CLASS

conference learning and scientific sharing program

at the

European Association
for the Study
of Diabetes
50th Annual Meeting

September 15-19, 2014

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Speaker Conflict of Interest Disclosure

- Consultant or speaker for:
  - NovoNordisk, Eli Lilly, Merck, Astra Zeneca, Sanofi, BD, Servier, Janssen.
- Received grant/research support from:
  - NovoNordisk, Eli Lilly, Merck, Sanofi, Eisai, Astra Zeneca, Servier.
- Received honoraria from:
  - NovoNordisk, Eli Lilly, Merck, Astra Zeneca, Sanofi, BD, Servier, Janssen.
- Received financial support from Novo Nordisk Canada Inc to attend the 50th annual meeting of the European Association for the Study of Diabetes in Vienna, Austria, September 15-19, 2014

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Relating to CLINICAL SCIENCE & CARE, presented at EASD 2014:

A Majority of Women with GDM Could Benefit from Oral Hypoglycemic Agents:

Successful glycemic control in > 60% of women taking mild doses of metformin-glyburide, with neonatal outcomes comparable to women on insulin therapy

PS 093-1094 – Gestational Diabetes Mellitus: The First Prospective Randomised-controlled Study of Metformin-Glyburide vs. Insulin

By Ardilouze J-L, Ménard J, Hivert M-F, et al

Objective(s): To assess maternal glycemic control and neonatal issues in a group of GDM women treated with metformin-glyburide combination vs. insulin

GDM = gestational diabetes mellitus

Results at Study Entry

At study entry*	Met–Gly (n = 35)	Insulin (n = 33)
Weeks of gestation	29.3 ± 3.8	30.1 ± 3.1
Age (years)	31.1 ± 4.7	30.7 ± 4.4
Weight (kg)	85.3 ± 17.5	85.3 ± 22.9
BMI (kg/m^2)	32.0 ± 5.4	32.2 ± 7.2
A1C (%)	5.5 ± 0.4	5.3 ± 0.3
Gravida/Para/Aborta	3 / 1 / 1	3 / 1 / 1
Glycemic control 2 weeks prior to study entry (mmol/L)		
Fasting 2-hr pc breakfast 2-hr pc lunch 2-hr pc supper	5.3 ± 0.7 6.3 ± 0.8 6.6 ± 0.8 6.8 ± 0.8	5.3 ± 0.6 6.3 ± 0.7 6.4 ± 0.6 6.8 ± 0.9

*All p = NS
Met-Gly = metformin-glyburide; BMI = body mass index; NS = not significant

Ardilouze J-L, et al. PS 093-1094, presented at the 2014 EASD
Reviewed by Dr. Joanne Liutkus

Results at Delivery

At delivery*	Met–Gly (n = 35)	Insulin (n = 33)
Glycemic control 2 weeks prior to study entry (mmol/L)		
Fasting 2-hr pc breakfast 2-hr pc lunch 2-hr pc supper	4.7 ± 0.3 5.8 ± 0.4 5.8 ± 0.5 6.0 ± 0.5	4.8 ± 0.3 5.9 ± 0.5 5.9 ± 0.5 6.1 ± 0.5
Hypoglycemias (< 3.3) (n and %)	11 (32.4)	2 (6.3)
Weight gain (kg)	12.4 ± 6.4	12.9 ± 4.5
Insulin doses (units)		
Breakfast Lunch Supper Bedtime	7.0 ± 4.2 8.5 ± 4.9 11.0 ± 4.2 11.0 ± 7.1	11.3 ± 9.0 9.6 ± 8.1 10.3 ± 6.8 18.7 ± 15.1

*All p = NS except for hypoglycemias $p < 0.01$

Ardilouze J-L, et al. PS 093-1094, presented at the 2014 EASD
Reviewed by Dr. Joanne Liutkus

Medications of Women in the Met–Gly Group at Delivery

N (%) of women	Met (mg/day)	Gly (mg/day)	Insulin (units)
8 (22.9)	844 ± 268		
14 (40.0)	1,179 ± 153	3.9 ± 1.9	
10 (28.6)	1,333 ± 250	8.6 ± 2.2	12.7 ± 9.9
3 (8.6)			9.4 ± 4.4

- In the 13 women taking insulin (37.2%), injections were started 4.2 ± 2.1 weeks after initiation of Met–Gly treatment

Ardilouze J-L, et al. PS 093-1094, presented at the 2014 EASD
Reviewed by Dr. Joanne Liutkus

Neonatal Issues

Neonatal issues*	Met (n = 35)	Insulin (n = 33)
Caesarean sections (n)	9	8
Neonates' weight (g)	3,360 ± 389	3,227 ± 570
Gestational age (weeks)	38.7 ± 1.1	38.4 ± 1.5
Hypoglycemias (n and %)	21 (60)	15 (45)

*All p = NS

Discussion & Implications

- Take-home messages:
  - evidence for alternatives to insulin for women with GDM
  - cost implications: OADs, insulin, OADs + insulin
  - increased risk of hypoglycemia with Met-Gly combination: clinical significance?
- Consider:
  - timing of delivery for obstetricians
  - home births
  - midwife-assisted deliveries
  - long-term effects of Met-Gly

OADs = oral antidiabetic drugs

Ardilouze J-L, et al. PS 093-1094, presented at the 2014 EASD
Reviewed by Dr. Joanne Liutkus

Assessing the Impact of Diabetes on Heart Failure with Preserved Ejection Fraction (HFpEF)

OP 08-045 – Impact of Diabetes Mellitus on Long-term Prognosis in Patients with Preserved Heart Failure: A Report from the Swedish Heart Failure Registry (S-HFR)

By Johansson I, Edner M, Rydén L, et al

Objective(s): To investigate the impact of diabetes on long-term prognosis in patients with heart failure and preserved left ventricular function from an everyday life perspective

Heart Failure Preserved Ejection Fraction (HFpEF): Background

- In the general population, prevalence of heart failure is 2% (10% after 70 years old), diabetes is 8%[1]
  - prevalence of 30% of patients with HF have type 2 diabetes

Clinical characteristics:

- High age
- Female gender
- Hypertension
- Obesity
- Diabetes

Diagnostic criteria:

1. Symptoms
2. Signs
3. Normal/mildly reduced left ventricular EF (≥ 40 or ≥ 50%)
4. Relevant structural heart disease* and/or diastolic dysfunction

*Left ventricular hypertrophy / left atrium enlargement

[1]McMurray JJ et al. Eur Heart J 2012; 33(14):1787-847

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin

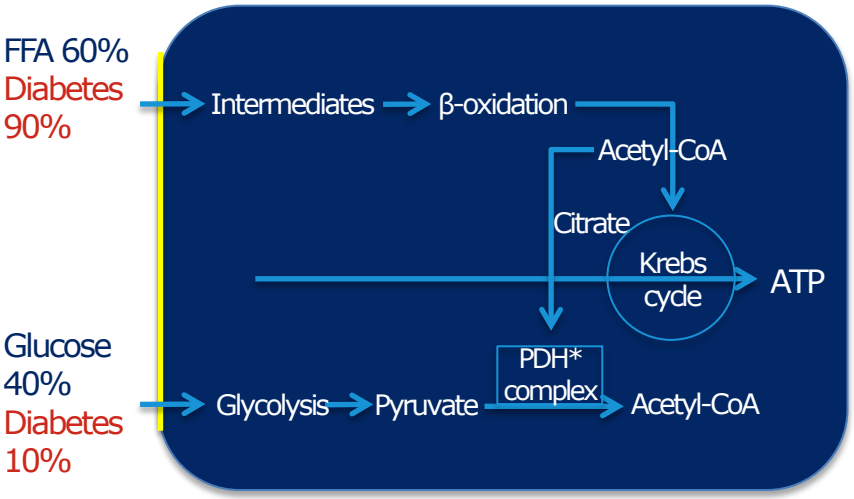
Heart Failure in Diabetes

- Causes of heart failure in diabetes:
  - co-morbidities
  - diabetes cardiomyopathy
    - more myocardial fibrosis and hypertrophy
    - different myocardial metabolism

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin

Diabetes Cardiomyopathy

- Deranged metabolism:
  - FFA use (oxydation) 90% vs. 60% in patients without diabetes mellitus
  - glucose use (oxydation) 10% vs. 40% in patients without diabetes mellitus
- Many diabetes mellitus patients do not have artery stenosis more than 50%, but:
  - microangiopathy disease
  - platelet hypereactivity
  - endothelial dysfunction



*PDH = pyruvate dehydrogenase; FFA = free fatty acid; ATP = adenosine triphosphate

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin

Prognosis in Diabetes Mellitus and HFpEF

- Worse prognosis in T2DM, regardless of EF
  - CHARM trial[1]: even with preserved EF, mortality at 3.5 years is 20% vs. 40% with reduced EF
    - n = 7,599; diabetes mellitus in 28%
    - diabetes mellitus: mortality predictor in HFpEF (HR 2.00)
- In S-HFR, better survival in patients without diabetes mellitus:
  - adjusted OR 1.39 (1.20–1.61)

T2DM = type 2 diabetes mellitus; HR = hazard ratio; OR = odds ratio

[1]MacDonald et al. Eur Heart J 2008; 1377-85

S-HFR Conclusions

- In 30,697 patients with T2DM, EF ≥ 50% (61% male, 39% female):
  - 25% of patients with HFpEF have type 2 diabetes
  - diabetes is an independent predictor of mortality even after adjustment of co-morbidities
  - co-morbidities common
    - 50% reported ischemic heart disease
    - 68% reported hypertension

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin

Telephone Intervention May Enhance Adherence to Insulin Therapy by Offering the Opportunity to Customize Information to Individuals Under Real-world Conditions

PS 075-941 – Adherence to Insulin Treatment in Insulin Naïve Type 2 Diabetic Patients: Results of Telephonic Intervention

By Gogas Yavuz D, Bilen H, Sancak S, et al

Objective(s): To assess the efficacy of phone-based support on insulin treatment adherence in insulin-naïve type 2 diabetic patients using different insulin treatment regimens (basal, basal-bolus and premix) in third-care medical centres in Turkey

Methods

- 12-week, open-label, randomized multicentre study
  - n = 1,456 insulin-naïve patients
- Randomized to standard of care of telephonic intervention (TI)
- Primary outcome: insulin treatment adherence
- TI group received 1 call every month with a detailed series of standardized questions
- Standard-of-care group received 1 call at the end of 12 weeks

Basal Demographic and Glycemic Parameters in Patients Adherent and Non-adherent to Insulin Treatment

	Adherent Group (n = 224)	Non-adherent Group (n = 1,232)	*P*
Age (yrs)	57 ± 13	56 ± 11	0.7
Duration of diabetes (yrs)	4.9 ± 6.9	6.6 ± 6.2	0.0001
Insulin dosage (IU/d)	31.5 ± 18	31.5 ± 19	0.9
FPG (mg/dL)	231 ± 83	231.7 ± 85	0.9
PPG (mg/dL)	298 ± 96	300 ± 111	0.8
A1C (%)	10 ± 2	10.5 ± 2	0.01

IU = international unit; FPG = fasting plasma glucose; PPG = postprandial glucose

Gogas Yavuz D, et al. PS 075-941, presented at the 2014 EASD
Reviewed by Lori Berard, RN

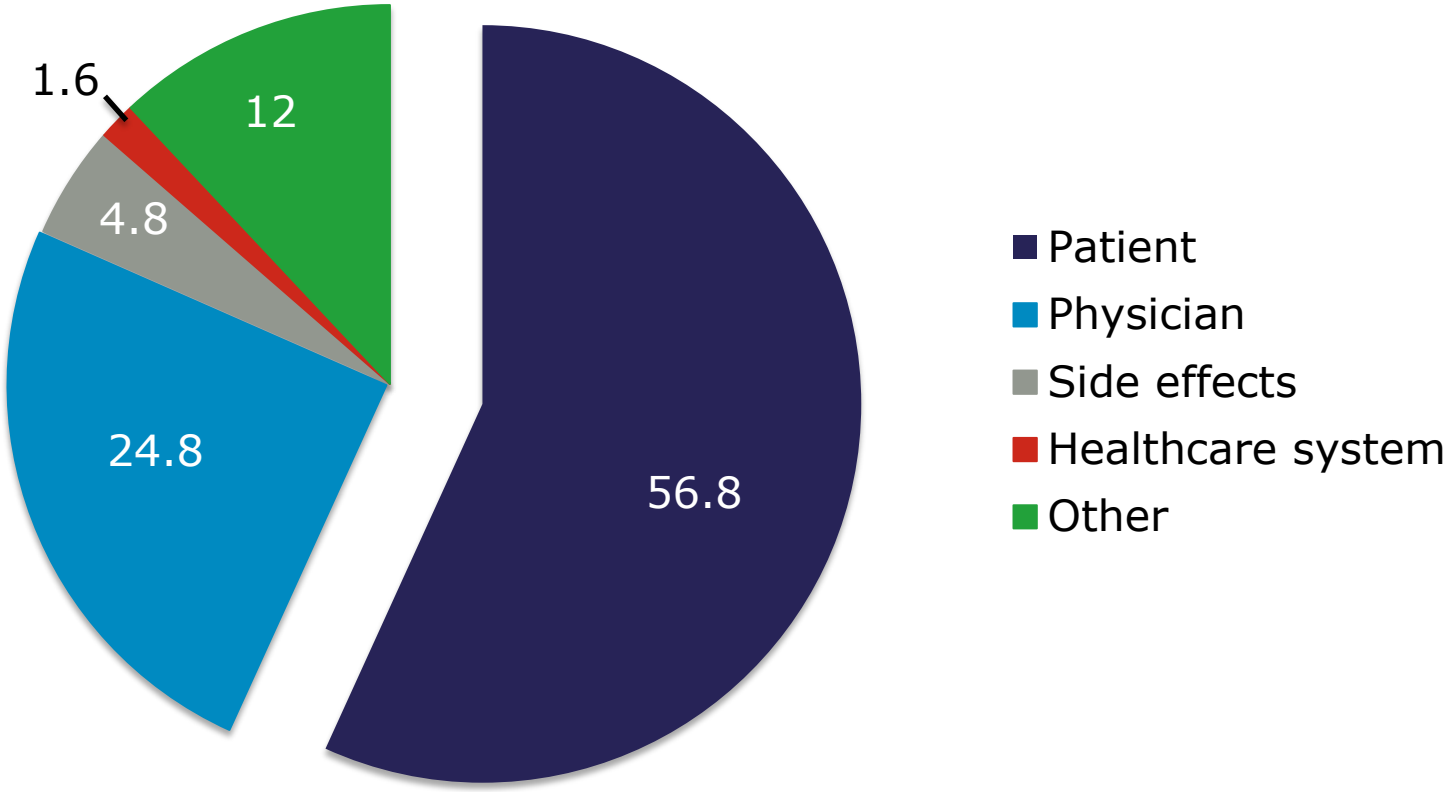
Insulin Injection Drop-off Rates According to Insulin Treatment Regimen

			Insulin Treatment Regimen			Total
			Basal Bolus	Premix	Basal	
Drop off at least 1 injection in a week	yes	n	81	71	52	204
		%	***27.0%**	15.0%	15.8%	18.5%
	no	n	219	401	277	897
		%	73.0%	85.0%	84.2%	81.5%
Total			300	472	329	1,101

*$p < 0.001$ vs. premix and basal group

Gogas Yavuz D, et al. PS 075-941, presented at the 2014 EASD
Reviewed by Lori Berard, RN

Reported Causes of Dropout for Insulin Therapy



Gogas Yavuz D, et al. PS 075-941, presented at the 2014 EASD

Reviewed by Lori Berard, RN

Discussion & Implications

- Take-home messages:
  - TI group compliance was 83.2% vs. 70.3% in standard group
  - in addition to a standardized education module, telephone support provided by trained nurses improved adherence to all insulin regimens
  - significant barriers to adherence include physician attitudes
- Consider:
  - phone sessions ~20 minutes, adherence self-reported
    - need to understand the 80-question survey
  - basal-bolus might be too difficult for some, even with support
  - demonstrates need for self-management support
  - may help form insulin support programs for DECs and industry, as insulin starts move to community

DEC = diabetes education centre

Addition of GLP-1 Analogue May be Better than Initiating Insulin in Some Patients Failing Oral Agents

OP 07-038 – Efficacy and Safety of Once Weekly Dulaglutide vs Insulin Glargine in Combination with Metformin and Glimepiride in Type 2 Diabetes Patients (AWARD-2)

By Giorgino F, Benroubi M, Sun J-H, et al

Objective(s): To compare efficacy and safety of 2 doses of dulaglutide with insulin glargine in type 2 diabetes inadequately controlled with maximally tolerated doses of metformin and glimepiride

Dulaglutide is not approved for use in Canada

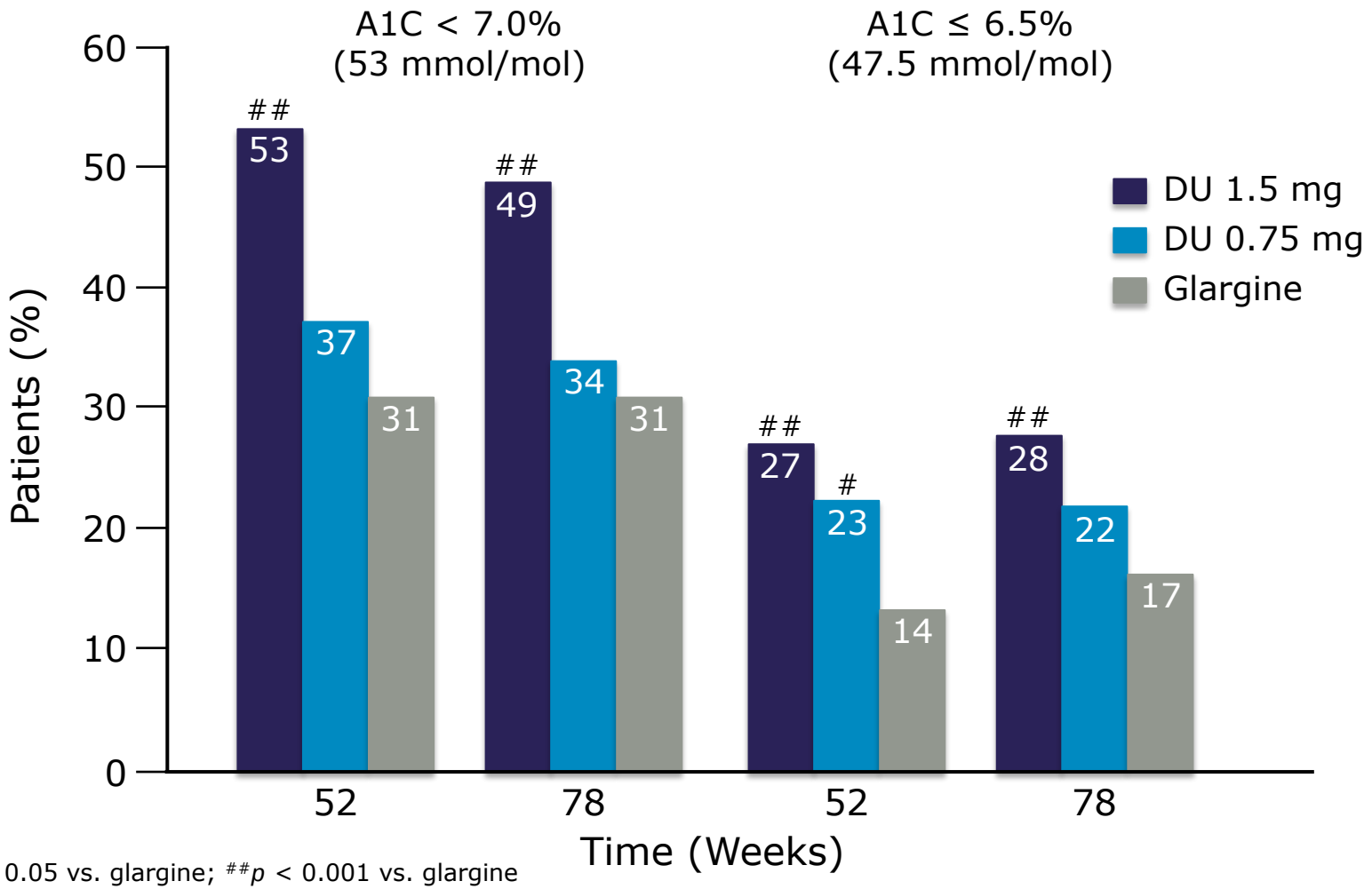
Baseline Characteristics

	DU 1.5 mg n = 273	DU 0.75 mg n = 272	Glargine n = 262
Sex, F, %	47	50	49
Age, years	56 (10)	57 (9)	57 (9)
BMI, kg/m^2	31 (5)	32 (5)	32 (6)
Duration of diabetes, years	9 (6)	9 (6)	9 (6)
A1C %	8.2 (1)	8.1 (1)	8.1 (1)
mmol/mol	66 (11)	65 (11)	65 (11)
Fasting serum glucose, mmol/L	9.2 (2.7)	9.0 (2.7)	9.1 (2.7)
Treatment at screening, %			
1 OAM	16.5	15.4	16.2
≥ 2 OAMs	83.5	84.6	83.8
At randomization			
Metformin dose, mg/day	2,379 (480)	2,412 (495)	2,419 (475)
Glimepiride dose, mg/day	6.3 (1.7)	6.3 (1.6)	6.2 (1.6)

Values shown are for mean (standard deviation [SD]) unless otherwise noted; intention to treat (ITT)
Dulaglutide is not approved for use in Canada
DU = dulaglutide; BMI = body mass index; OAM = oral antidiabetic medication

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala

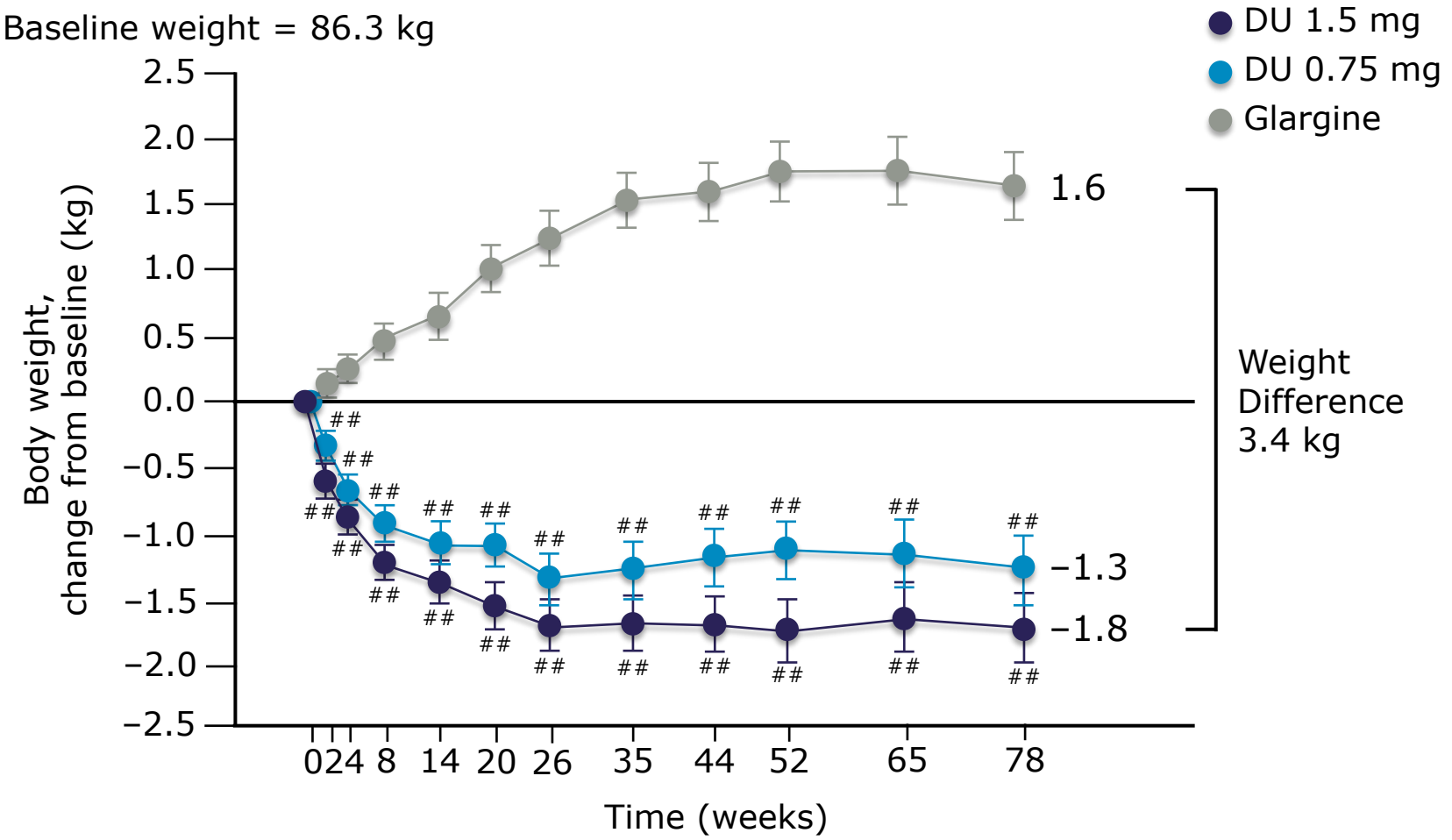
A1C Targets at 52 and 78 Weeks



#$p < 0.05$ vs. glargine; ##$p < 0.001$ vs. glargine
ITT logistic regression using last observation carried forward (LOCF) analysis
Dulaglutide is not approved for use in Canada

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala

Body Weight Change Over Time



Data presented are least squares [LS] means ± standard error [SE]
$^{##}p < 0.001$ vs. glargine
Dulaglutide is not approved for use in Canada
ITT, Mixed-effect Model Repeated Measure (MMRM) analysis

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala

Cumulative Adverse Events Through 78 Weeks

	DU 1.5 mg n = 273	DU 0.75 mg n = 272	Glargine n = 262
Any adverse event, n (%)	201 (73.6)	188 (69.1)	192 (73.3)
GI adverse event, n (%)			
Nausea	42 (15.4)##	21 (7.7)##	4 (1.5)
Diarrhea	29 (10.6)	25 (9.2)	15 (5.7)
Vomiting	18 (6.6)#	10 (3.7)	3 (1.1)
Severe hypoglycemia, n (%)	2 (0.7)	0 (0.0)	2 (0.8)
Injection-site reactions, n (%)	2 (0.7)	2 (0.7)	0 (0.0)
Adjudicated pancreatitis, n (%)	2 (0.7)	1 (0.4)	0 (0.0)
Pancreatic cancer, n	0	0	0

#$p < 0.05$ vs. glargine; ##$p < 0.001$ vs. glargine
Dulaglutide is not approved for use in Canada
GI = gastrointestinal

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala

Discussion & Implications

- Take-home messages:
  - insulin is generally considered to be best option for patients failing oral agents
  - in this study, addition of 0.75 mg dulaglutide QW is as effective as insulin glargine; 1.5 mg is superior to insulin glargine
    - both doses cause less hypoglycemia
  - insulin glargine is associated with weight gain, whereas both doses of dulaglutide caused weight loss
  - dulaglutide treatment was well tolerated with no significant increase in overall adverse reactions
  - addition of a GLP-1 analogue may be a better option than initiating insulin therapy in some patients failing oral agents
  - QW formulation of dulaglutide may be more acceptable to patients and may improve compliance
  - further studies are needed to show if effects on glycemic control, weight etc, compared to insulin are sustained

Dulaglutide is not approved for use in Canada
QW = once weekly; GLP-1 = glucagon-like peptide-1

Once-weekly Dulaglutide 1.5 mg Demonstrates Noninferior Glycemic Control Compared to Once-daily Liraglutide 1.8 mg, with a Similar Safety and Tolerability Profile

OP 07-040 – Efficacy and Safety of Once Weekly Dulaglutide Versus Once Daily Liraglutide in Type 2 Diabetes (AWARD-6)

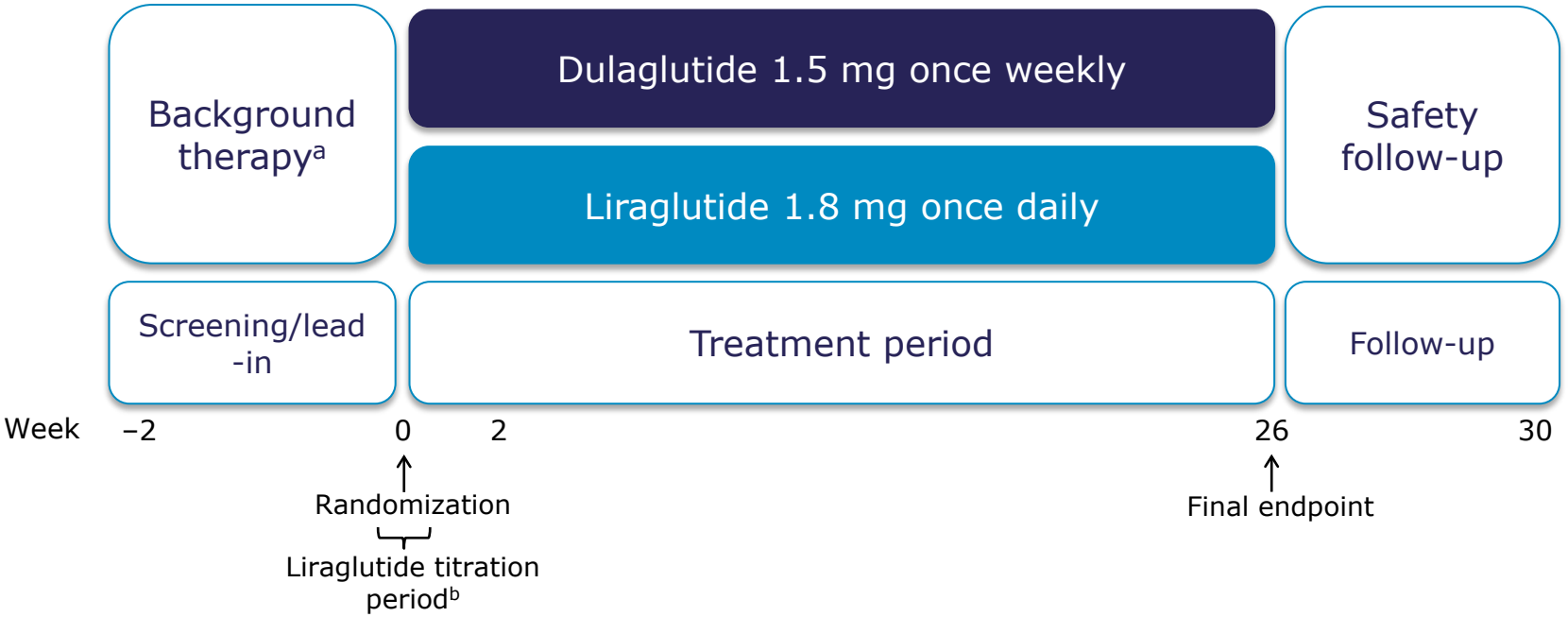
By Tofé Povedano S, Dungan KM, Forst T, et al

Objectives: To compare the efficacy and safety of once-weekly dulaglutide (DU) 1.5 mg with once-daily liraglutide (LIRA) 1.8 mg in metformin-treated (≥ 1,500 mg) patients with type 2 diabetes

Dulaglutide is not approved for use in Canada

Study Design

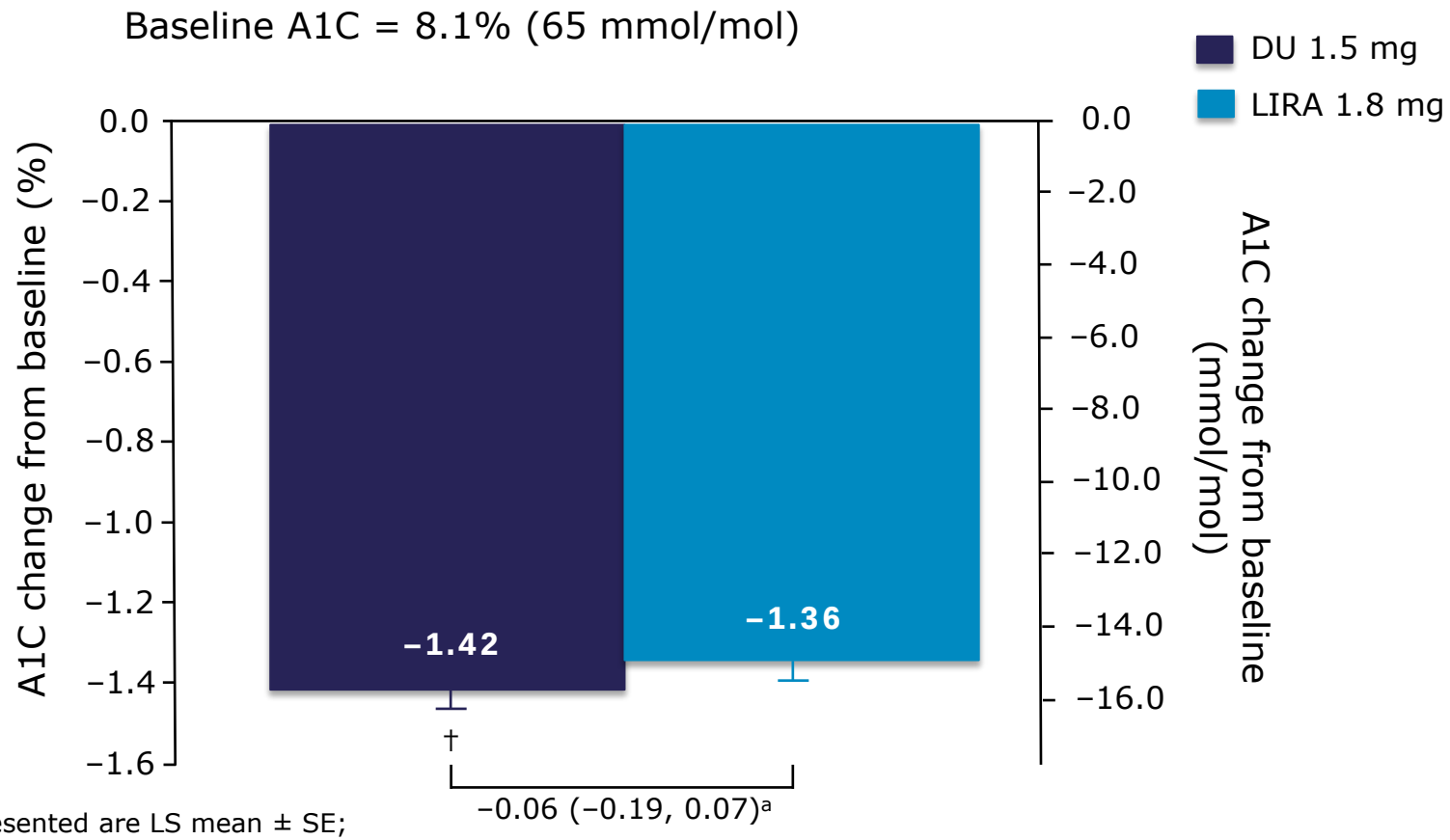
- Key inclusion criteria:
  - type 2 diabetes
  - A1C ≥ 7.0% (≥ 53 mmol/mol) and ≤ 10.0% (≤ 86 mmol/mol)
  - stable dose of metformin (≥ 1,500 mg/day) for ≥ 3 months



[a]Patients received metformin ≥ 1,500 mg/day throughout the study; [b]Patients randomized to liraglutide were initiated at a dose of 0.6 mg/day in Week 1 then up-titrated to 1.2 mg/day in Week 2 and 1.8 mg/day in Week 3
Patients who could not tolerate the full dose for the treatment duration were required to discontinue study drug
Dulaglutide is not approved for use in Canada
Dungan et al. Lancet 2014 (ahead of print)

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak

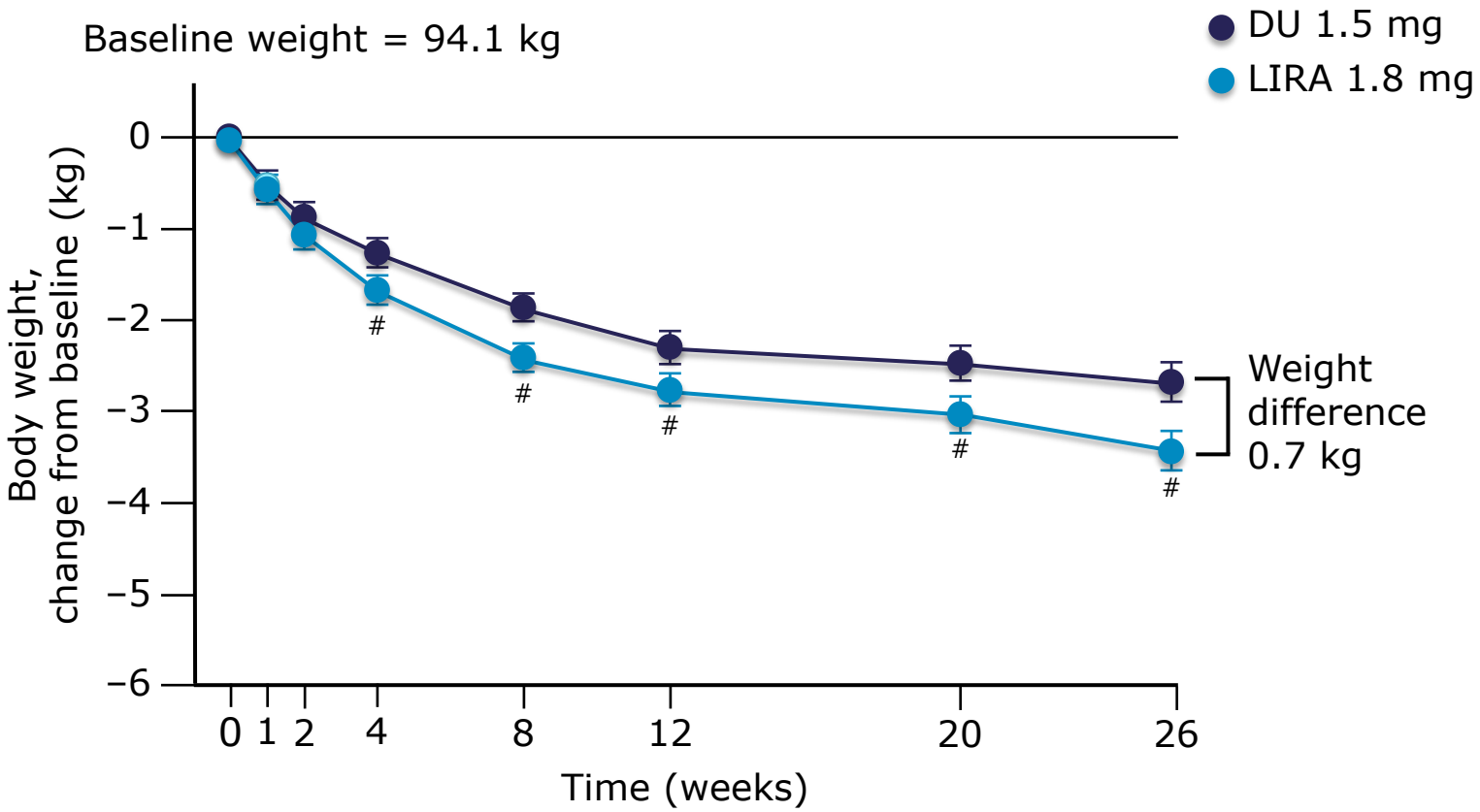
A1C Change from Baseline at 26 Weeks



Data presented are LS mean ± SE;
†$p < 0.001$, noninferiority vs. liraglutide; [a]Treatment difference (nominal 95% CI), ITT, MMRM analysis
Dulaglutide is not approved for use in Canada
LS = least squares; SE = standard error; CI = confidence interval; ITT = intention to treat; MMRM = Mixed-effect Model Repeated Measure
Dungan et al. Lancet 2014 (ahead of print)

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak

Body Weight Change Over Time



Data presented are LS means ± SE; #$p < 0.05$ vs. dulaglutide; ITT, MMRM analysis
Dulaglutide is not approved for use in Canada
Dungan et al. Lancet 2014 (ahead of print)

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak

Cumulative Adverse Events Through 26 Weeks

	DU 1.5 mg n = 299	LIRA 1.8 mg n = 300
Any AE, n (%)	185 (61.9)	189 (63.0)
GI adverse events, n (%) Nausea Vomiting Diarrhea Dyspepsia	107 (35.8) 61 (20.4) 21 (7.0) 36 (12.0) 24 (8.0)	107 (35.7) 54 (18.0) 25 (8.3) 36 (12.0) 18 (6.0)
Study/study drug discontinuations for GI AE	9 (3.0)	13 (4.3)
Hypoglycemia (≤ 3.9 mmol/L ± symptoms) Total (events/pt/year), mean (SD) Severe hypoglycemia	 0.02 (0.08) 0	 0.03 (0.17) 0
Injection-site reactions, n (%)	1 (0.3)	2 (0.7)
Adjudicated pancreatitis, n Pancreatic cancer, n	0 0	0 0

Dulaglutide is not approved for use in Canada
AE = adverse event; GI = gastrointestinal; SD = standard deviation
Dungan et al. Lancet 2014 (ahead of print)

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak

Discussion & Implications

- Take-home messages:
  - liraglutide is the current comparator for GLP-1 trials of QW products
  - dulaglutide has shown non-inferiority for glycemic control
  - liraglutide provides better weight loss
  - advantage of once-daily GLP-1 for patient compliance remains to be established
- Consider:
  - will probably have 2 QW analogues in next 12 months
  - some QW analogue preparations require reconstitution and special injection techniques

Dulaglutide is not approved for use in Canada
GLP-1 = glucagon-like peptide-1; QW = once weekly

Empagliflozin Improves Glucose Variability in Type 1 Diabetes

PS 076-956 – Sodium Glucose Co-transporter-2 (SGLT2) Inhibitor Empagliflozin in Type 1 Diabetes (T1D): Impact on Diurnal Glycemic Patterns

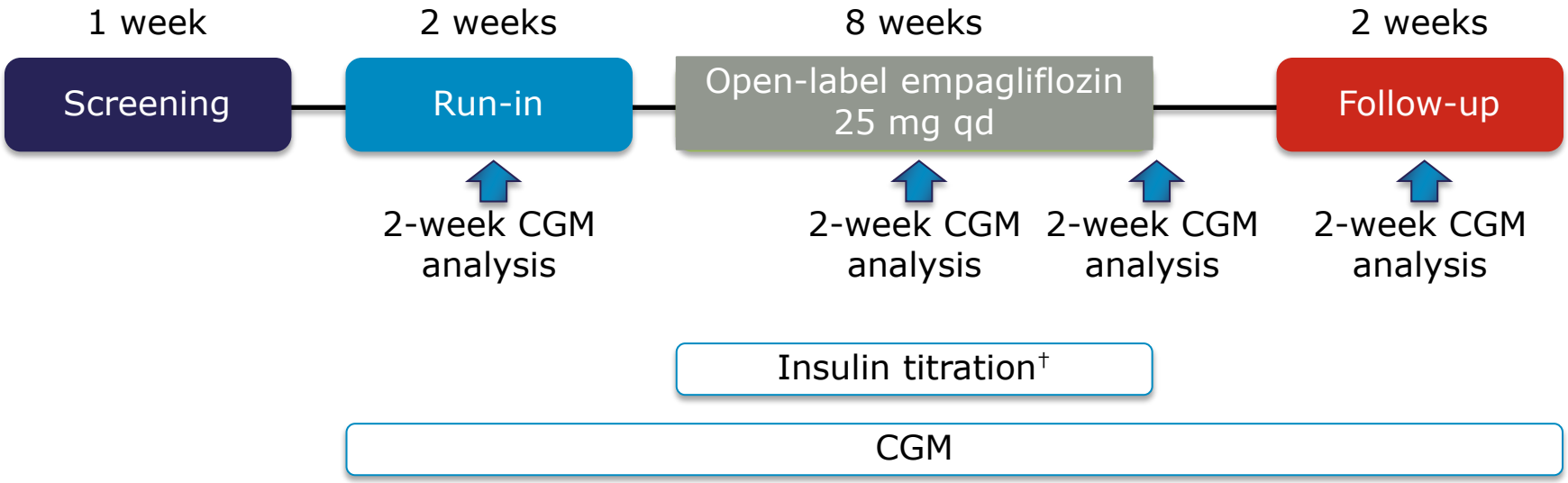
By Perkins B, Cherney D, Partridge H, et al

Objective: To assess how 8 weeks' treatment with empagliflozin as adjunct to insulin therapy in T1DM impacts diurnal CGM patterns, as well as time spent in hyper- and hypoglycemia

Empagliflozin is not approved for use in Canada
CGM = continuous glucose monitoring

Study Design

- Proof-of-concept study, 2 months in duration



†Basal and bolus insulin doses were reduced at onset of treatment with empagliflozin as recommended by the investigator and adjusted thereafter

Empagliflozin is not approved for use in Canada

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca

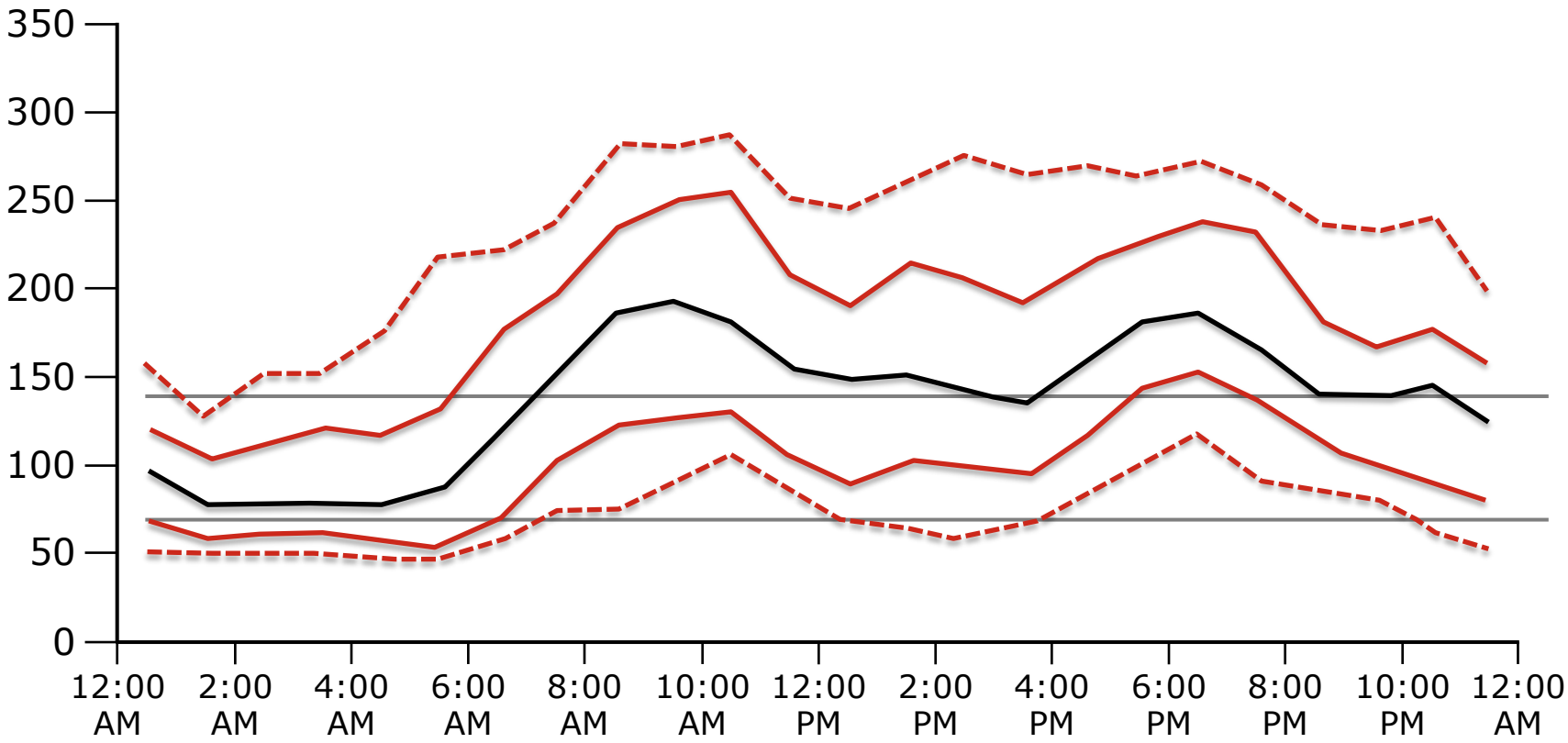
Study Cohort Characteristics

Clinical characteristics, n = 40	
Male sex (%)	20 (50)
Age (years)	24.3 ± 5.1
Diabetes duration (years) > 1 to 5 > 5	 4 (10) 36 (90)
Insulin regimen Insulin pump MDI	 26 (65) 14 (35)
Total daily insulin (U)	54.7 ± 20.4
BMI (kg/m^2)	24.5 ± 3.2
Urine albumin to creatinine ratio (mg/mmol)	1.2 ± 0.9
GFR_{INULIN} ($mL/min/1.73\ m^2$)	154 ± 33
A1C (%)	8.0 ± 0.9

Data are mean ± standard deviation (SD) or n (%)
Empagliflozin is not approved for use in Canada
MDI = multiple dose insulin; BMI = body mass index; GFR = glomerular filtration rate

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca

Visual AGP Display for a Single Subject

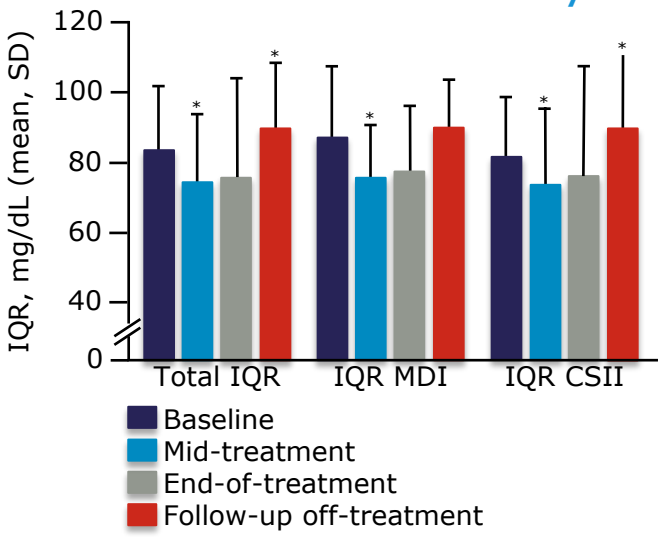


The visual AGP display (for a single subject) represents data collapsed over 24 hours where the median (black line) and percentiles are indicated (25th and 75th percentile in solid red, 10th and 90th in dotted red)
Empagliflozin is not approved for use in Canada
AGP = ambulatory glucose profile

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca

Time Spent at Various Glycemic Levels (%)

Glucose Variability



*p < 0.05 vs. baseline

Variables	Baseline	Mid-treatment	End-of-treatment	Follow-up off-treatment
Total (md/dL)				
% > 180	34.1 (14.4)	29.7 (13.4)	29.1 (14.9)	39.8 (15.7)
% > 140	54.8 (14.2)	53.4 (13.7)	51.6 (14.8)	60.0 (15.3)
% 70-140	40.2 (11.9)	42.0 (12.8)	43.1 (13.5)	35.0 (12.1)
% < 70	5.0 (4.6)	4.6 (4.0)	5.2 (6.4)	5.0 (4.9)
MDI (mg/dL)				
% > 180	32.6 (10.8)	32.2 (14.9)	27.8 (14.3)	41.5 (17.4)*
% > 140	51.5 (12.2)	54.1 (15.1)	49.2 (15.2)	60.9 (16.8)*
% 70-140	40.9 (7.1)	40.1 (12.4)	41.7 (12.2)	32.2 (11.2)*
% < 70	7.6 (6.2)	5.8 (5.4)	9.1 (9.4)	6.9 (6.5)*
CSII (mg/dL)				
% > 180	34.8 (16.0)	28.5 (12.7)	29.8 (15.5)	38.9 (15.0)
% > 140	56.4 (15.0)	53.1 (13.2)	52.8 (14.8)	59.6 (14.7)
% 70-140	39.9 (13.8)	42.9 (13.1)	43.9 (14.2)	36.4 (12.5)
% < 70	3.7 (2.9)	4.0 (3.1)	3.3. (2.8)	4.0 (3.5)

Data are mean standard deviation (SD). Proportion of individual values for entire period. *p < 0.05 vs. baseline. Similar pattern as for % < 70 mg/dL was seen for % < 60 mg/dL in all categories with ranges: Total: 2.4–2.6%, MDI: 3.2-5.7%, CSII: 1.1–1.8%
Empagliflozin is not approved for use in Canada
IQR = interquartile range; CSII = continuous subcutaneous insulin infusion

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca

Discussion & Implications

- Take-home message:
  - empagliflozin x 8 weeks improved glycemic control, reduced incidence of hypoglycemic events, reduced insulin doses and weight, and improved glycemic variability in T1DM patients
- Considerations, limitations:
  - proof-of-concept, single-arm, open-label pilot study: short duration, small sample size
  - improved night-time glycemia more prominent than daytime
- Clinical implications:
  - too early to assess clinical impact in Canada
  - future research needed to prove safety
    - *e.g.*, degree of basal/short-acting insulin adjustment upon initiation/interruption of empagliflozin

Empagliflozin is not approved for use in Canada

Fixed-dose Combination of Empagliflozin/Linagliptin as Add-on to Metformin in T2DM Lowers A1C More than Either Agent Alone

OP 01-001 – Fixed-dose Combinations of Empagliflozin/Linagliptin for 52 Weeks as Add-on to Metformin in Subjects with Type 2 Diabetes

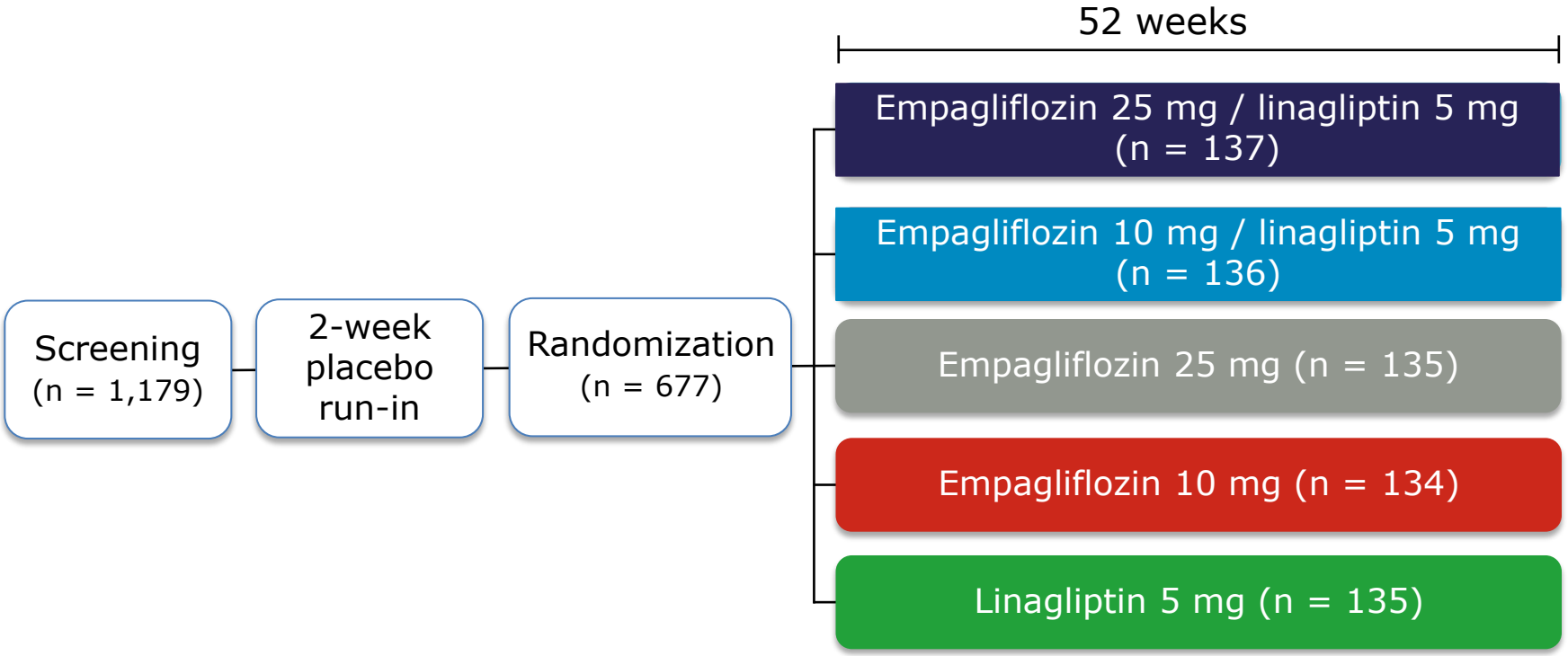
By De Fronzo RA, Lewin A, Patel S, et al

Objectives: To evaluate the efficacy and safety of fixed-dose combinations of empagliflozin/linagliptin as add-on to metformin in subjects with type 2 diabetes mellitus (T2DM)

Empagliflozin is not approved for use in Canada

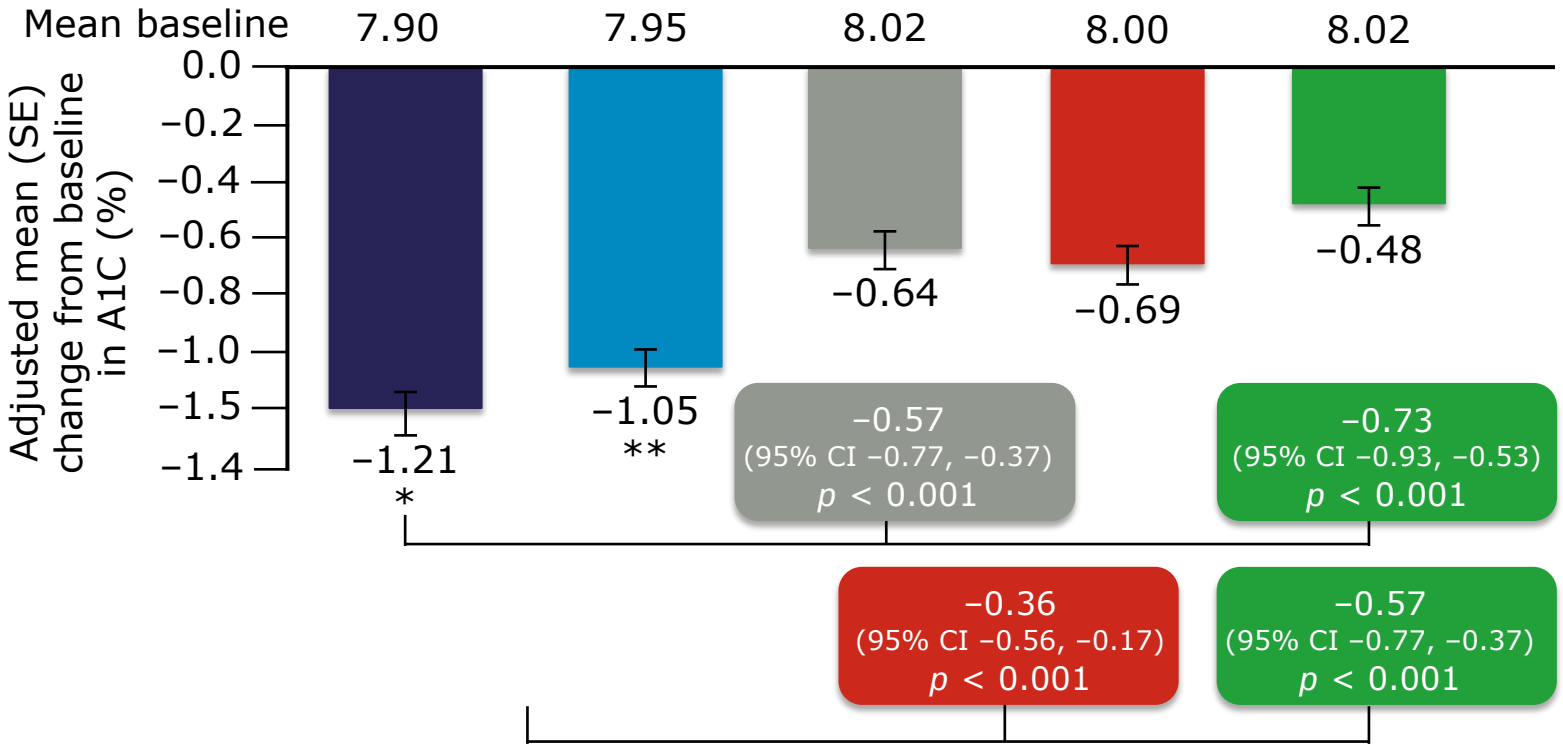
Study Design

- Phase III, double-blind, RCT in T2DM, BMI < 45 kg/m^2, eGFR > 60 mL/min/1.73 m^2, on metformin ≥ 1,500 mg/day



Empagliflozin is not approved for use in Canada
RCT = randomized control trial; BMI = body mass index; eGFR = estimated glomerular filtration rate

Change from Baseline in A1C at Week 52



*Significantly better ($p < 0.001$) vs empa 25 mg or lina 5 mg
**Significantly better ($p < 0.001$) vs empa 10 mg or lina 5 mg

ANCOVA in full analysis set with last observation carried forward (LOCF) imputation
Empagliflozin is not approved for use in Canada
SE = standard error; CI = confidence interval

De Fronzo RA, et al. OP 01-001, presented at the 2014 EASD
Reviewed by Dr. David Shu

Selected Adverse Events

	Empagliflozin 25 mg/ linagliptin 5 mg (n = 137)	Empagliflozin 10 mg/ linagliptin 5 mg (n = 136)	Empagliflozin 25 mg (n = 141)	Empagliflozin 10 mg (n = 140)	Linagliptin 5 mg (n = 132)
Urinary tract infection[a] Male Female	14 (10.2) 2 (2.7) 12 (18.8)	13 (9.6) 2 (2.4) 11(21.2)	19 (13.5) 2 (3.0) 17 (22.7)	16 (11.4) 3 (3.7) 13 (22.0)	20 (15.2) 3 (4.5) 17 (26.2)
Genital infection[b] Male Female	3 (2.2) 2 (2.7) 1 (1.6)	8 (5.9) 2 (2.4) 6 (11.5)	12 (8.5) 3 (4.5) 9 (12.0)	11 (7.9) 5 (6.2) 6 (10.2)	3 (2.3) 2 (3.0) 1 (1.5)
Volume depletion[c]	1 (0.7)	2 (1.5)	2 (1.4)	1 (0.7)	4 (3.0)
Hypersensitivity reactions[d]	1 (0.7)	1 (0.7)	0	0	1 (0.8)
Pancreatitis[e]	0	0	0	0	1 (0.8)

N (%) in subjects who received ≥ 1 dose of study drug
[a]Based on 77 preferred terms; [b]Based on 89 preferred terms; [c]Based on 8 preferred terms; [d]Based on 3 Standardized MedDRA Queries (SMQs); [e]Based on SMQ and 1 preferred term
Empagliflozin is not approved for use in Canada

De Fronzo RA, et al. OP 01-001, presented at the 2014 EASD
Reviewed by Dr. David Shu

Discussion & Implications

- Take-home messages:
  - combination therapy with empagliflozin /linagliptin 5 mg:
    - lowered A1C more than either as monotherapy
    - provides a simple, well-tolerated therapy that effectively lowers A1C, with minimal hypoglycemia and weight loss

Empagliflozin is not approved for use in Canada

Type II diabetes is a complex progressive disease involving many different disease pathways that requires early onset of novel combination therapy in order to maximize lowering of A1c while at the same time reducing the risk of hypoglycemia and weight gain.

Is there a role for early combination therapy in the management of patients with Type 2 diabetes?

By B. Zinman (CA)

Objectives: 1. To review the specific reasons why early combination therapy may be beneficial in Type 2 diabetes and 2. To review the evidence regarding effectiveness of different combination therapies.

B. Zinman. Astra Zeneca Symposium presented at the 2014 EASD
Reviewed by Dr. Joanne F. Liutkus

Specific reasons why early combination therapy may be beneficial in Type 2 diabetes

- Early robust lowering of A1c
- Avoidance of clinical inertia associated with a stepwise approach to therapy
- Potential for early combination therapy to impact Beta-cell function
- Initiation of a therapeutic intervention with a complementary mechanism of action
- Potential to use less than maximal doses of individual agents, minimizing side effect.

» Zinman B. Am J Med 2011; 124:S19-34

B. Zinman. Astra Zeneca Symposium presented at the 2014 EASD
Reviewed by Dr. Joanne F. Liutkus

Key Findings

1. The vast majority of patients with Type 2 diabetes eventually require combination therapy:

   50% of patients at 3 years; 75% of patients at 9 years

   Turner RC et al for the UKPDS Group (UKPDS 49) JAMA 1999; 281: 2005-12.

2. There is significant clinical inertia in response to inadequate glycemic control (A1c >8%): specialist and primary care physicians similar except when initiating insulin therapy

   Shah BR, et al Diabetes Care 2005; 28: 600-6

3. Secondary failure of metformin monotherapy is increased when initial A1c is $\geq$8%: approximately 19% per year.

   Brown JB, et al Diabetes Care 2010; 33: 501-6

Combination Therapy vs.. each as monotherapy

1. Metformin + SU:Hypoglycemia, weight gain, lack of durability.
   Morgan C et al J Clin Endocrinol Metab 2012; 97: 4605-12; Nathan DM et al. Diabetes Care 2009; 32: 193-203
2. Saxagliptin + Metformin: superior glycemic control
   Pfutzner A et al. Diab Obes Metab 2011; 13: 567-76.
3. Saxagliptin + Dapagliflozin+Metformin=superior
4. Sitagliptin + metformin: plus lower post meal glucose levels.
   Williams-Herman D, et al. Diab Obes Metab 2010; 12:442-51
5. Linagliptin + Metformin
   Hack T et al. Diab Obes Metab 2012; 14: 565-74
6. Metformin XR + Dapagliflozin: plus weight loss
   Henry RR et al. Int J Clin Pract 2012; 66:446-56
7. Exenetide BID + Metformin
   DeFronzo RA et al. Diabetes Care 2005; 28: 1092-100
8. Saxagliptin + Dapagliflozin
   Rosenstock J et al. presented at the ADA Congress 2014. Abstract #127-LB
9. Dapagliflozin + Insulin: reduction of insulin dosage by 20 units

B. Zinman. Astra Zeneca Symposium presented at the 2014 EASD
Reviewed by Dr. Joanne F. Liutkus

Discussion & Implications

- Take-home messages:
  - Good evidence that initiating dual therapy for new onset diabetes results in:
    - Improved glycemic control
    - Less hypoglycemia
    - Weight loss or no weight gain
    - Improved adherence
    - Cost effective
    - Reduced number of pills per day
    - Fewer SFX
  - No threshold for A1c as to when combination therapy should be initiated.
  - Need to educate both specialists and primary care providers of the importance of early, aggressive glycemic control
- Consider:
  - Impact on Canadian health care system.

B. Zinman. Astra Zeneca Symposium presented at the 2014 EASD
Reviewed by Dr. Joanne F. Liutkus

Questions, comments?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