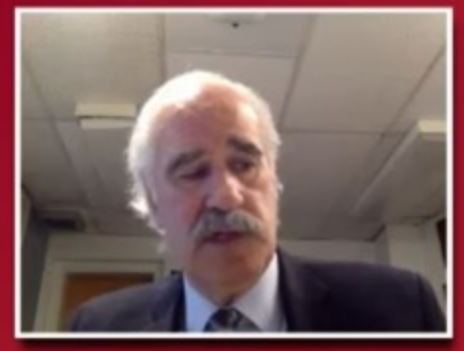


Metabolic endpoints:

Primary : time to a confirmed HbA1c ≥ 7% a

Secondary : time to a confirmed >7.5% and initiate glargine in non-glargine groups

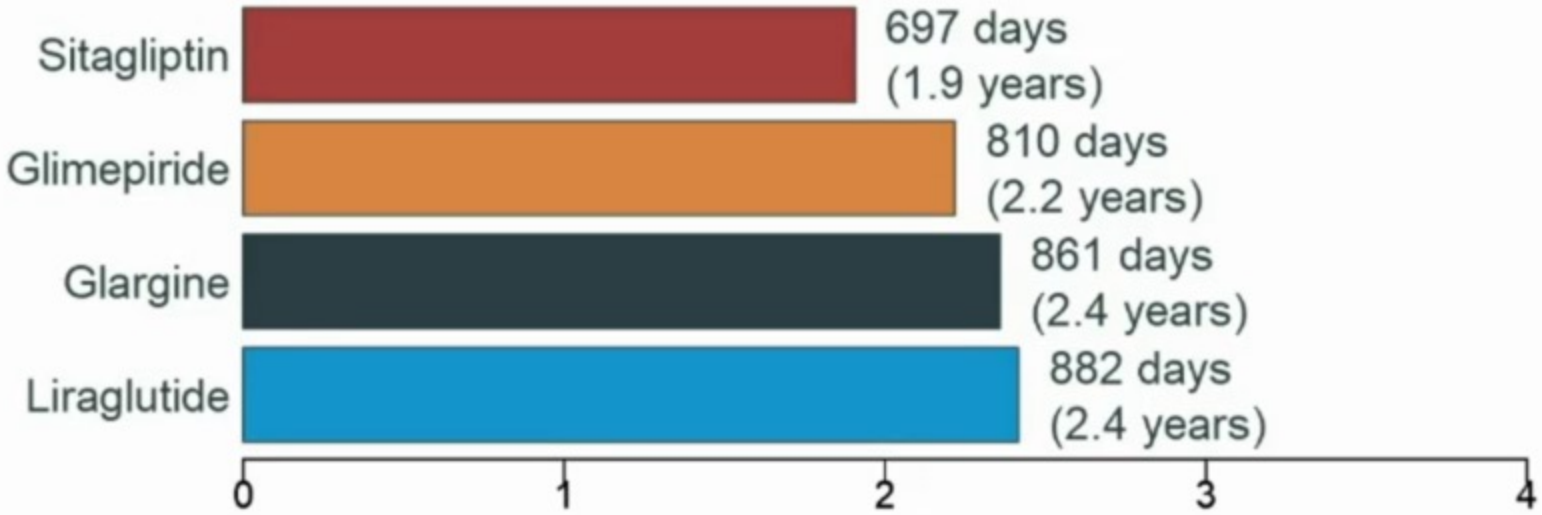
Tertiary : time to an HbA1c of >7.5% following the initiation of glargine.

Secondary endpoints: microvascular outcomes, cardiovascular disease (CVD) outcomes, and adverse effects.

Study Medications Average Dose at 4 Years

	Glargine (units/day)	Glimepiride (mg/day)	Liraglutide (mg/day)	Sitagliptin (mg/day)
Mean ± SD	38.8 ± 32.1	3.5 ± 3.1	1.3 ± 0.7	82.9 ± 36.8
Median (IQR)	32.0 (15.0, 55.0)	3.0 (0.5, 8.0)	1.8 (1.2, 1.8)	100.0 (100.0, 100.0)

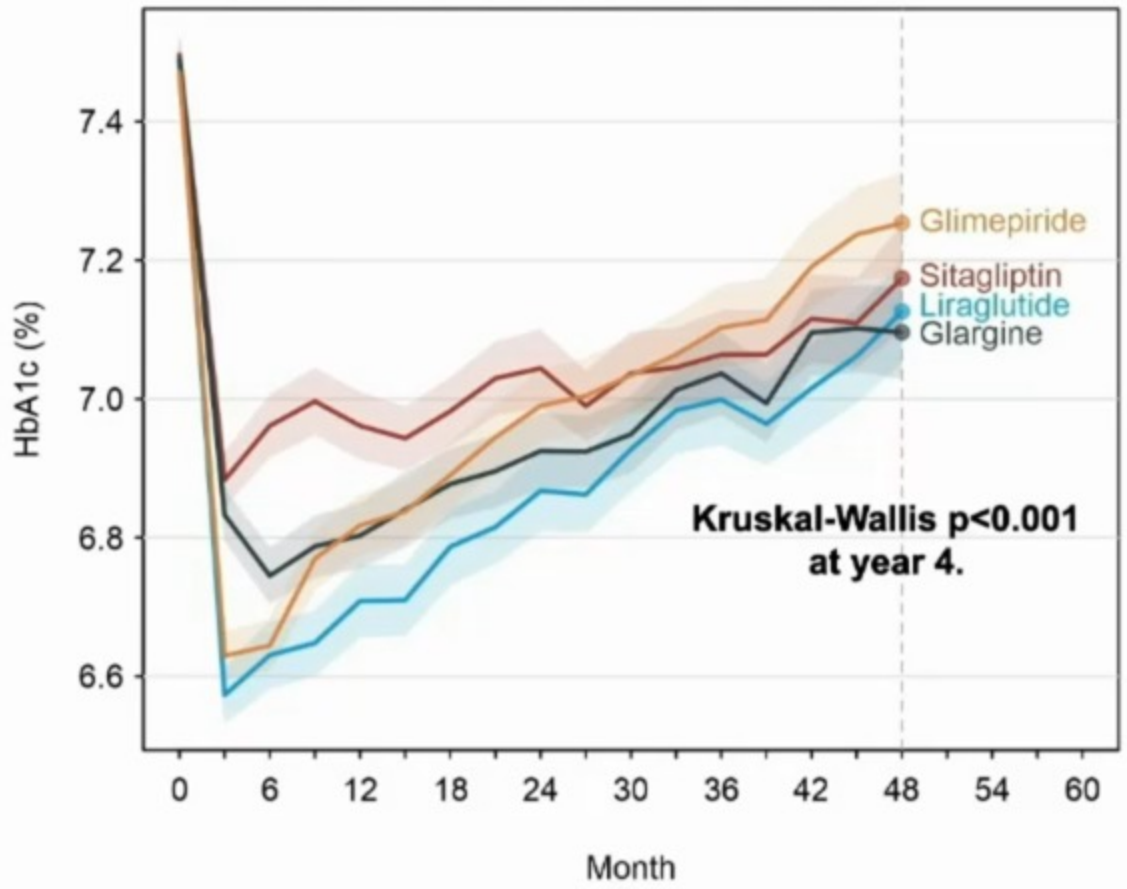
Mean Time to Primary Outcome



Liraglutide and glargine had the longest time until reaching the primary metabolic outcome followed by glimepiride and with sitagliptin the shortest time period.

GRADE

HbA1c Levels Over First Four Years



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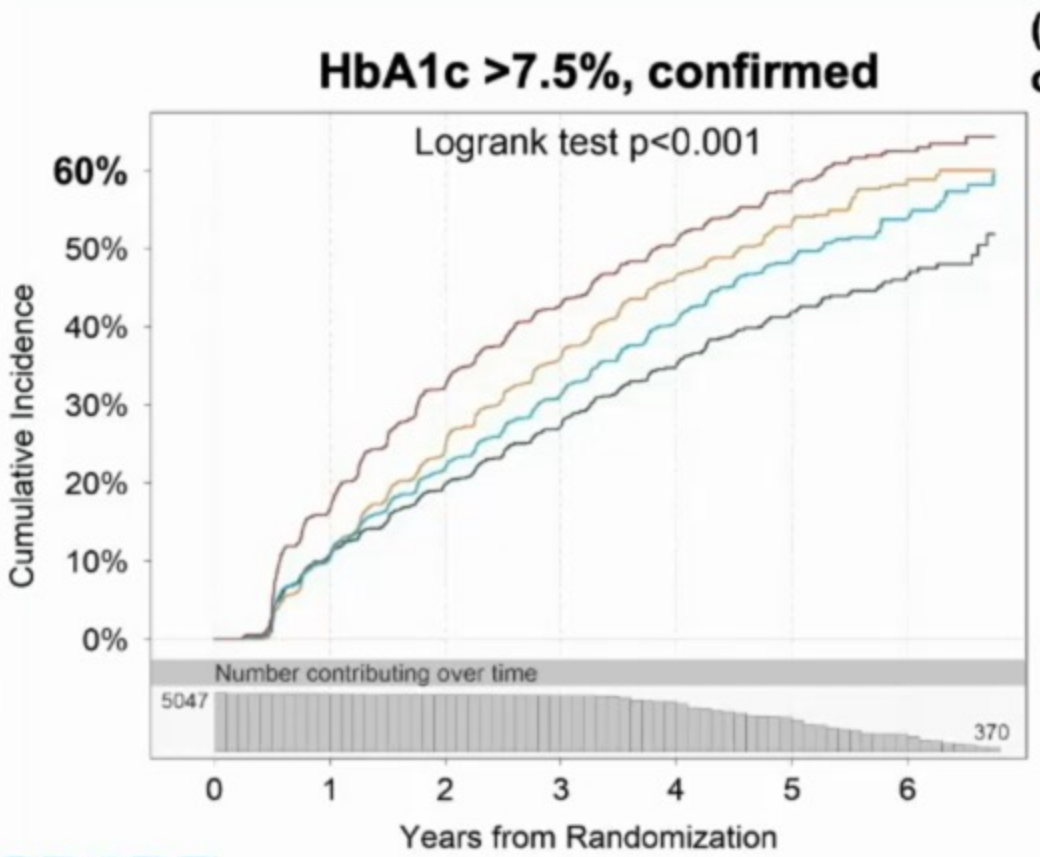
Secondary Metabolic Outcome



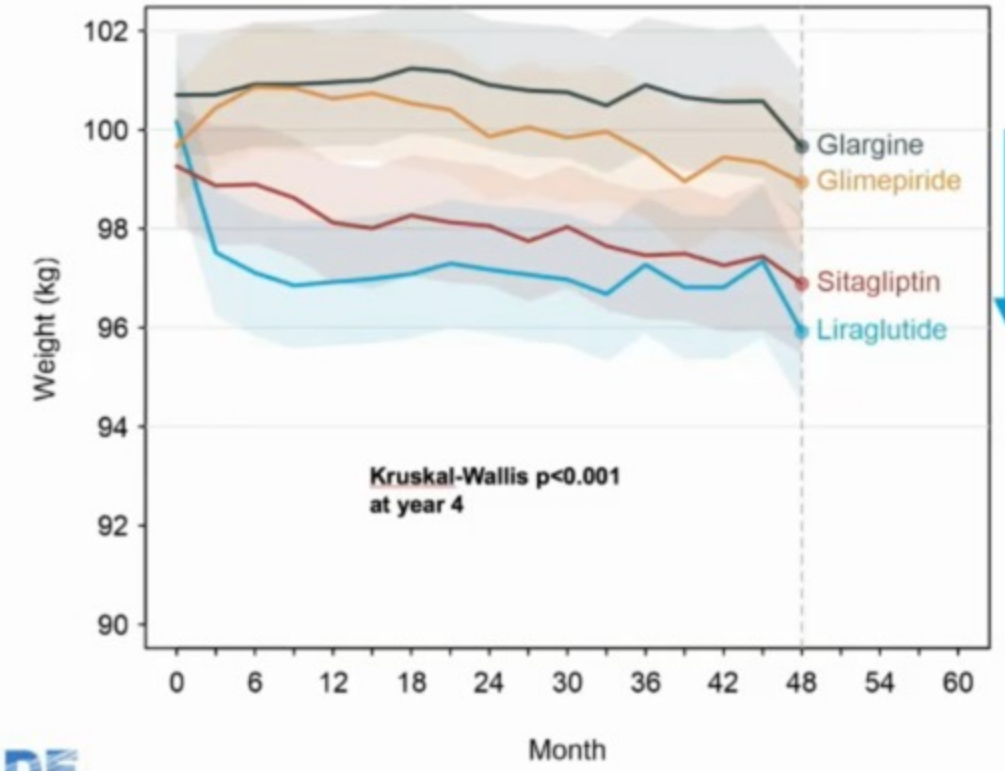
At the time of secondary metabolic outcome (or censoring), percent on non-GRADE or off-protocol glucose-lowering medication

Glargine	3.9%
Glimepiride	4.4%
Liraglutide	4.0%
Sitagliptin	3.8%

Over the course of the study, glargine was more effective at maintaining a HbA1c <7.5% than liraglutide which in turn was more effective than glimepiride and sitagliptin.

GRADE

Results: Weight

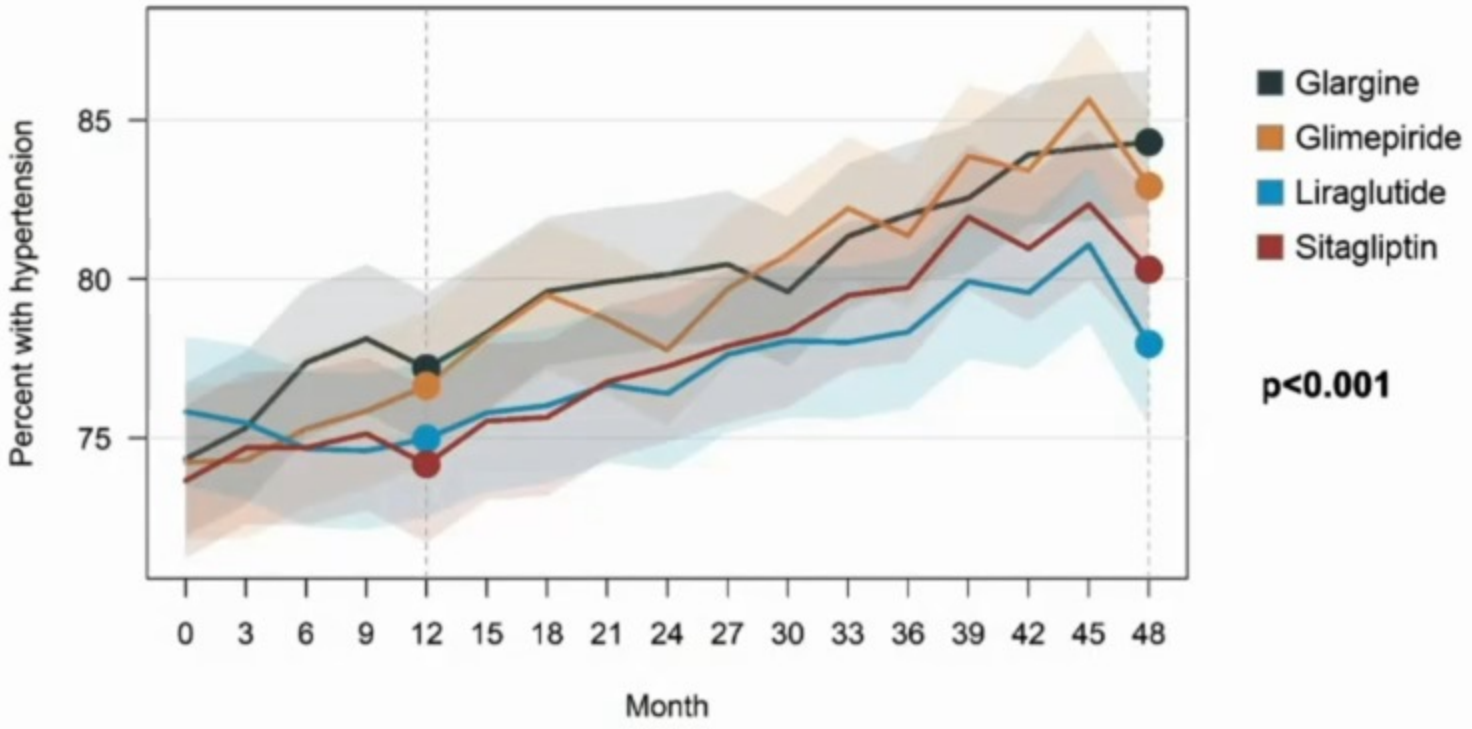


Liraglutide 4kg

GRADE

Prevalence of Hypertension Over Four Years

Blood pressure ≥140/90 mmHg or use of blood pressure lowering medication



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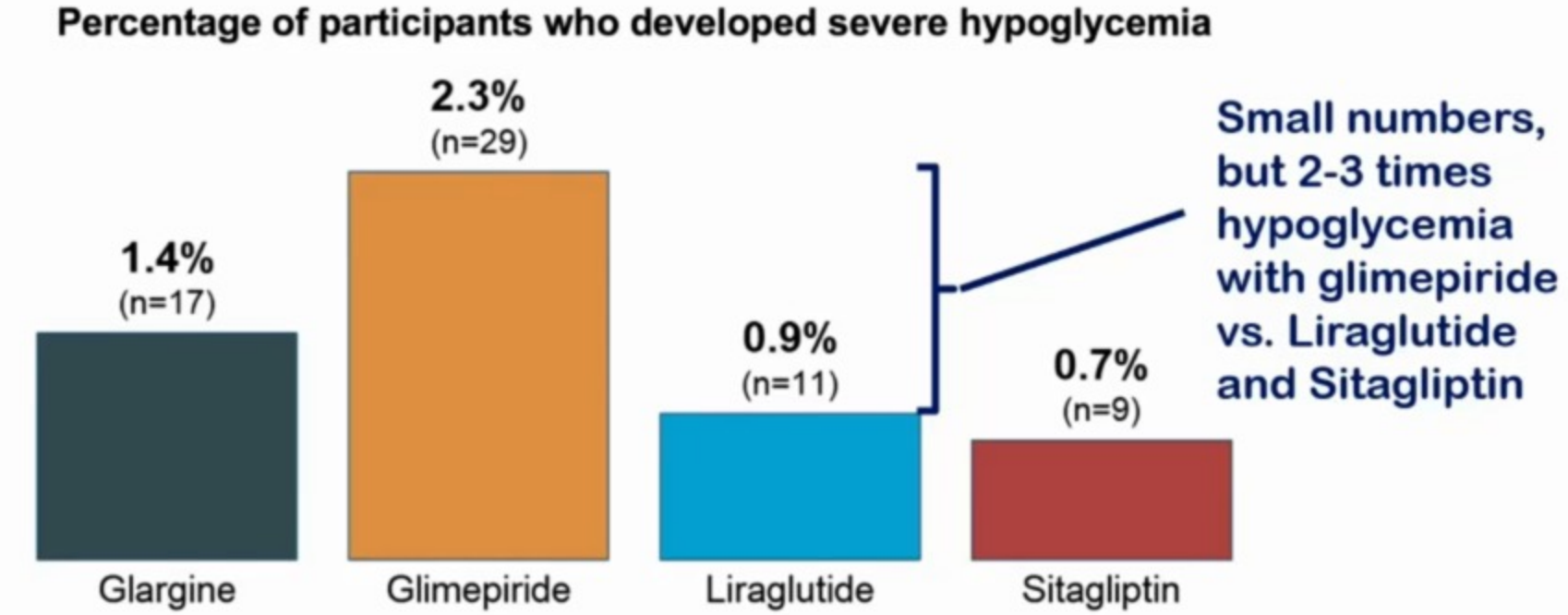
Results: Hypoglycemia



GRADE

Summary: Primary Metabolic Outcome

The primary metabolic outcome, a HbA1c level ≥7%, confirmed:

1. Overall, the majority (71%) of participants reached the primary outcome with >50% doing so within three years. This metabolic outcome was reached despite attentive diabetes care and glucose-lowering medications provided free-of-charge.
2. The primary metabolic outcome occurred less frequently in the glargine and liraglutide-treated groups compared with the glimepiride and sitagliptin-treated groups.
3. Sitagliptin-treated participants reached the primary outcome 113 days before participants treated with glimepiride, and 164 and 185 days before those treated with glargine and liraglutide, respectively.

GRADE

Summary: Primary Metabolic Outcome

4. The temporal pattern of the primary metabolic outcome showed that the main differences between treatment groups occurred in the first year of therapy, being earlier with sitagliptin followed by glimepiride. Subsequently, the cumulative incidence curves, were parallel, increasing at a similar rate in all groups.
5. There were significant differences in response to the therapies by baseline HbA1c levels, but no significant heterogeneity by race or ethnic subgroups.
   Glargine and liraglutide were relatively more effective than glimepiride and all three were more effective than sitagliptin with the relative benefits increasing as the HbA1c increased.

GRADE

Summary: Cardiovascular Outcomes and Mortality

1. Across the four treatment groups, there was a significant difference in the composite outcome of any cardiovascular disease defined as 3-point MACE (non-fatal MI, non-fatal stroke and CV death), hospitalization for heart failure, TIA, revascularization, or unstable angina. This difference favored liraglutide.
2. There was no difference among treatment groups for MACE, hospitalization for heart failure, or mortality. For each of these outcomes, liraglutide appeared to have somewhat lower rates than the other 3 groups.
3. Considering the incomplete adjudication of CVD outcomes at this time, we have been cautious not to report the pairwise comparisons for MACE, hospitalized heart failure or mortality.

GRADE

Future Plans: Glycemic Trajectory and HbA1c

1. **The trajectory of HbA1c over time is in keeping with the known progression of type 2 diabetes.**
   - Address potential mechanisms, such as temporal changes in insulin sensitivity, beta-cell function and alpha-cell function, to understand better the causes of glycemic worsening.
2. **Racial and ethnic differences in the relationship between mean glycemia and HbA1c levels have been reported.**
   - The relationship of average glycemia with HbA1c will be determined from CGM done for two weeks in a subset of 1,749 participants from different racial/ethnic groups (Larkin ME et al: Diabetes Technol Ther 2019;21:682-690).

GRADE

Prior Cardiovascular Outcome Trials

In very high-risk populations:

Glargine: No effect of glargine vs standard of care in ORIGIN[1]

Sitagliptin: No effect of sitagliptin vs placebo in TECOS[2]

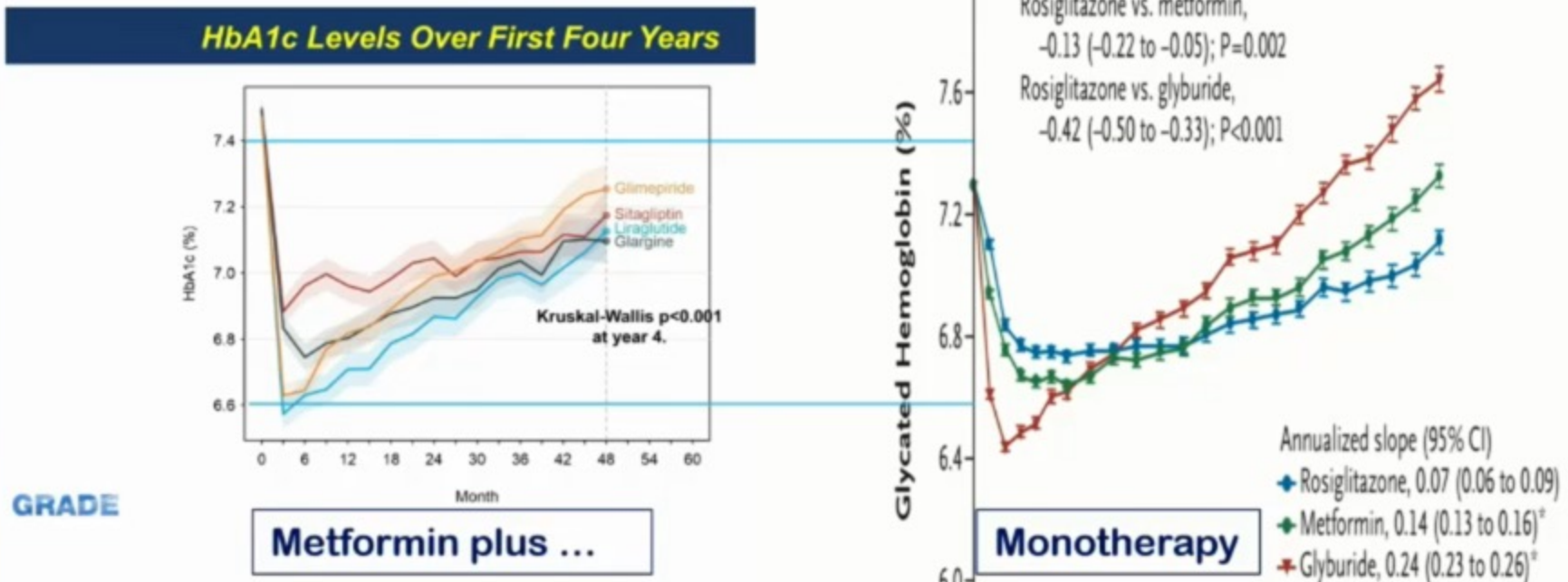
Liraglutide: MACE HR 0.87 (0.78–0.97); mortality HR 0.85 (0.74–0.97) in LEADER[3]

Glimepiride: No difference between glimepiride and linagliptin in CAROLINA[4]

1. ORIGIN Trial Investigators. *NEJM*. 2012; 367:319-28.
2. Green JB, et al. *NEJM* 2015; 373:232-42.
3. Marso SP, et al. *NEJM*. 2016; 375:311-22.
4. Rosenstock J, et al. *JAMA*. 2019; 322:1155-66.

GRADE

Results: HbA1c time course

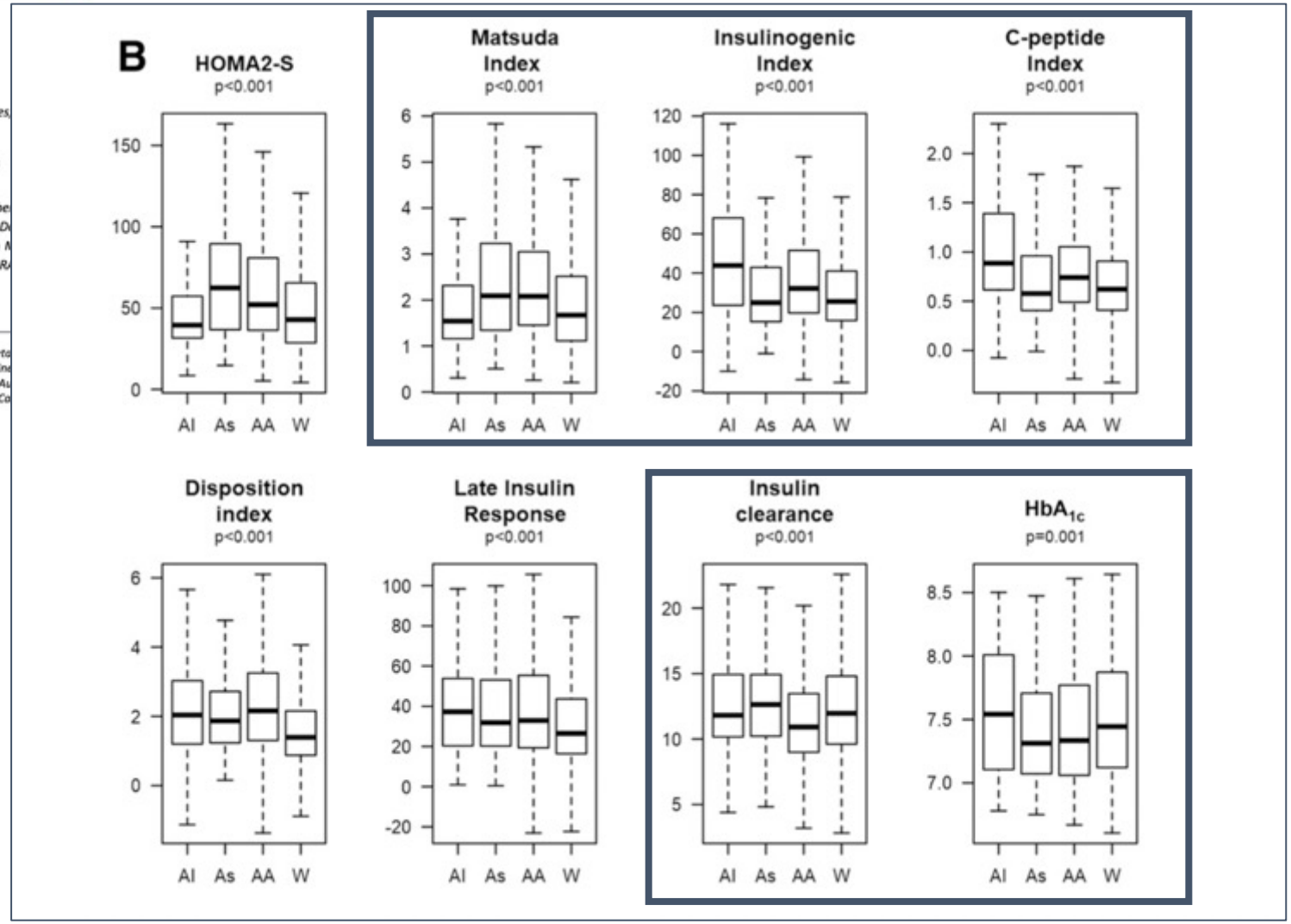


Association of Baseline Characteristics With Insulin Sensitivity and β-Cell Function in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study Cohort

Neda Rasouli,[1,2] Naji Younes, Kristina M. Utzschneider,[4] Silvio E. Inzucchi,[5] Ashok Balasubramanyam,[6] Andrea L. Cherrington,[7] Faramarz Ismail-Beigi,[8] Robe Darin E. Olson,[10] Ralph A. D William H. Herman,[12] John M Steven E. Kahn,[4] and the GR Group*

[1]Division of Endocrinology, Meta abetes, Department of Medicine Colorado School of Medicine, Au [2]VA Eastern Colorado Health Ca rora, CO

Diabetes Care 2021;44:340–349 | https://doi.org/10.2337/dc20-1787



b-cell function differed by sex and race and was associated with the concurrent level of HbA_{1c}.

Values of HbA_{1c} differed among the races

Rasouli N. et al. Diabetes Care 2021

Glycemia Reduction Approaches in Diabetes A Comparative Effectiveness (GRADE)

- T2D evolution → HbA1c progression similar to ADOPT study
- Insulin glargin is as effective as lira, sita or glimep to keep HbA1c undercontrol (cavea : low dosage (< 0.5Ui/kg)
- Glargin choice : → do not have an impact on HbA1c progression (mechanisms : b-cell apoptosis, insulin clearance, etc.)
  - weight neutral
  - increase blood pressure
  - Low risk of hypo
  - CV neutral

PLAN

- Living with diabetes
- New Insulins on the market
- **Recent data about insulin initiation, use and <u>adverse events</u>**
- Clinical practice : what will change in 2021

Hypoglycemia

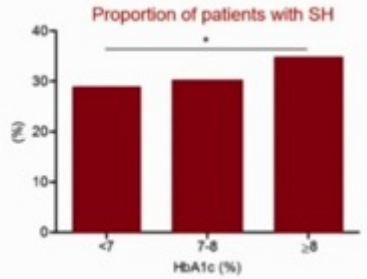
- A reduction in plasma glucose concentration to a level that may induce symptoms or signs such as altered mental status and/or sympathetic nervous system stimulation[1].
- The most common cause of hypoglycemia in patients with diabetes is injecting a shot of insulin and skipping a meal or overdosing insulin[1].
- Severe hypoglycemic (SH) events are reported in 14% of people with T1D and 8.9% with T2D (27'585 insulin treated patients 24 countries[2])
- Impaired Awarness of Hypoglycemia (IAH) is common in T1D (11.8%) and T2D (9.7%) independently of HbA1c level [3,4]) → Risk Factor for SH

1.Frier B, Nature Rieview Medicine, 2014
2.Khunti K et al. Diabetes, Obesity and Metabolism, 2016
Lian A et al. BMJ Open Diab Res Care 2020
Weinstock RS et al J Clin Endocrinolo Metab, 2013

Hypoglycemia burden

IAH and severe hypoglycemia are common in people with type 2 diabetes on insulin therapy

- Dutch Diabetes Pearl observational Cohort of patients with T2D
- 2350 people with insulin treated T2D (mean age 61), 80% on basal-bolus regimen.
- IAH assessed using Dutch modified version of the Clarke questionnaire
- **9.7% were classified as having IAH and 31.6% reported severe hypoglycemia in the past 12 months**



Multivariate analysis found higher risk of SH associated with:
- Non-Caucasian ethnicity
- Complex insulin regimen
- Use of psychoactive drugs

- In this cohort 1 out of 10 people with T2D on insulin had IAH and 1 out of 3 had a SH in the past year.

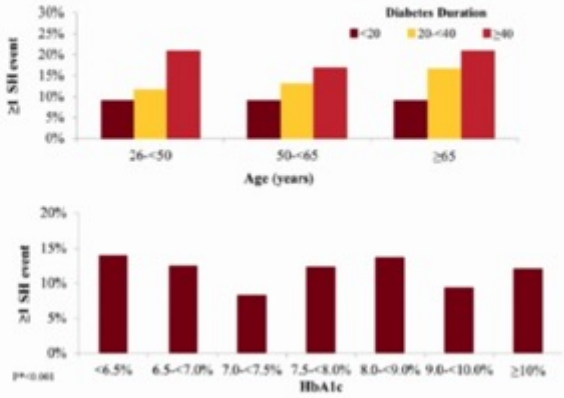
Lian A van Meijel et al. BMJ Open Diab Res Care 2020

T2D

Severe hypoglycemia in common in T1D and associated with diabetes duration

T1D Exchange clinic registry data

- Cross-sectional analysis from the T1D Exchange clinic registry at 70 U.S. endocrinology centers.
- 4973 participants aged 26 to 93 years old with T1D for ≥2 years.
- One or more severe hypoglycemia (SH) events (seizure or LOC) within 12 months was reported by **11.8%** of the participants



Weinstock RS et al. J Clin Endocrinol Metab, 2013, 98(8):3411–3419

T1D

ADA 2021 and Hypoglycemia burden

Comparison of Treatment with Insulin Degludec and Glargine U100 in Patients with Type 1 Diabetes Prone to Nocturnal Severe Hypoglycaemia (HypoDeg): A Prospective, Randomized, Open-Label, Crossover Trial

Materials and Methods: Pre-defined optional substudy of the HypoDeg trial, a 2-year investigator-initiated, randomized, cross-over trial where 149 participants with T1D were randomized to treatment with IDeg or IGlar. Fifty-one participants (mean (SD) age 58 (13) years, diabetes duration 28 (14) years and HbA1c 7.8 (1) %) were admitted for two nights for hourly blinded plasma glucose measurements for a minimum of one night (23:00h to 07:00h) during each 1-year treatment period. The primary endpoints were NH at level 1 (PG ≤ 3.9 mmol/L) and level 2 (PG < 3.0 mmol/L).

Conclusion: In people with T1D and recurrent nocturnal severe hypoglycemia, treatment with IDeg as compared to IGlar results in a clinically significant lower rate of NH at both levels of hypoglycemia.

737-P: Efficacy and Safety of Insulin Glargine 300 U/mL (Gla-300) in People with Type 2 Diabetes Mellitus (T2DM) Uncontrolled on Basal Insulins (BI): ARTEMIS-DM Study

Patients were then randomized 1:1 to receive Gla-100 + OADs (n=192) or Asp 30 + OAD (n=192) for 24 weeks. Mean (SD) age was 54.2 (8.8) years, BMI was 26.0 (3.1) kg/m^2, and duration of diabetes was 6.8 (3.0) years. At week 24, the least square mean (SE) change from baseline in HbA1c was -1.72% (0.07) and -1.70% (0.07) in the Gla-100 and Asp 30 groups, respectively (Table); group difference (-0.01%; 95% CI -0.20, 0.17) met the pre-specified non-inferiority criteria (upper bound 95% CI <0.4%). All hypoglycemia events were significantly lower in the Gla-100 group.
In conclusion, compared with Asp 30 + OAD, Gla-100 + OAD showed similar efficacy but lower hypoglycemia risk in Chinese T2D patients.

ADA 2021 and Hypoglycemia burden

Does hypoglycemia awareness status on Gold and Clark questionnaires predict hormonal and symptomatic responses to hypoglycemia in type T1D?

- We examined data from 78 subjects with T1D who completed both Gold and Clark questionnaires and underwent a hyperinsulinemic hypoglycemic clamp on the same day.
- Epinephrine and hypoglycemia symptoms were measured at euglycemia (100 mg/dl) and during experimental hypoglycemia (target 50 mg/dl).
- Symptoms of hypoglycemia were quantified by using a previously validated questionnaire[1] at baseline and during hypoglycemia at the end of the insulin clamp.

1. Towler DA et al. 1993 Diabetes, 42, 1791-1798

Amir Moheet

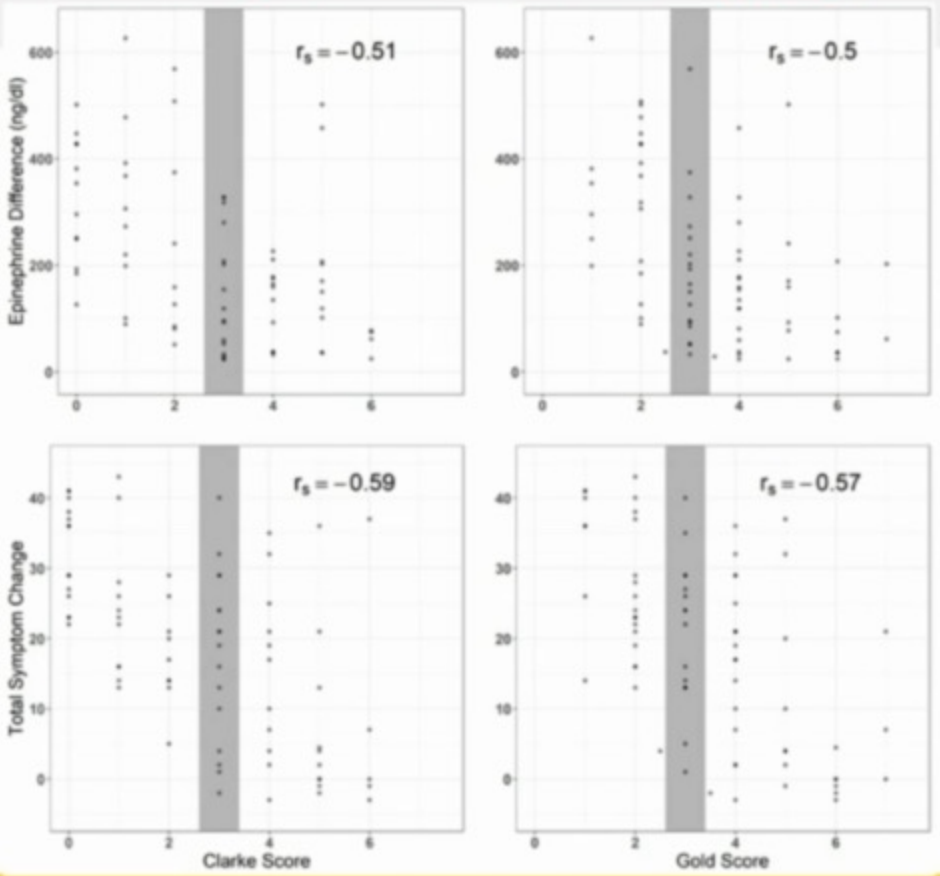
Discordance in hypoglycemia awareness classification between Clark and Gold questionnaires

		Clarke Questionnaire			
		Aware	Indeterminant	Unaware	Total
Gold Questionnaire	Aware	**23 (92.0% / 65.7%)**	2 (8.0% /11.8%)	0 (0% / 0%)	25
	Indeterminant	9 (47.4% / 25.7%)	**7 (36.8% / 41.2%)**	3 (15.8% / 11.5%)	19
	Unaware	3 (8.8% / 8.6%)	8 (23.5 % / 47.1%)	**23 (67.6% / 88.5%)**	34
	Total	35	17	26	78

The agreement table of the Clarke and Gold questionnaire awareness status (N 78) .

- The first % represents the row percentage, i.e. the percent of each Clarke status among that Gold status. The second % represents the column percentage, i.e. the percent of each Gold status among that Clarke awareness status.
- **Among the participants who completed both questionnaires, 32% were classified differently by the two instruments .**
- These two measures have a linear weighted Kappa statistic of 0.63 (0.31, 0.95).

Both Gold and Clarke questionnaires have moderate negative relationships to the epinephrine response and symptom response to hypoglycemia

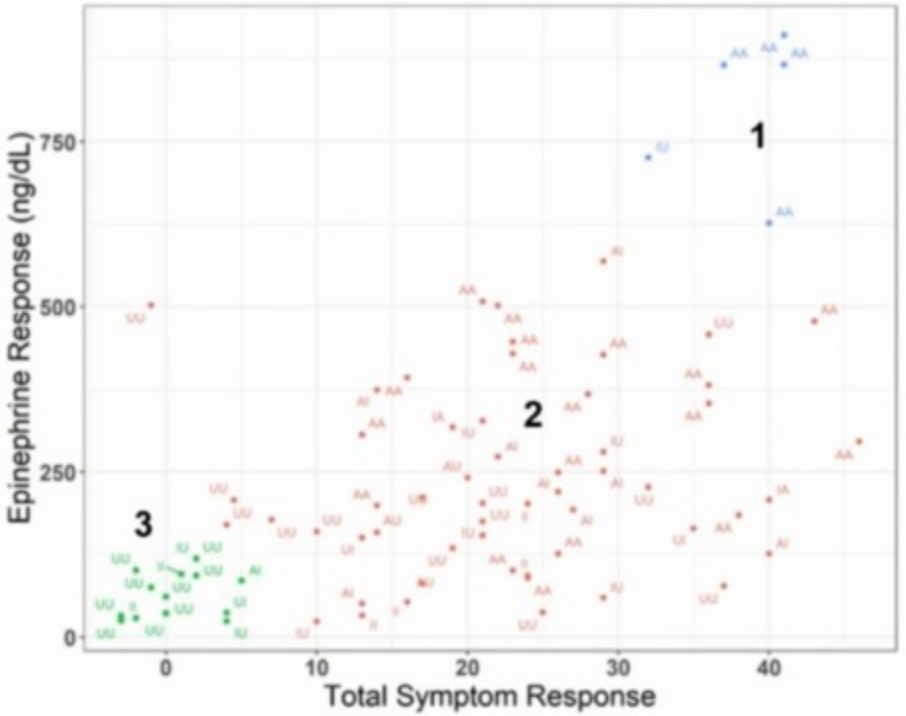


The shaded vertical line represents the "indeterminant" scores.
Spearman correlations were calculated for each of the four scatterplots.

Cluster analysis to examine how disagreement between the Clarke and Gold methods on IAH classification relate to epinephrine and symptoms responses

- The clustering analysis (N 75) showed three general types of epinephrine and symptomatic response patterns:
  1. High epi + high symptom.
  2. Low epi + mod-high symptom.
  3. Low epi + low symptom.

- These questionnaires are more accurate in classifying awareness status when subjects are at the more extremes of the IAH spectrum with either intact (cluster 1) or total loss of symptoms and epinephrine responses (cluster 3).



The letters corresponding to each data point show the awareness status (A = aware, I = indeterminant, U = unaware) for both the Clarke (first letter) and Gold (second letter) scores.

Summary

- Despite the strong correlation between the scores of the Clarke and Gold instruments, we observe that there are considerable differences in how these questionnaires assign hypoglycemia awareness status.
- Our results also show that hypoglycemia awareness status on Clarke and Gold questionnaires poorly predicts hormonal and symptomatic responses to hypoglycemia in T1D.
- If classification of hypoglycemia awareness status is to be done using these survey instruments, it be may be better to use both the Clarke and Gold instruments and assign a category only when both surveys are in agreement.

45-OR: Hypoglycemia, Glycemic Variability, and Risk of Cardiac Arrhythmias in Insulin-Treated Patients with Type 2 Diabetes

Insulin-treated patients with type 2 diabetes (T2D) are at risk of hypoglycemia, which is associated with an increased risk of cardiovascular disease.

We investigated the association between episodes of hypoglycemia, glycemic variability and cardiac arrhythmias in a real-life setting.

Insulin-treated patients with T2D (N=21, [mean±SD] age 66.8±9.6 years, BMI 30.1±4.5 kg/m^2, HbA1c 6.8±0.4% [51.0±4.8 mmol/mol]) were included for a one-year observational study employing continuous glucose monitoring (118±6 days) and implantable cardiac monitors (ICMs).

The ICMs detected 724 episodes of clinically relevant arrhythmias in 12 (57%) patients, with atrial fibrillation and pauses accounting for 99% of the episodes. No association between hypoglycemia and cardiac arrhythmia was found during daytime.
During nighttime, subject-specific hourly incidence of cardiac arrhythmias tended to increase with the occurrence of hypoglycemia but only slightly with increasing time in hypoglycemia (Figure).
Subject-specific incidence of cardiac arrhythmias during nighttime increased with increasing glycemic variability as estimated by coefficient of variation and standard deviation.

45-OR: Hypoglycemia, Glycemic Variability, and Risk of Cardiac Arrhythmias in Insulin-Treated Patients with Type 2 Diabetes

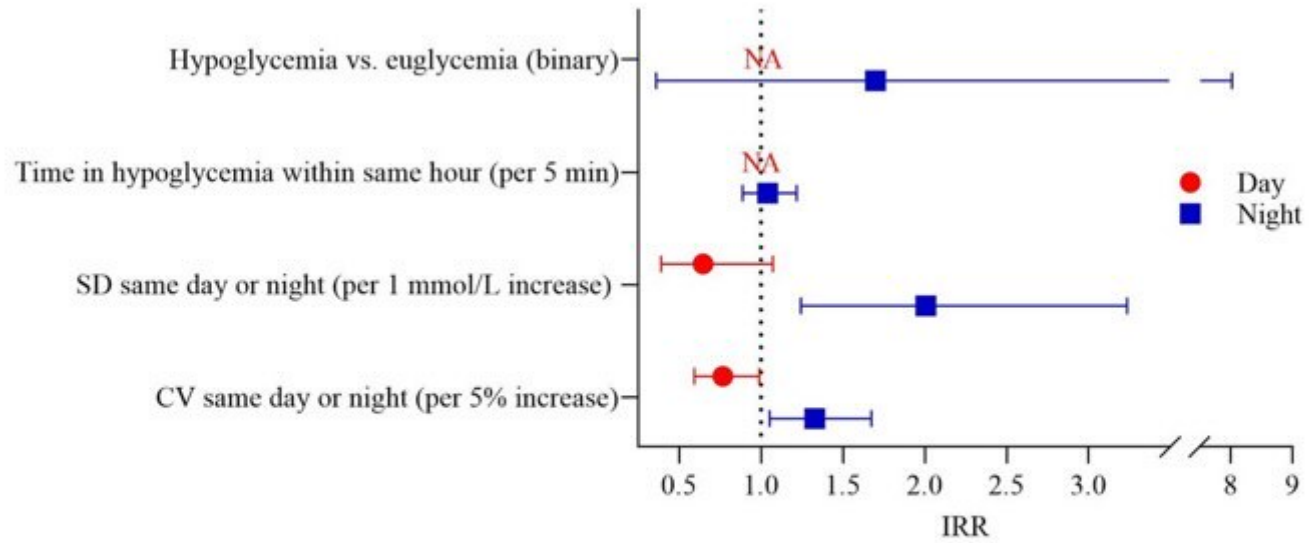


Figure. Incident rate ratio (95% CI) for cardiac arrhythmia (as defined by the study protocol) according to within-subject change in glycemic summaries (generalized linear mixed model). Note that no arrhythmias were detected during daytime hypoglycemia. Abbreviations: CV, coefficient of variation; NA, not applicable; SD, standard deviation.

In conclusion, cardiac arrhythmias were common in insulin-treated patients with T2D and were associated with glycemic variability, whereas arrhythmias were not strongly associated with hypoglycemia.

ANDREAS ANDERSEN et al. Diabetes 2021;70:45-OR

American Diabetes Association.

46-OR: Hypoglycemia Increases the Left Ventricular Ejection Fraction in People with Diabetes and Healthy Controls

To investigate the effect of hypoglycemia on left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) in people with type 1 diabetes (T1DM) and in healthy controls (HC).

Methods: We enrolled 15 adults with T1DM (M/F 9/6, age 47±19 years, HbA1c 7.9±2.9%, diabetes duration 22.5±12.6 years) and 14 HCs (M/F 7/7, age 39±17 years).

All participants underwent a hyperinsulinemic normoglycemic (5.3±0.4 mmol/L, 30 min) hypoglycemic (2.8±0.5 mmol/L, 60 min) glucose clamp. At baseline and approximately 30 min into the hypoglycemic phase (steady-state), a cardiac ultrasound was performed (by the same person), for later analysis.

Results: All participants had sinus rhythm at baseline and none developed arrhythmias during hypoglycemia. We found no difference between T1DM and HC for LVEF measured at baseline. In response to hypoglycemia, LVEF increased from 58.1±2.6% at baseline to 63.7±4.0% in the T1DM group ($p<0.0005$) and from 58.0±3.8% to 64.7±2.4%, ($p<0.005$) in the HC group.

GLS was unchanged (-20.9±1.5% to -21.3±3.5% ($p=0.800$)) in the T1DM group, but a numerical decrease from -19.6±3.0% to -22.0±2.7% ($p=0.084$) was seen in the HC.
Age did not modulate the effect of hypoglycemia on LVEF or GLS.

46-OR: Hypoglycemia Increases the Left Ventricular Ejection Fraction in People with Diabetes and Healthy Controls

Conclusion: An event of hypoglycemia increases the LVEF significantly in people with diabetes.

Presumably due to the catecholamines chronotropic, inotropic and peripheral contracting effect. The result of this would be increased cardiac output, increased oxygen consumption and metabolism and thereby increased load on the heart. This may contribute to explain the link between hypoglycemia and cardiovascular disease.

Effect of Continuous Glucose Monitoring on Glycemic Control in Patients With Type 2 Diabetes Treated With Basal Insulin A Randomized Clinical Trial

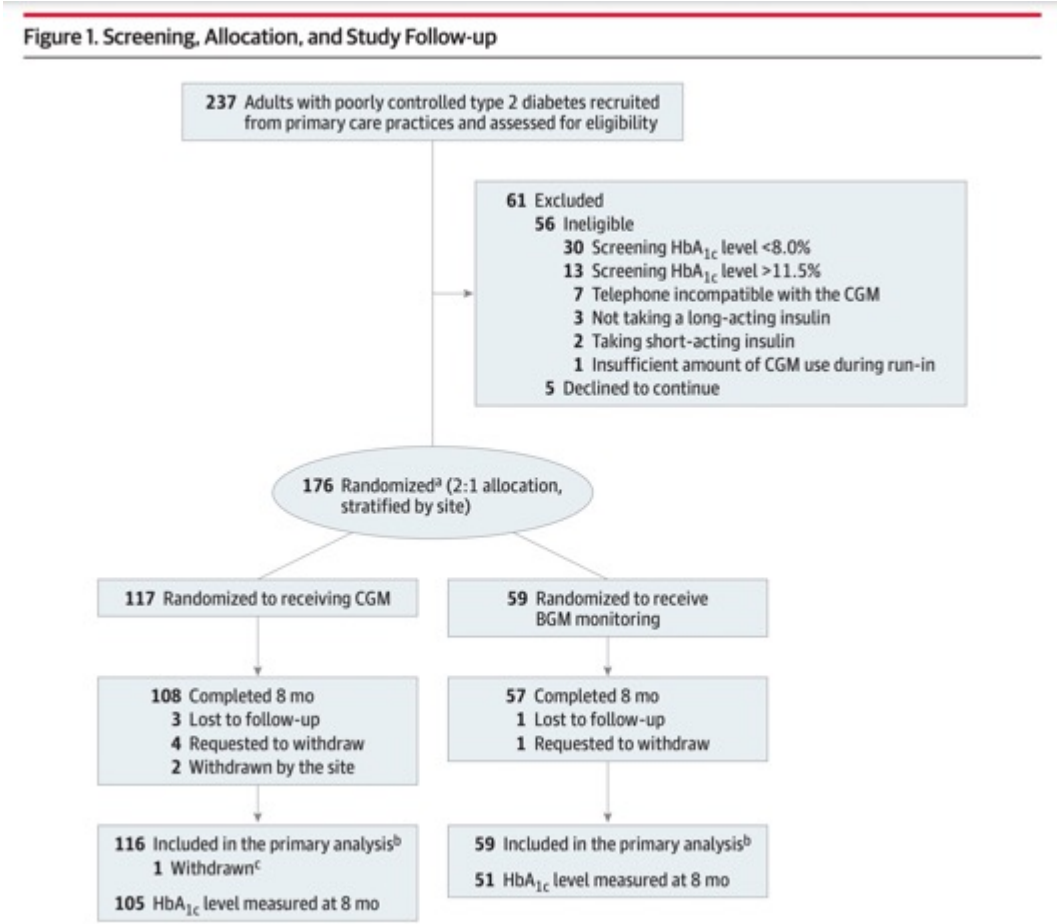
A six-month study that assessed the effect of Dexcom G6 use among people with type 2 diabetes on basal insulin-only, other glucose-lowering medications, or diet and exercise.

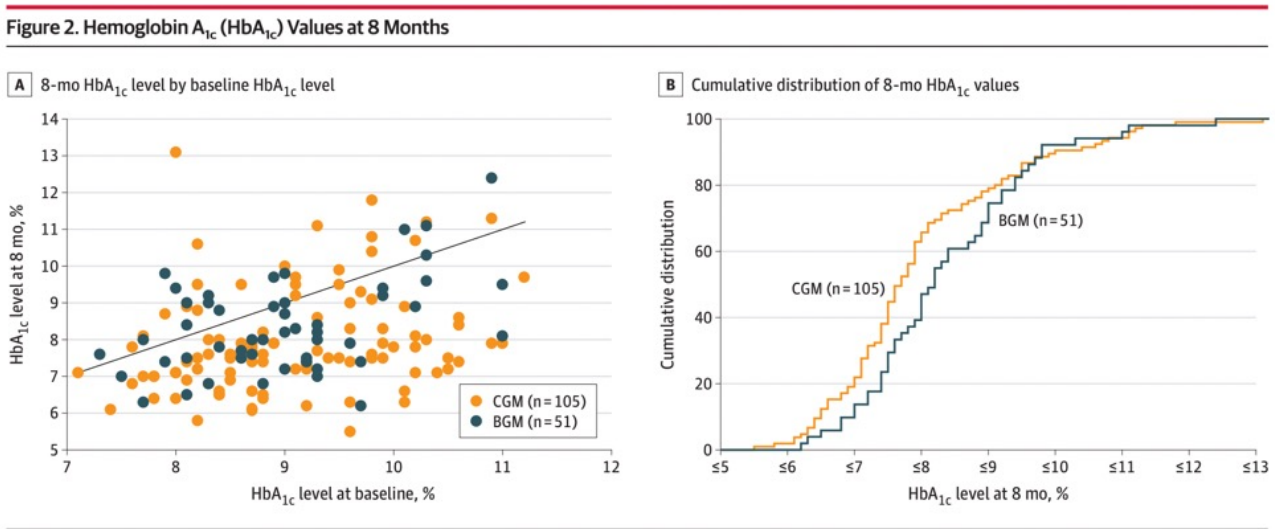
The study included 38 participants with an average A1C of 10.1% (and all participants had values above 7.5%). Basal Insulin mean : 0,47Ui/kg.

Time in Range of 57%, BMI of 36 kg/m2, average age of 59 years, who had lived with diabetes for 14 years on average, and typically completed fewer than three fingerstick tests per day.

Participants received CGM training from the clinic staff and attended three- and six-month clinic visits to review data and adjust medications as needed.

Martens T et al. JAMA. 2021;325(22):2262-2272





A1C reduction: A1C went down to 7.1% (baseline 10.1%). This was seen among people using one, two, or more medications

Martens T et al. JAMA. 2021;325(22):2262-2272

Table 3. Adverse Events and Serious Adverse Events[a]

	No. (%)	
	Continuous glucose monitoring (n = 116)	Blood glucose meter monitoring (n = 59)
Adverse events (including serious adverse events)[b]		
No. of adverse events	45	16
Participants with ≥1 adverse events	30 (26)	12 (20)
Serious adverse events (excluding severe hypoglycemia and diabetic ketoacidosis events)[b]		
No. of adverse events	14	7
Participants with ≥1 adverse events	10 (9)	5 (9)
Severe hypoglycemic events		
No. of severe hypoglycemic events	1	1
Participants with ≥1 severe hypoglycemic events	1 (1)	1 (2)
Diabetic ketoacidosis events		
No. of diabetic ketoacidosis events	1	0
Participants with ≥1 diabetic ketoacidosis events	1 (1)	0

RESULTS:

- Time in Range (70-180 mg/dL): increased by 3.6H/day to 72%.
- **Time in hyperglycemia (above 10 mmol/l): fell 3.6 hours per day, from 43% to 28%.**
- **two fewer hours per day in severe hyperglycemia (above 250 mg/dL).**

CONCLUSION:

Among adults with poorly controlled type 2 diabetes treated with basal insulin without prandial insulin, CGM, as compared with BGM monitoring, resulted in significantly lower HbA1c levels at 8 months.

Martens T et al. JAMA. 2021;325(22):2262-2272

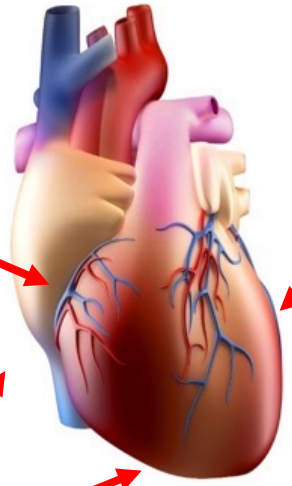
Impact of hypoglycemia : Take home message ADA 2021

Coronary arteries:

Endothelial dysfunction

Calcification

Atherosclerosis



Cardiac muscle:

Specific heart disease (cardiomyopathy)

Diastolic and systolic dysfunction

Autonomic nerves:

Neuropathy

Impaired coronary vasomotor capacity

- Hypoglycaemia is a common adverse effect of insulin and sulphonylureas.
- Severe hypoglycemia are associated with increased mortalité in T1D + T2D
- Sympathoadrenal activation in response to hypoglycaemia has haemodynamic, and electrophysiological effects (LVFE, bradycardia at night).
- Prevention of hypoglycaemia is key --> of IAH in T2D and T1D
- New technologies, such as real-time continuous glucose monitoring and insulin pumps, might also help.

Modified from: Retnakaran & Zinman, Lancet 2008; 371:1790-99

PLAN

- Living with diabetes
- New Insulins on the market
- Recent data about insulin initiation, use and adverse events
- **Clinical practice : what will change in 2021**

Prior to insulin start

- Clinical situation (physiopathology, c
  - Contraindication to anti-diabeti
  - Diabetic decompensatio
- Human F
  - Dia
  - Adju
  - Clinic
  - Diabet ation, training and support
- Insulin mar ment
  - **Patient autonomy**
  - Dosage et follow up
  - Periodic reassessments

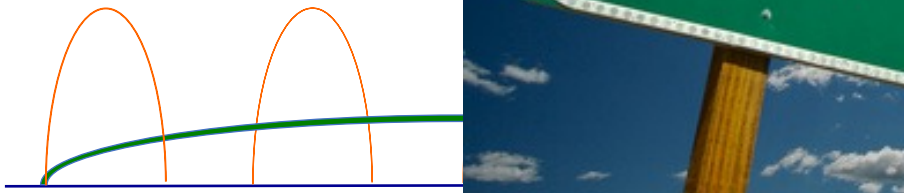
Never forget in the hierarchy of diabetes management that the aim of therapy is :

1. Symptomatic relief
2. Glucometabolic control
3. Vasculometabolic control

Diabetes self management : a full time job !

4-7 Glycémies/j

CGM use > 75%



8h

Insulinothérapie maitrisée

Primary (Level 1) education

At diagnosis: Survival skills

1. Explanation of how the diagnosis has been made and reasons for symptoms.

Secondary (level 2) education

Continuing curriculum

1. Pathophysiology, epidemiology, classification and metabolism.

etion, action and physiology.

tions, types, absorption, action profiles, nd adjustments.

food plans; qualitative and quantitative take of carbohydrate, fat, proteins and g with special events and eating out; weight gain; "diabetic foods"; sweeteners

including HbA_{1c} and clear (agreed) tar- rol.

mia and its prevention, recognition and nt including glucagon.

t illness, hyperglycaemia, ketosis and f ketoacidosis.

lving and adjustments to treatment.

ar and macrovascular complications and tion. The need for regular assessment.

liday planning and travel, including edu- idays and camps.

cohol and drugs.

ege, employment and driving vehicles.

ntraception, pregnancy and childbirth

research.

Educational skills : IDF

Advanced skills