Incretins and SGLT-2 Inhibitors in the Treatment of Diabetes.

March 18, 2017
American Diabetes Association
2017 Professional Diabetes
Education Conference

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Presenter Disclosure Information

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure :

Steven B. Magill, MD, PhD

Has disclosed no conflict of interest

Overview

- **Case.**
- **American Diabetes Association Guidelines-2016.**
- **Incretins.**
- **SGLT-2 inhibitors.**
- **Incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?**
- **Cardiovascular and renal outcomes.**
- **Case.**
- **History lesson.**

Case 1

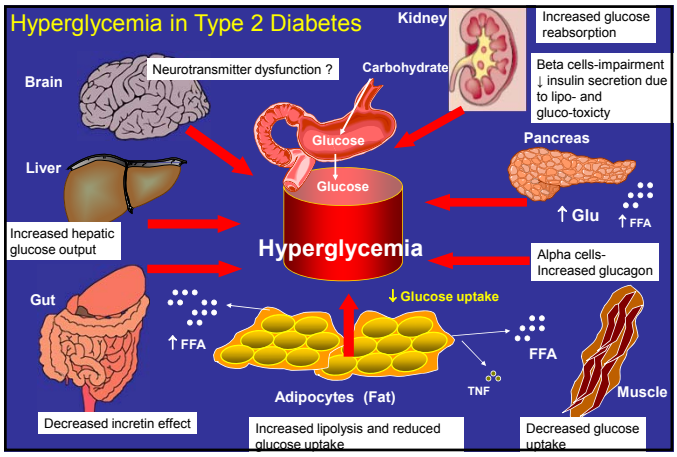
- A 58 year old man comes to the clinic for a diabetes visit.
- He was diagnosed with type 2 diabetes in 2007.
- The antiglycemic regimen:
  - Metformin, 1000 mg bid
  - Glimepiride, 4 mg/day
- The HbA1c in clinic is 9.3%.

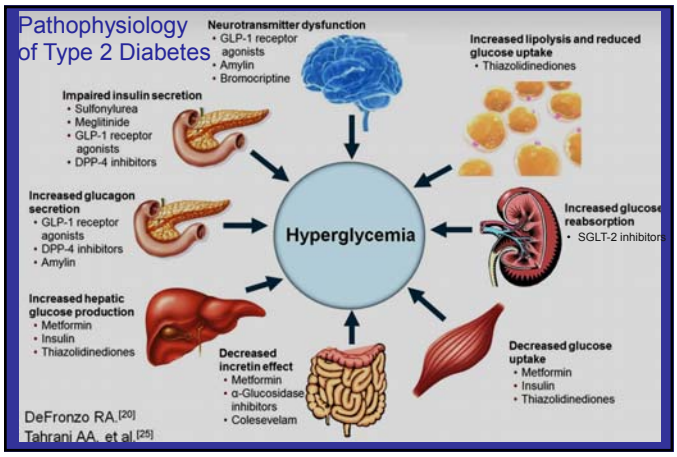
Case

- He has hypertension.
  - 20 mg of lisinopril/day
  - 25 mg of hydrochlorothiazide/day
- Dyslipidemia
  - 40 mg of atorvastatin/day
- Exam
  - Ht 70 inches (1.78 m), weight 247 pounds (112.3 kg), BMI 35.4, BP 140/84 mm Hg, p 78 bpm
  - He has central weight distribution without acanthosis nigricans

Steps in the Treatment of the Diabetes

- What is the goal HbA1c?
  - This needs to be discussed with each patient.
- Nutrition counseling.
- Exercise.
- Weight loss.
- He needs to be started on a third antiglycemic agent.
  - There are multiple medication classes available.





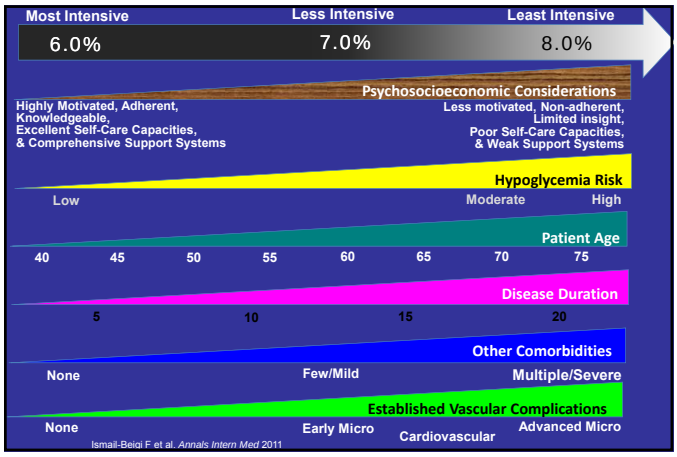
Traditional ADA Targets for Diabetes Treatment

Biochemical Index	ADA[1] Goal
HbA1c	<7.0%
Preprandial glucose†	90-130 mg/dL
Peak postprandial glucose†	<180 mg/dL

[1] American Diabetes Association (ADA)

*The 2007 American Diabetes Association (ADA) guidelines suggest that the A1c goal for the individual patient is an A1c as close to normal (< 6%) as possible without significant hypoglycemia.

† Based on measurements of plasma glucose



ANTI-HYPERGLYCEMIC THERAPY in Type 2 Diabetes

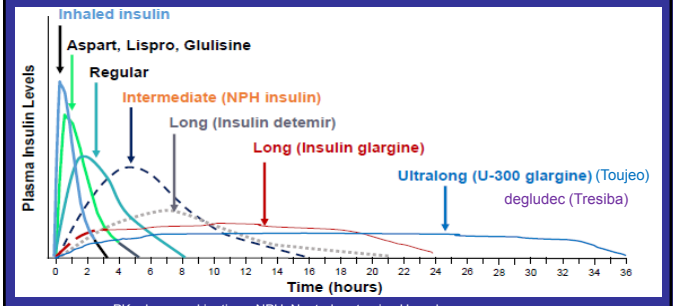
Therapeutic options:

Oral agents & non-insulin injectables

- Metformin
- Sulfonylureas
- Thiazolidinediones
- DPP-4 inhibitors
- GLP-1 receptor agonists
- SGLT-2 inhibitors
- Meglitinides
- α-glucosidase inhibitors
- Bile acid sequestrants
- Dopamine-2 agonists
- Amylin mimetics

Diabetes Care 35: 1364-1379, 2012. Diabetologia 55: 1577-96, 2012.

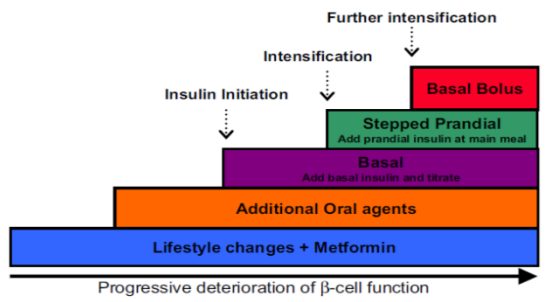
PK Profile of Available Insulins in the US



PK: pharmacokinetics. NPH: Neutral protamine Hagedorn

Adapted from Hirsh IB. *NEJM*. 2005;352:174-183. Flood TM. *J Fam Pract*. 2007;56(suppl 1):S1-S12. Becker RH, et al. *Diabetes Care*. 2014;pii:DC_140006. http://www.pdr.net/full-prescribing-information/afrezza?druglabelid=3540. Accessed April 5, 2015.

Step-Care Approach to Treatment with Insulin in Type 2 Diabetes



Leahy, JL. Endocrinol Clin N America. 41: 119-144, 2012.

Overview

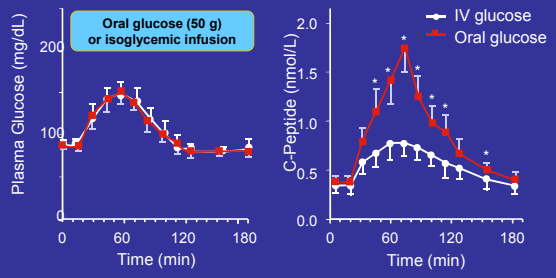
- Case.
- American Diabetes Association Guidelines-2016.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.

Incretins

- Gut peptides stimulated by nutrient ingestion.
- Favorable effects on glucose metabolism.
- Major human incretins[1,2]
  - Glucagon-like peptide-1 (GLP-1) √
  - Glucose-dependent insulinotropic polypeptide (GIP)

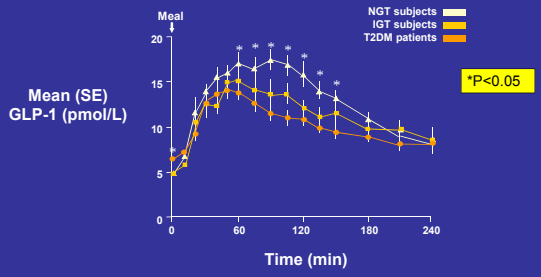
[1]Drucker DJ. Diabetes Educator. 32 (Suppl 2):65S-71S, 2006.
[2]Vilsbøll T, Holst JJ. Diabetologia. 47:357-366, 2004.

Incretin Effect - Difference in the Insulin Response to Oral vs IV Glucose



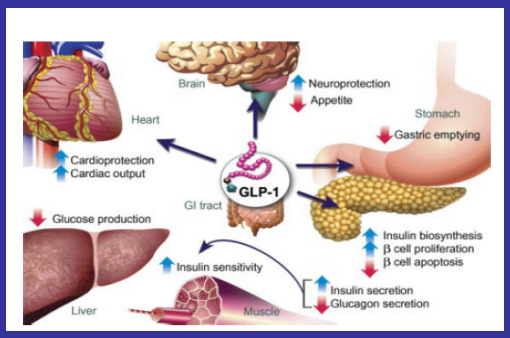
Adapted from Nauck MA, et al. *J Clin Endocrinol Metab* 1986;63:492-498.

Postprandial GLP-1 Levels are Decreased in Subjects With IGT and Type 2 Diabetes



Toft-Nielsen M, et al. J Clin Endocrinol Metab. 86:3717-3723, 2001.

GLP-1 Acts Directly on the Endocrine Pancreas, Stomach, Brain and Possibly the Heart.

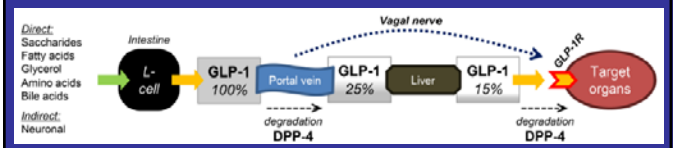


J Clin Endocrinol Metab, June 2009, 94(6):1843–1852

GLP-1 Agonists

- Augment insulin secretion.
- Decrease hepatic glucose output via inhibition of glucagon.
- Increase satiety.
- Weight loss of 5-7% in most patients.
- Delay stomach emptying.

Secretion and Metabolism of Glucagon-like Peptide-1 (GLP-1)



GLP-1 also indirectly affects target organs via stimulation of the vagus nerve in the portal vein.

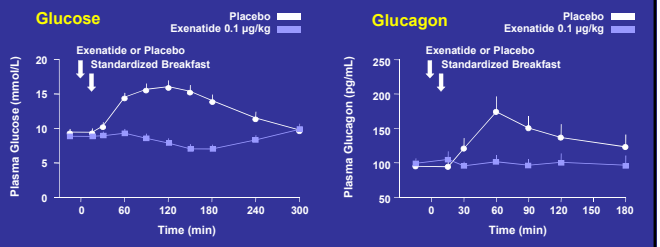
GLP-1 glucagon like peptide 1; DPP-4: dipeptidyl peptidase-4
GLP-1R: glucagon like peptide 1 receptor.

Smits MM. Gut 2016. 65:702-11.

Exenatide

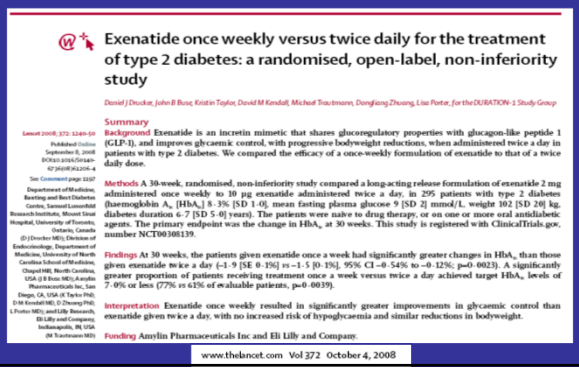
- Exenatide is the synthetic recombinant version of exendin-4.
- Exendin-4 was derived from the saliva of the Gila monster.

Effect of Exenatide on Postprandial Glucose and Glucagon in Type 2 Diabetes



Kolterman OG, et al. J Clin Endocrinol Metab. 88:3082-3089, 2003.

Extended Release Exenatide



Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study

Daniel J Drucker, John B Buse, Kristin Taylor, David M Kendall, Michael Trautmann, Dongfang Zhuang, Lisa Porter, for the DURATION-1 Study Group

Summary

Background Exenatide is an incretin mimetic that shares glucoregulatory properties with glucagon-like peptide 1 (GLP-1), and improves glycaemic control, with progressive bodyweight reductions, when administered twice a day in patients with type 2 diabetes. We compared the efficacy of a once-weekly formulation of exenatide to that of a twice daily dose.

Methods A 30-week, randomised, non-inferiority study compared a long-acting release formulation of exenatide 2 mg administered once weekly to 10 µg exenatide administered twice a day, in 295 patients with type 2 diabetes (haemoglobin A_{1c} [HbA_{1c}] 8·3% [SD 1·0], mean fasting plasma glucose 9 [SD 2] mmol/L, weight 102 [SD 20] kg, diabetes duration 6·7 [SD 5·0] years). The patients were naive to drug therapy, or on one or more oral antidiabetic agents. The primary endpoint was the change in HbA_{1c} at 30 weeks. This study is registered with ClinicalTrials.gov, number NCT00308139.

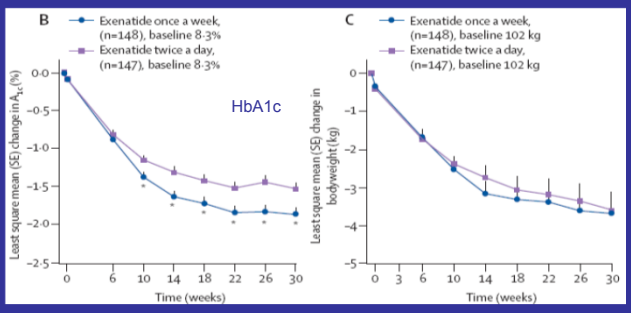
Findings At 30 weeks, the patients given exenatide once a week had significantly greater changes in HbA_{1c} than those given exenatide twice a day (−1·9 [SE 0·1%] *vs* −1·5 [0·1%], 95% CI −0·54% to −0·12%; p=0·0023). A significantly greater proportion of patients receiving treatment once a week versus twice a day achieved target HbA_{1c} levels of 7·0% or less (77% *vs* 61% of evaluable patients, p=0·0039).

Interpretation Exenatide once weekly resulted in significantly greater improvements in glycaemic control than exenatide given twice a day, with no increased risk of hypoglycaemia and similar reductions in bodyweight.

Funding Amylin Pharmaceuticals Inc and Eli Lilly and Company.

www.thelancet.com Vol 372 October 4, 2008

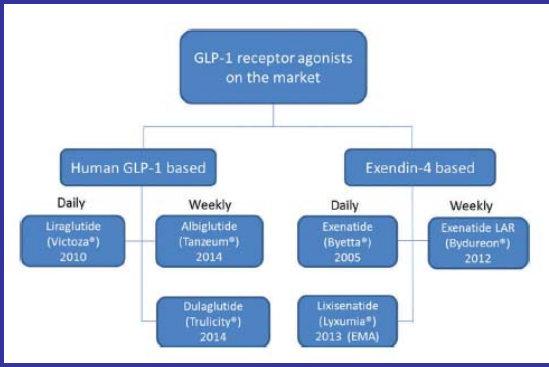
Change in HbA1c (B) and Body Weight (C) over 30 Weeks in Patients with Type 2 Diabetes Treated with Exenatide ER (2 mg) vs Exenatide (10 mcg bid).



Least square mean ±SE, intention-to-treat, n=295.

www.thelancet.com Vol 372 October 4, 2008

GLP-1 Analogs Available in the US

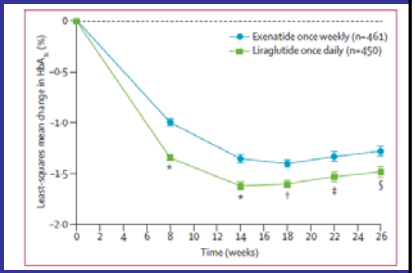


Liraglutide

- Liraglutide is a recombinant analog of human GLP-1.
- Close homology with native GLP-1.
- Has plasma half life of 13 hours.
- Administered sc once daily.
- Does not have to be timed before a meal.

Change in HbA1c With Liraglutide vs Exenatide LAR.

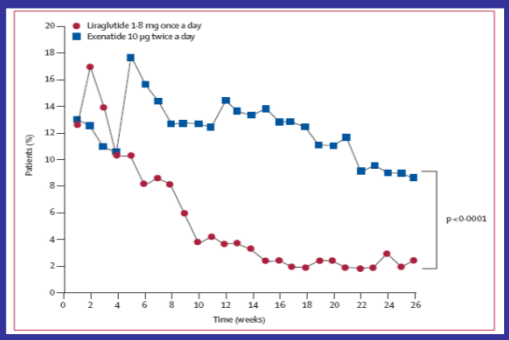
- Open-label randomized, parallel 26 week trial in patients with T2DM treated with oral anti-glycemic agents.
- 1.8 mg of liraglutide Qd vs 2 mg of exenatide LAR given once weekly.
- Liraglutide was more potent than exenatide LAR.



*p<0.0001. † p=0.0005. ‡ p=0.0012. § p=0.0018.

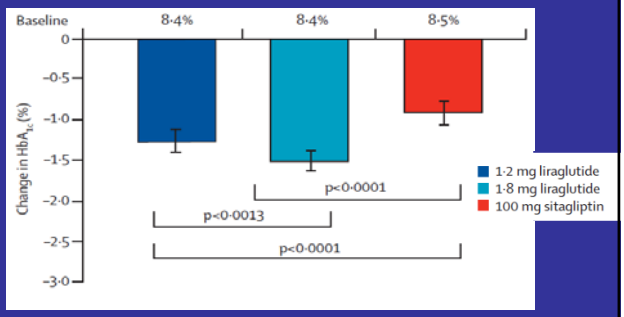
Buse JB, et al. Lancet. 381: 117-24, 2013.

Proportion of Patients who Develop Nausea



www.thelancet.com Vol 374 July 4, 2009

Change in HbA1c in Patients With T2DM Randomized to Liraglutide vs Sitagliptin.



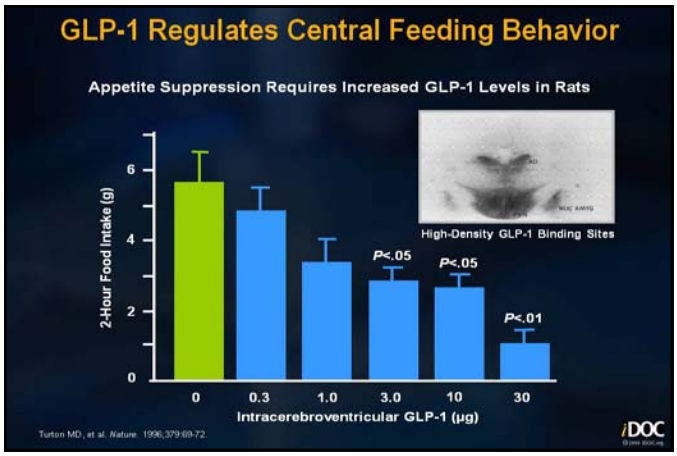
All patients were also treated with ≥1500 mg/day of metformin.

Pratley, RE, Nauck, M, et al. Lancet. 375: 1447-56, 2010.

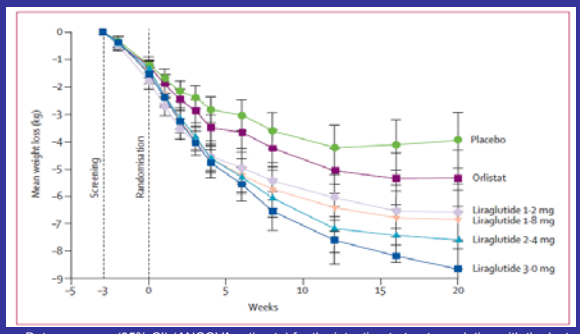
Liraglutide (Victoza)

- Available as a single pen for all doses.
- Start with 0.6 mg sc dose given once daily for the first week.
  - To reduce any GI side effects.
- After one week increase to the 1.2 mg per day dose.
- If the 1.2 mg dose is not effective:
  - The dose can be increased to 1.8 mg per day after several months.

GLP-1 Regulates Central Feeding Behavior



Change in Body Weight with Liraglutide



Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward. These data were used in part for FDA approval for Saxenda for obesity.

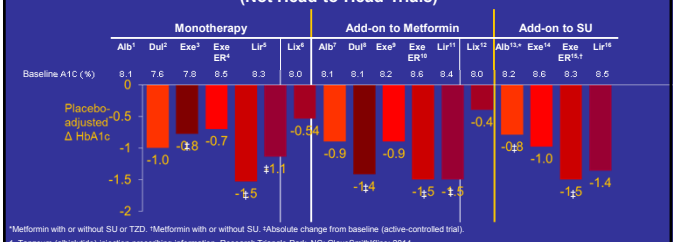
Astrup, A, et al. Lancet. 374: 1606-16, 2009.

GLP-1 Receptor Agonists

Generic Trade name	Exenatide (Byetta)	Liraglutide (Victoza)	Exenatide ER (Bydureon)	Dulaglutide (Trulicity)
1. Half-life 2. Administered	**2-4 hr bid**	**12-14 hr Qd**	**> 1 wk Once weekly**	**>1 week Once weekly**
↓ Fasting blood glucose	↓↓	↓↓↓	↓↓↓	↓↓↓
↓ Postprandial plasma glucose	↓↓↓	↓↓	↓↓	↓↓
↓ HbA1c (%)	**~0.7 -0.9**	**~1.1-1.6**	**~1.4 to 1.7**	~1.2 *to* 1.6%
Weight change (kg)	**Decrease 1-5 % of body weight (in some patients -even more)**			
Common adverse effects	**Nausea, other GI side effects**			

Glucose Control with GLP-1 Receptor Agonists

Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)



*Metformin with or without SU or TZD. †Metformin with or without SU. ‡Absolute change from baseline (active-controlled trial).

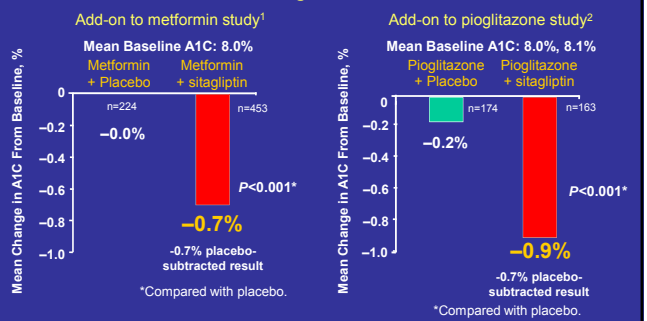
1. Tanzeum (albiglutide) injection prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2014. 2. Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176. 3. Moretto TJ, et al. *Clin Ther*. 2008;30:1448-1460. 4. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258. 5. Garber A, et al. *Lancet*. 2009;373:473-481. 6. Trautmann M, et al. *Diabetes Care*. 2013;36:2541-2547. 7. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 8. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 9. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 10. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 11. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 12. Rosenstock J, et al. *Diabetes Care*. 2013;36:2945-2951. 13. Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2014;2:289-297. 14. Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635.
15. Diamant M, et al. *Lancet*. 2010;375:2234-2243. 16. Marre M, et al. *Diabet Med*. 2009;26:268-278.

DPP-4 Inhibitors

- Prolong the action of native GLP-1 by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4).
- Oral agents.
- Less potent than GLP-1 analogs.
- Weight neutral.

Sitagliptin (100 mg/day): Effect on A1C When Added to Metformin or Pioglitazone

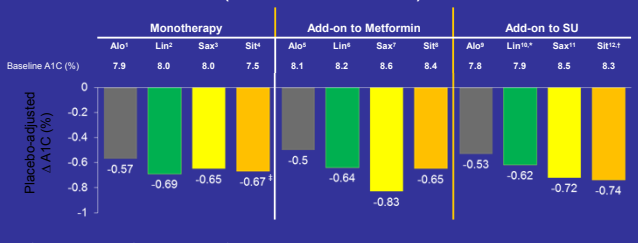
24-week change from baseline



Charbonnel B et al. Diabetes Care. 29:2638–2643, 2006. Rosenstock J et al. Clin Ther. 28:1556–1568, 2006.

Glucose Control with DPP-4 Inhibitors

Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)



*SU + metformin. †With or without metformin. ‡Absolute change from baseline (active-controlled trial).

1. DeFronzo RA, et al. *Diabetes Care*. 2008;31:2315–2317. 2. Del Prato S, et al. *Diabetes Obes Metab*. 2011;13:258-267. 3. Rosenstock J, et al. *Curr Med Res Opin*. 2009;25:2401-2411. 4. Nauck MA, et al. *Diabetes Obes Metab*. 2007;9:194-205. 5. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 6. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 7. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 8. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 9. Pratley RE, et al. *Diabetes Obes Metab*. 2009;11:167-176. 10. Owens DR, et al. *Diabet Med*. 2011;28:1352-61. 11. Chacra AR, et al. *Int J Clin Pract*. 2009;63:1395-1406. 12. Hermansen K, et al. *Diabetes Obes Metab*. 2007;9:733-745.

Comparison of DPP-4 Inhibitors

Generic Trade name	Sitagliptin Januvia	Saxagliptin Onglyza	Linagliptin Tradjenta	Alogliptin Nesina
Dosage	**25, 50, 100 mg once daily**	**2.5, 5.0 mg once daily**	**5 mg once daily**	**6.25 to 25 mg day**
24-h DPP-4 inhibition	**≈ 80%**	**5 mg: ≈ 55%**	**> 90%**	**>80%**
Elimination	**Kidney (mostly unchanged)**	**Liver and kidney active metabolite**	**Liver, <5% renal**	**Liver and kidney**
Dose adjustments for renal impairment	**50 mg eGFR<50 25 mg eGFR<30**	**2.5 mg eGFR<50**	**None**	**12.5 mg eGFR<60 6.25 mg eGFR<30**
Drug interaction potential	**Low**	**Strong CYP3A4/5 inhibitors**	**Strong CYP3A4/5 inhibitors**	**Low**

Safety Considerations with DPP-4 Inhibitors

GI adverse events	• Minimal
Pancreatitis	• Pancreatitis has been reported with postmarketing use of some of incretin agents, although no causal relationship has been established • Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents • Labeling for all incretins states these agents should be immediately discontinued if pancreatitis is suspected
Pancreatic cancer	• Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents • Further assessments required from long duration-controlled studies or epidemiological databases
Renal impairment	• Kidney function monitoring and dose reduction required for alogliptin, saxagliptin, and sitagliptin when used in patients with moderate-to-severe renal impairment • Linagliptin does not require dose adjustment or periodic monitoring of drug-related kidney function
CHF	• Potentially increased risk of congestive heart failure hospitalization with alogliptin and saxagliptin

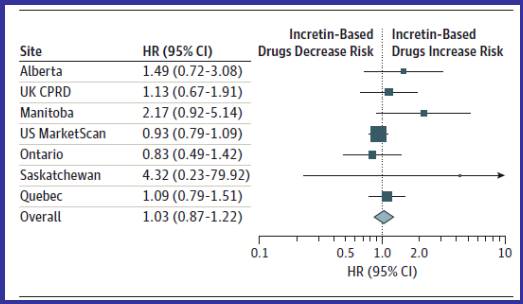
Garber AJ, et al. *Endocr Pract*. 2016;22:84-113. White W, et al. *N Engl J Med*. 2013;369:1327-1335. Scirica BM, et al. *Circulation*. 2014;130:1579-1588. ADA/EASD/IDF statement concerning the use of incretin therapy and pancreatic disease [news release]. Alexandria, VA: American Diabetes Association, European Association for the Study of Diabetes, International Diabetes Federation; June 28, 2013. http://www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html.

Pancreatitis and Incretins: Is There a Link?

- Pancreatitis first reported by the FDA in 2006 in patients treated with exenatide.
- The first FDA report of pancreatitis associated with sitagliptin was announced in 2009.
- Subsequent studies:
  - Exenatide:
    - No relationship found between use of exenatide and the risk of pancreatitis.
      - » Dore, DD, et al. Curr Med Res Opin. 25: 1019-27, 2009.
      - » Dore, DD, et al. Diabetes Obes Metab. 13: 559-66, 2011.
  - Sitagliptin:
    - No increased risk of pancreatitis in patients treated with sitagliptin.
      - » Engel SS, et al. Int J Clin Pract 64: 984-90, 2010.

Disclosure: These three studies were sponsored by industry.

The Risk of Acute Pancreatitis in Patients With Type 2 DiabetesTreated with Incretins



Large International nested case control study of 1,532,513 patients with type 2 diabetes treated with incretins between 1/1/2007 and 6/30/2013.

Azoulay, L, et al. JAMA Intern Med. 2016.1522 published online August 1 2016.

Incretins and Pancreatitis

- Association does not equal causation.
- However, use caution in prescribing incretins in the following situations:
  - Prior history of pancreatitis.
    - Especially if possibly induced by an incretin.
  - Active cholelithiasis.
  - Alcohol dependency.
  - Triglycerides >1000 mg/dl.

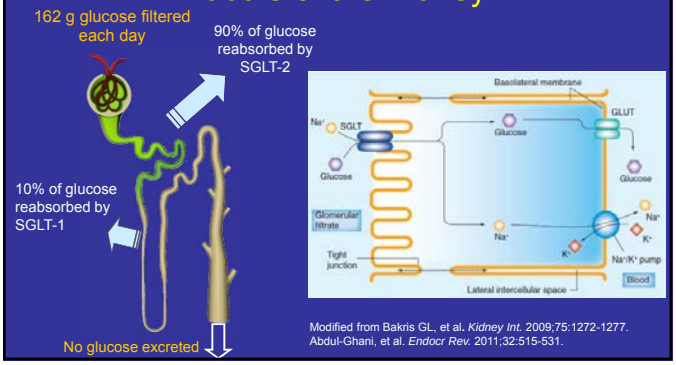
Overview

- Case.
- American Diabetes Association Guidelines-2016.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.

Sodium Glucose Transporter-2 Inhibitors (SGLT-2)

- Inhibit the action of sodium-glucose transporter 2 (SGLT-2) in the proximal convoluted tubule of the kidney.
- No direct effect on the beta cell, adipocytes or liver.
- Oral agents.

Glucose Handling in the Proximal Tubule of the Kidney



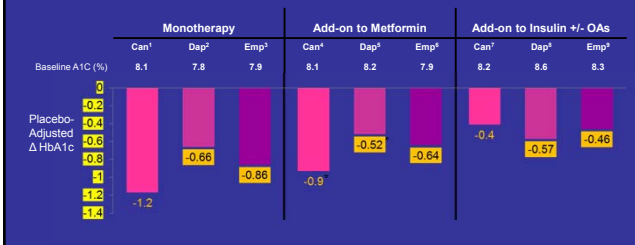
Modified from Bakris GL, et al. *Kidney Int.* 2009;75:1272-1277.
Abdul-Ghani, et al. *Endocr Rev.* 2011;32:515-531.

SGLT-2 Inhibitors

- **Canagliflozin (Invokana)**
  - **100 and 300 mg tablets**
- **Dapagliflozin (Farxiga)**
  - **5 and 10 mg tablets**
- **Empagliflozin (Jardiance)**
  - **10 and 25 mg tablets**

Glucose Control with SGLT2 Inhibitors

Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)



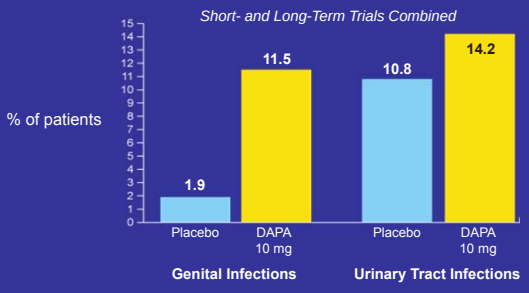
*Absolute change from baseline (active-controlled trial).

1. Stenlof K, et al. *Diabetes Obes Metab.* 2013;15:372-382. 2. Ferrannini E, et al. *Diabetes Care.* 2010;33:2217-2224. 3. Roden M, et al. *Lancet Diabetes Endocrinol.* 2013;1:208-219. 4. Cefalu WT, et al. *Lancet.* 2013;382:941-950. 5. Nauck MA, et al. *Diabetes Care.* 2011;34:2015-2022. 6. Haring HU, et al. *Diabetes Care.* 2014;37:1650-1659. 7. Yale J-F, et al. *Diabetes Obes Metab.* 2013;15:463-473. 8. Wilding JPH, et al. *Ann Intern Med.* 2012;156:405-415. 9. Rosenstock J, et al. *Diabetes Care.* 2014;37:1815-1823.

SGLT-2 Inhibitors- Precautions

- Patients with CKD.
  - Reduce the dose if the eGFR is between 40 and 50.
  - Contraindicated if the eGFR <30.
- May reduce intravascular volume (diuresis effect).
  - ↑ risk for hypotension.
  - Especially common in the first few weeks of treatment.
  - Use cautiously in elderly patients.
- The SGLT-2 inhibitors can increase fracture risk.
  - Pooled analysis from 8 phase III studies with canagliflozin demonstrated a 30% increased risk of fracture. Kwon H. FDA Drug Advisory Committee Meeting, 2013. UCM336234.pdf.
  - Increased fracture risk in patients with stage III CKD treated with dapagliflozin. Kohan et al. Kidney Int 85: 962, 2014.

Infections in Women Treated with Dapagliflozin



Statistical significance not reported.
FDA Advisory Committee 19th July 2011:http://www.fda.gov.

SGLT-2 Inhibitors and Euglycemic Ketoacidosis

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition

- 13 episodes of "Euglycemic" DKA.
  - Nine patients with T1DM
  - Two patients with T2DM
  - Glucose levels generally in the 100-200 mg/dl range.
- Possible precipitants:
  - Reduced insulin doses
  - Reduced caloric intake
  - Surgery
  - EtoH
- Ketoacidosis went unrecognised by the patients and providers.

SGLT-2 Inhibitors and Euglycemic Ketoacidosis

- I would not use the SGLT-2 inhibitors in patients with type 1 diabetes until we have more information.
- Use caution in patients with latent autoimmune diabetes in adults (LADA) treated as T1DM.
- These agents may need to stopped several days before surgery.
- It may be prudent to provide patients with ketostix for urine ketone testing.

Overview

- Case.
- American Diabetes Association Guidelines-2016.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Validity?
- Cardiovascular outcomes.
- Case.
- History lesson.

Liraglutide and T1DM

- 72 overweight or obese patients with T1DM randomized to 1.2 or 1.8 mg of liraglutide vs placebo and followed for 12 weeks.
- 63 patients completed the study .

	1.2 mg Liraglu	1.8 mg Liraglu
HbA1c	-0.78% *	-0.42% (ns)
Weight loss	↓5 kg **	↓5 kg **
Total insulin dose	↓12.1 units*	↓10 units*
Hypoglycemia	↑	↑

*p<0.05, **P<0.01, ns: not significant.

Kuhadiya ND, et al. Diabetes Care. 39: 1027, 2016.

Liraglutide in T1DM

- Double blind, treat- to- target trial of 1398 patients with type 1 diabetes randomized 3:1 to liraglutide (0.6, 1.2 or 1.8 mg/day) vs placebo added to insulin for 52 weeks.

	1.2 mg Liraglu	1.8 mg Liraglu
HbA1c	↓0.15%	↓0.20%
Insulin dose (total dose/day)	↓5%	↓8%
Mean weight loss	↓3.6 kg	↓4.9 kg
Symptomatic hypo	↑1.27 RR	↑1.31 RR
Hyperglycemia with ketosis	-	↑2.22 RR (1.13 to 4.34)

Mathieu, C, et al. Diabetes Care, published online, Aug 8, 2016.

Canagliflozin and T1DM

- Double blind phase II study of 351 patients with T1DM, randomized to 100 or 300 mg of canagliflozin and followed for 18 weeks.

	100 mg Cana	300 mg Cana
HbA1c	-0.29%	-0.24%
Δ Weight	↓3.4%	↓5.3%
Insulin dose	↓4.1 units	↓7.6 units
Severe hypoglyc	2.6%*	6.8%*
Ketone AE	5.1%	9.4%

*Placebo incidence 0%

Henry, RR, et al. Diabetes Care. 38: 2258-65, 2015.

Dapagliflozin Added to Liraglutide in T1DM (!!!)

- 30 patients with T1DM were randomized in a 2:1 ratio to receive 10 mg of dapagliflozin vs placebo in addition to liraglutide for 12 weeks .

	Dapagliflozin (vs placebo)
HbA1c	↓0.66%*
Δ Weight	↓1.9 kg**
Hypoglycemia rate	Unchanged.
Acetoacetate level	↑67%**
Hydroxybutyrate	↑254%**

Two patients in the Dapagl group developed DKA (10%). *P<0.01, ** P<0.05

Kuhadiya ND, et al. J Clin Endocrinol Metab. Published ahead of print, 2016.

GLP-1 Analogs or SGLT-2 Inhibitors in T1DM?

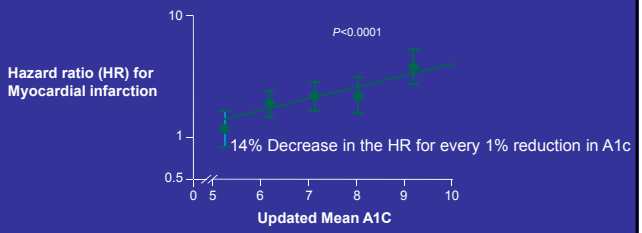
- The jury is still out.
- The benefit ratio for GLP-1 analogs or SGLT-2 inhibitors in the treatment of T1DM is slim.
- There are potential risks.
  - SGLT-2 inhibitors may lead to euglycemic ketoacidosis or frank DKA in a subset of patients with T1DM.
  - Added cost.
  - Increased complexity of the antidiabetic regimen.

Overview

- Case.
- American Diabetes Association Guidelines-2016.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.

Lower A1C: Decreased Risk of Myocardial Infarction

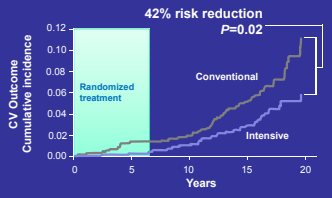
United Kingdom Prospective Diabetes Study



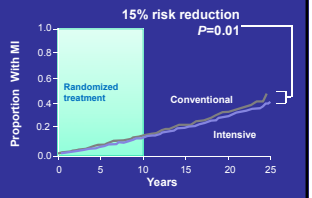
Stratton IM et al. *BMJ*. 2000;321:405-412.

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

DCCT
T1DM, 5-6 years duration (N=1441)



UKPDS
T2D, newly diagnosed (N=4209)



CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.

Intensive Glycemic Control Does Not Reduce Macrovascular Risk in Older Patients With Longer Duration of Disease

	ACCORD	ADVANCE	VADT
T2D duration (years)	10	8	12
A1C reduction (%)*	0.9	0.8	1.3
Macrovascular risk (%)*	10	6	12
	P=0.16	*P*=0.32	*P*=0.14
	Mortality increased in intensively treated patients (*P*=0.04)		

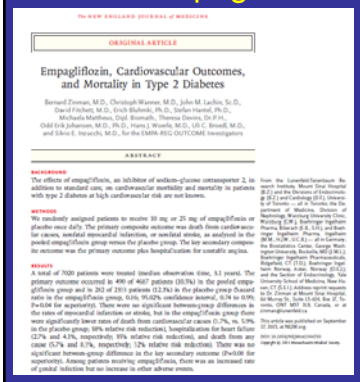
*Intensive vs standard glucose control.

ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559.
ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572.
Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

CAD Outcomes and Newer Antiglycemic Agents

	N	Population	HbA1c	Duration	Primary Outcome
Saxagliptin	16,492	80% +CAD	-0.2-0.3	24 mos	Non-inferiority for CAD events
		*Slight but significant ↑CHF events			
Alogliptin	5.380	MI or angina	-0.36	18 mos	Non-inferiority for
		*Trend toward more CHF events			CAD events
Sitagliptin	14, 671	+CAD	-0.3	36 mos	Non-inferiority for CAD events
Lixisenatide	6,068	MI or angina	-0.27	25 mos	Non-inferiority for CAD events

Empagliflozin and CAD Events



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

ABSTRACT

- **7028 patients with T2DM randomized to 10 or 25 mg of empagliflozin vs placebo as add-on to antiglycemic treatment.**
- **99% had established CAD.**
- **Median duration of treatment 2.6 yrs.**
- **Primary outcome was a composite of CAD mortality, non-fatal MI and non-fatal stroke.**
- **Industry supported study.**

Zinman B, et al. N Engl J Med. Published online 9/17/15

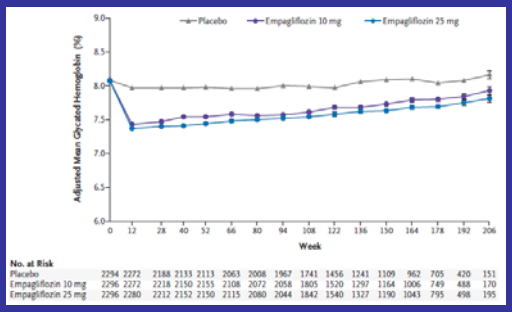
EMPA-REG Baseline Characteristics

Characteristic[1]	Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)
Age – years	63.2 ± 8.6	63.0 ± 8.6	63.2 ± 8.6	63.1 ± 8.6
Male – no. (%)	1680 (72.0)	1653 (70.5)	1683 (71.9)	3336 (71.2)
Race – no. (%)				
White	1678 (71.9)	1707 (72.8)	1696 (72.4)	3403 (72.6)
Asian	511 (21.9)	505 (21.5)	501 (21.4)	1006 (21.5)
Black/African-American	120 (5.1)	119 (5.1)	118 (5.0)	237 (5.1)
Other/Missing	24 (1.0)	14 (0.6)	27 (1.2)	41 (0.9)
Ethnicity – no. (%)				
Not Hispanic or Latino	1912 (82.0)	1909 (81.4)	1926 (82.2)	3835 (81.8)
Hispanic or Latino	418 (17.9)	432 (18.4)	415 (17.7)	847 (18.1)
Missing	3 (0.1)	4 (0.2)	1 (<0.1)	5 (0.1)
Region – no. (%)				
Europe	959 (41.1)	966 (41.2)	960 (41.0)	1926 (41.1)
North America (plus Australia and New Zealand)	462 (19.8)	466 (19.9)	466 (19.9)	932 (19.9)
Asia	450 (19.3)	447 (19.1)	450 (19.2)	897 (19.1)
Latin America	360 (15.4)	359 (15.3)	362 (15.5)	721 (15.4)
Africa	102 (4.4)	107 (4.6)	104 (4.4)	211 (4.5)
Weight – kg	86.6 ± 19.1	85.9 ± 18.8	86.5 ± 19.0	86.2 ± 18.9
Body mass index – kg/m^2	30.7 ± 5.2	30.6 ± 5.2	30.6 ± 5.3	30.6 ± 5.3
CV risk factor – no. (%)	2307 (98.9)	2333 (99.5)	2324 (99.2)	4657 (99.4)
Coronary artery disease	1763 (75.6)	1782 (76.0)	1763 (75.3)	3545 (75.6)
Multi-vessel coronary artery disease	1100 (47.1)	1078 (46.0)	1101 (47.0)	2179 (46.5)
History of myocardial infarction	1083 (46.4)	1107 (47.2)	1083 (46.2)	2190 (46.7)
Coronary artery bypass graft	563 (24.1)	594 (25.3)	581 (24.8)	1175 (25.1)
History of stroke[3]	553 (23.7)	535 (22.8)	549 (23.4)	1084 (23.1)
Peripheral artery disease	479 (20.5)	465 (19.8)	517 (22.1)	982 (21.0)
Single vessel coronary artery disease[2]	238 (10.2)	258 (11.0)	240 (10.2)	498 (10.6)
Cardiac failure[4]	244 (10.5)	240 (10.2)	222 (9.5)	462 (9.9)
Glycated hemoglobin – %[5]	8.08 ± 0.84	8.07 ± 0.86	8.06 ± 0.84	8.07 ± 0.85
Time since diagnosis of type 2 diabetes – no. (%)				

Baseline Characteristics

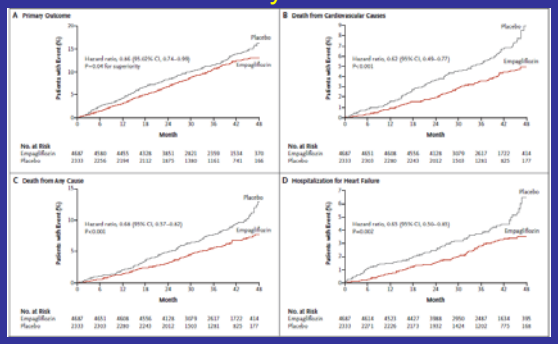
<1 years	52 (2.2)	68 (2.9)	60 (2.6)	128 (2.7)
>1 to 5 years	371 (15.9)	338 (14.4)	374 (16.0)	712 (15.2)
>5 to 10 years	571 (24.5)	585 (24.9)	590 (25.2)	1175 (25.1)
>10 years	1339 (57.4)	1354 (57.7)	1318 (56.3)	2672 (57.0)
Glucose-lowering therapy – no. (%)				
Medication taken alone or in combination				
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)	3459 (73.8)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)	2252 (48.0)
Median daily dose – IU[3]	52.0	52.5	54.0	54.0
Sulfonylurea	992 (42.5)	985 (42.0)	1029 (43.9)	2014 (43.0)
Dipeptidyl peptidase-4 inhibitor	267 (11.4)	282 (12.0)	247 (10.5)	529 (11.3)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)	198 (4.2)
Glucagon-like peptide-1 agonist	70 (3.0)	68 (2.9)	58 (2.5)	126 (2.7)
Monotherapy	691 (29.6)	704 (30.0)	676 (28.9)	1380 (29.4)
Dual therapy	1148 (49.2)	1110 (47.3)	1149 (49.1)	2259 (48.2)
Anti-hypertensive therapy – no. (%)	2221 (95.2)	2227 (95.0)	2219 (94.7)	4446 (94.9)
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	1868 (80.1)	1896 (80.9)	1902 (81.2)	3798 (81.0)
Beta-blockers	1498 (64.2)	1530 (65.2)	1526 (65.2)	3056 (65.2)
Diuretics	988 (42.3)	1036 (44.2)	1011 (43.2)	2047 (43.7)
Calcium channel blockers	788 (33.8)	781 (33.3)	748 (31.9)	1529 (32.6)
Mineralocorticoid receptor antagonists	136 (5.8)	157 (6.7)	148 (6.3)	305 (6.5)
Renin inhibitors	19 (0.8)	16 (0.7)	11 (0.5)	27 (0.6)
Other	191 (8.2)	193 (8.2)	190 (8.1)	383 (8.2)
Lipid-lowering therapy – no. (%)	1864 (79.9)	1926 (82.1)	1894 (80.9)	3820 (81.5)
Statins	1773 (76.0)	1827 (77.9)	1803 (77.0)	3630 (77.4)
Fibrates	199 (8.5)	214 (9.1)	217 (9.3)	431 (9.2)
Ezetimibe	81 (3.5)	95 (4.1)	94 (4.0)	189 (4.0)
Niacin	35 (1.5)	56 (2.4)	35 (1.5)	91 (1.9)
Other	175 (7.5)	172 (7.3)	193 (8.2)	365 (7.8)
Anti-coagulants – no. (%)	2090 (89.6)	2094 (89.5)	2064 (88.1)	4162 (88.8)
Acetylsalicylic acid	1927 (82.6)	1939 (82.7)	1937 (82.7)	3876 (82.7)

Glycemic Control with Empagliflozin



Zinman, B, et al. N Engl J Med. Published online Sept. 17, 2015

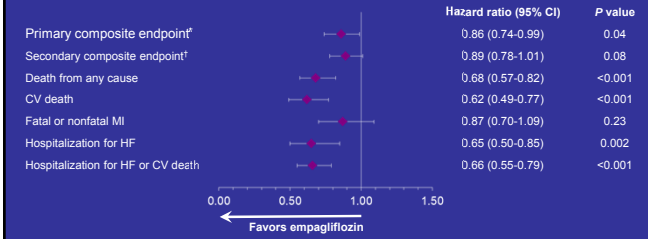
Cardiovascular Outcomes and All Cause Mortality in EMPA-REG



Zinman, B, et al. N Engl J Med. Published online Sept. 17, 2015.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

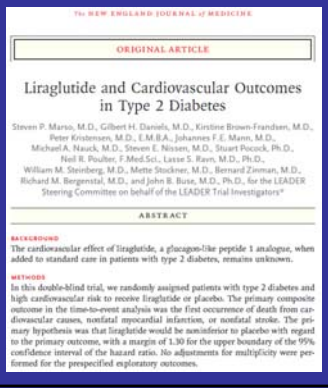


*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Liraglutide and CAD Outcomes



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ABSTRACT

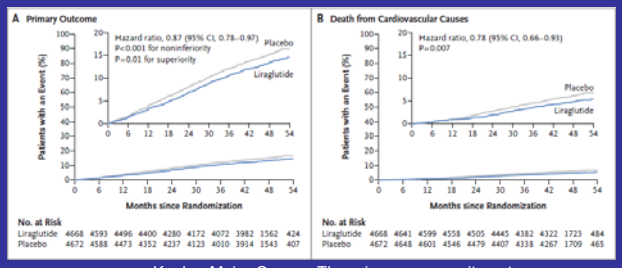
BACKGROUND
The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS
In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

- **Double-blind randomized, controlled trial of 9340 patients with T2DM treated with 1.8 mg of liraglutide vs placebo.**
- **Age >50 with CAD or >60 with one or more CV risk factors.**
- **Median followup 3.8 yrs.**
- **Primary outcome- a composite of CAD mortality, non-fatal MI or stroke.**

Marso, SP, et al. N Engl J Med.
Pub online 6/13/2016.

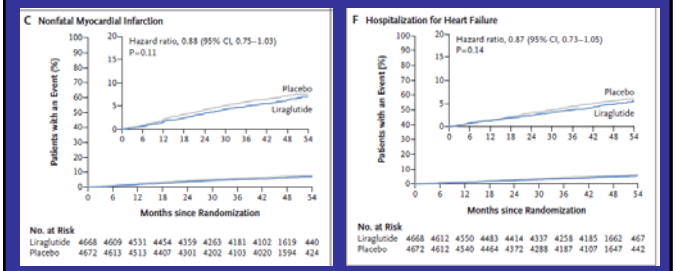
Cardiovascular Outcomes in the LEADER Trial



Kaplan-Meier Curves. The primary composite outcome.

Marso, SP, et al. N Engl J Med.
Pub online 6/13/2016.

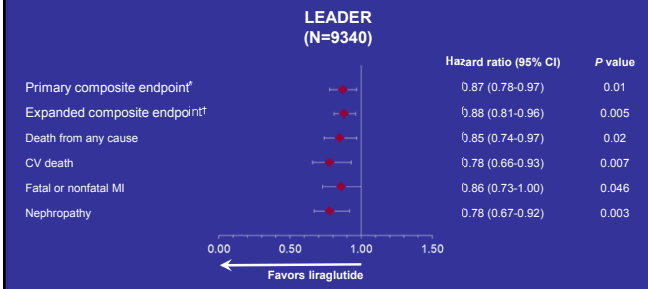
Cardiovascular Outcomes in the LEADER Trial



Kaplan-Meier Curves.

Marso, SP, et al. N Engl J Med.
Pub online 6/13/2016.

Clinical Outcomes with Liraglutide

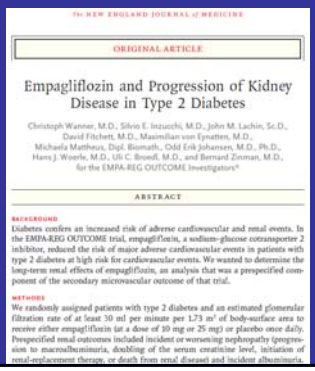


*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med*. 2016 Jun 13. [Epub ahead of print]

Empagliflozin and Kidney Disease



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

ABSTRACT

BACKGROUND

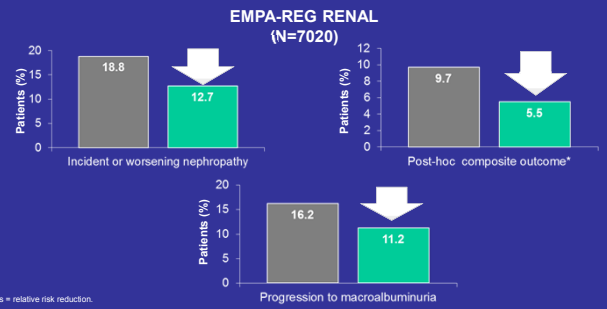
Diabetes confers an increased risk of adverse cardiovascular and renal events. In the EMPA-REG OUTCOME trial, empagliflozin, a sodium–glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. We wanted to determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial.

METHODS

We randomly assigned patients with type 2 diabetes and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m² of body-surface area to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.

- **Randomized , double blind study of 6185 patients with T2DM who were assigned 10 or 25 mg of empagliflozin vs placebo.**
- **Renal outcomes: incident or worsening nephropathy (progress to macroalb, doubling of creatinine, initiation of renal replacement or death from renal disease) or incident albuminuria.**
- **99% had established CHD.**

Renal Outcomes with Empagliflozin Over 3.2 Years



Arrows = relative risk reduction.

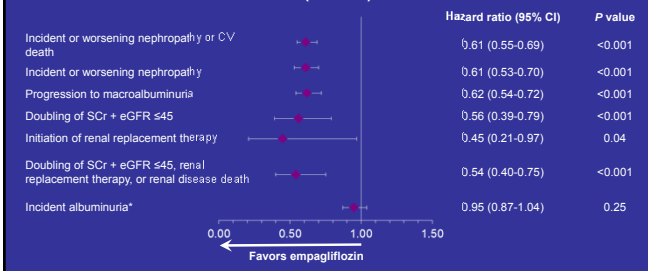
*Doubling of SCr + eGFR ≤45 mL/min/1.73 m², initiation of renal replacement therapy, or death from renal disease.

CI, confidence interval; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Wanner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL
(N=7020)

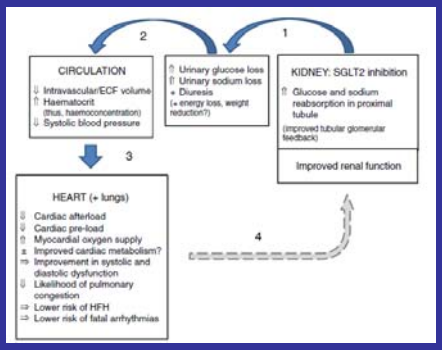


*In patients with normal albuminuria at baseline.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine

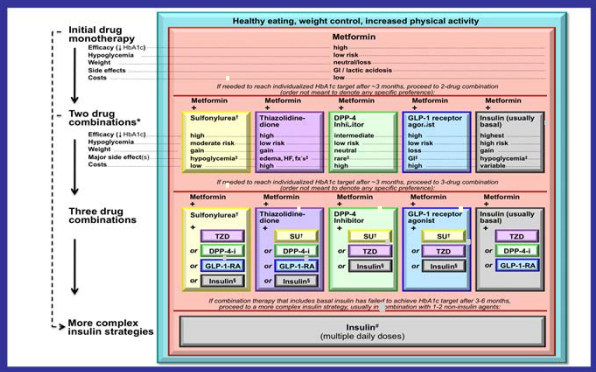
Warner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

SGLT-2 Inhibition and Heart Failure



Sattar N, et al. Diabetologia. 59: 1333-39, 2016.

ADA Treatment Algorithm



T2DM Anti-hyperglycemic Therapy: General Recommendations

Points to Consider when Choosing a Diabetes Agent

- Efficacy
  - HbA1c
  - Fasting glucose
- Mechanism of action
- Side effects
  - Hypoglycemia
  - Other side effects
- Effect on weight
- Patient considerations
  - Oral vs injectable
  - Convenience
  - Complexity of regimen
  - Cost
- Outcomes
  - Microvascular
  - Macrovascular

Overview

- Case.
- American Diabetes Association Guidelines-2016.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History lesson.

Case 1

- A 58 year old man comes to the clinic for a diabetes visit.
- He was diagnosed with type 2 diabetes in 2007.
- The antiglycemic regimen:
  - Metformin, 1000 mg bid
  - Glimepiride, 4 mg/day
- BMI 35.4
- The HbA1c in clinic is 9.3%.

Case 1a
Traditional approach

Plan:

1. Start basal or intermediate insulin in the evening.
2. Or use 70/30 insulin before dinner.

-Start with 0.1 to 0.15 units/kg
~11-17 units
-He should continue to take the two oral agents.
-The sulfonylurea should be stopped once the patient is on ≥ 2 injections of insulin per day.

Case 1b
The patient refuses to consider any injectable medication

Plan:

1. Start empagliflozin at 10 mg/d and increase to 25 mg/d if needed.
   - Or use one of the other SGLT-2 inhibitors.
2. Adding a DPP-IV inhibitor would not be a good option as the goal HbA1c of 7 to 7.5% would not be achieved.
4. Continue the metformin and glimepiride.

Case 1c
The patient's chief concern is obesity and weight gain

Plan:

1. Start one of the GLP-1 analogs.
   - Liraglutide (Victoza), 1.2 to 1.8 mg sc/day.
   - Extended release exenatide (Bydureon), 2 mg sc /week.
   - Dulaglutide (Trulicity), 1.5 mg sc/week.
2. Continue the metformin and glimepiride.

Case 1d

- If he is treated with a non-insulin approach, eventually- basal insulin will need to be started.
- If he fails to lose weight, bariatric surgery may be considered as a treatment option.

Key Points in the Management of Hyperglycemia in Diabetes

- Glucose targets and glucose lowering therapies need to be individualized.
  - Focus on the patients' needs and preferences.
- Diet, exercise and education remain the foundation.
- Unless contraindicated, metformin in the optimal 1st line drug in the treatment of type 2 diabetes.
- Combination therapy with 2 -3 oral antiglycemic medications is reasonable. Weigh the pros and cons of each agent for the individual.
- Ultimately many patients will require insulin, initially in combination with oral agents.
- Cardiovascular risk reduction is still a goal.

Overview

- Case.
- American Diabetes Association Guidelines-2016.
- Incretins.
- SGLT-2 inhibitors.
- Use of incretins and SGLT-2 inhibitors for treatment of type 1 diabetes. Is this valid?
- Cardiovascular outcomes.
- Case.
- History of Diabetes and the ADA.

1921-Insulin is Shown to Control Diabetes in Pancreatectomized Dogs.

Student assistant Charles H. Best (left) with Dr. Frederick Banting

- **1921.** Frederick Banting, MD, and his medical student assistant, Charles Best, extract a crude form of insulin from dog pancreata.
- They used laboratory space at the University of Toronto provided by Professor J. J. R. Macleod.
-
- They injected the insulin extract into dogs whose pancreases had been removed, and the animals' blood sugar levels decreased.

First Human Patient

On Jan. 11, 1922, 14-year-old Leonard Thompson was the first human patient to receive insulin made by Banting and Best.

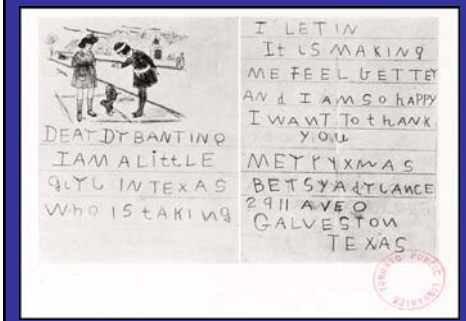
The initial test failed, causing only slight reductions in blood glucose levels.

A second series of "purified" insulin injections, produced by J.B. Collip, achieved the desired results.

Leonard's blood glucose dropped to normal, and he began to gain weight.

Banting and Macleod were Awarded the Nobel Prize in Medicine for the discovery of insulin in 1923.

Insulin-the Game-Changer



1923-Commercial Production of Insulin Began

1923-Eli Lilly and Company and Nordisk Insulin Laboratorium began commercial production of insulin in North America and Europe, respectively.

Labelling boxes of insulin at Eli Lilly, ca. 1924. Photo Credit: Smithsonian Institution, The National Museum of American History

1940 -The American Diabetes Association is Founded.

The American Diabetes Association is founded to address:
-The increasing incidence of diabetes
-The complications that develop from the disease.

Professional Membership: **$2** per year.

1947- The First Diabetes Camp for Children is Established.

In 1947, an American Diabetes Association Affiliate sponsored Camp Seale Harris in Montgomery, Alabama.

In 2014, the Association hosted more than 5,400 children with diabetes at more than 50 sessions of camps in 24 states.

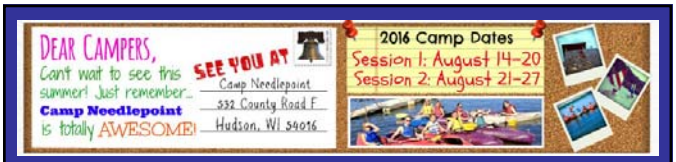
The average A1c of campers dropped from 7.63% before camp to 7.05% following camp.

Photo from Camp Seale Harris, ca. 1988

Camp Lakota – Session I

When: June 18 to June 23, 2017
Ages: 9 to 16 years
Where: Wisconsin Lions Camp
3834 County Road A
Rosholt, Wisconsin 54473
- See more at: http://www.diabetes.org/in-my-
- community/diabetes-camp/camps/Lakota-
- 1.html#sthash.1LYKyIGs.dpuf

Camp Lakota-Session II



Camp Needlepoint, Hudson, WI

Camp Needlepoint - Session 1
When: August 14 to August 20, 2016
Ages: 8 to 16 years
Where: YMCA Camp St. Croix 532 County Road F
Hudson, Wisconsin 54016
Related Sessions: Camp Needlepoint - Session 2 –
See more at: http://www.diabetes.org/in-my-community/diabetes
-camp/camps/needlepoint-1.html#sthash.STjZ3gl4.dpuf

The First Insulin Pump Prototype was Developed in 1963.

- Dr. Arnold Kadish of Los Angeles developed the first "portable" insulin pump in 1963.
- The pump was the size of a marine backpack.

1977- HbA1c Test Developed

CORRELATION OF GLUCOSE REGULATION AND HEMOGLOBIN A_{1c} IN DIABETES MELLITUS

RONALD J. KOENIG, B.S., CHARLES M. PETERSON, M.D., ROBERT L. JONES, M.D., CHRISTOPHER SAUDEK, M.D., MARK LEHRMAN, M.D., AND ANTHONY CERAMI, PH.D.

Abstract We studied the increased levels of hemoglobins A_{1a+b} and A_0 in five hospitalized diabetic patients to determine whether changes in diabetic control would cause parallel changes in the levels of these hemoglobins. Before control of diabetes the mean fasting blood sugar for all patients was 343 mg per deciliter (range, 280 to 450), and hemoglobin A_{1c} concentration 9.8 per cent (range, 6.8 to 12.1). During optimal diabetic control the blood sugar concentration was 84 mg per deciliter (range, 70 to 100), and hemoglobin A_{1c} concentration 5.8 per cent (range, 4.2 to 7.6). Hemoglobin A_0 concentration appears to reflect the mean blood sugar concentration best over previous weeks to months. The periodic monitoring of hemoglobin A_{1c} levels provides a useful way of documenting the degree of control of glucose metabolism in diabetic patients and provides a means whereby the relation of carbohydrate control to the development of sequelae can be assessed. (N Engl J Med 295:417-420, 1976)

THE introduction of insulin in 1922 by Banting and Best[1] seemed to offer the ideal therapy for the treatment of diabetes mellitus: replacement of the missing hormone. Indeed, in the past 50 years, the judicious use of insulin has made it possible to control the symptoms of hyperglycemia and to avoid death from ketoacidosis. However, despite the continual use of insulin, many pathologic changes (e.g., retinopathy, angiopathy, nephropathy, and neuropathy) still develop and now account for the major morbidity and mortality associated with the disease.[2] One of the major controversies among diabetologists has been the relation between the degree of control of blood sugar and the development of secondary sequelae. Although a priori one would assume that a strict control of carbohydrate metabolism should more closely mimic the situation in normal persons and thus reduce the risk of secondary changes, it has been difficult to document this hypothesis convincingly,[3] in part because of the inadequate means of measuring both the degree of control and the development of pathologic changes that occur over long periods.

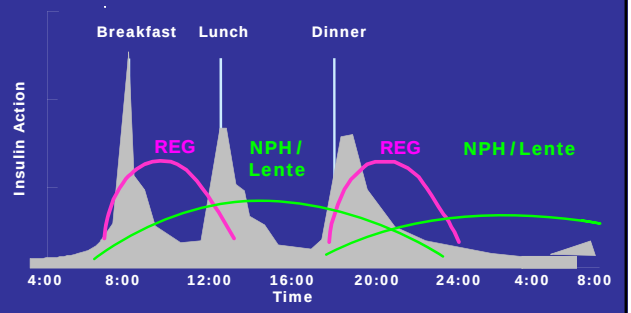
...ally analogous to the human type and becomes increased in the diabetic state.[4] The rise in the concentration of hemoglobin A_{1c} in diabetic mice (C57BL/Ksj-db/db) occurs three to four weeks after the onset of hyperglycemia. Radiolabeling experiments in mice revealed that hemoglobin A_{1c} results from a post-synthetic modification of hemoglobin A and that its production occurs throughout the life of the red cell. Its rate of synthesis depends on the metabolic state of the animal; the rate is nearly three times faster when the red cells are circulating in a diabetic animal. If the diabetes is brought under control, as occurs naturally in the C57BL/6J-db/db mouse, the concentration of hemoglobin A_{1c} declines.[5]

These findings in man and laboratory animals suggested the measurement of hemoglobin A_{1c} concentration as a means of monitoring the degree of control of diabetic patients. It has recently been found that the level of hemoglobin A_{1c} in diabetic patients is linearly correlated with the peak or area under the curve of the glucose tolerance test.[6] We have studied the utility of hemoglobin A_{1c} concentration as a monitor

410 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 19, 1976

Boston researchers developed a test to measure glycosylated hemoglobin (A1C). A1C testing became the gold standard for measuring long-term diabetes control.

1980-Intensive Insulin Therapy Used Twice-Daily Split-Mixed Regimen



Adapted with permission from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy*. New York: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med*. 2002;347:1342

1991-First Step Out Walk Held

STEP OUT | WALK TO STOP DIABETES™

American Diabetes Association.

Step Out: Walk to Stop Diabetes is the signature fundraising walk of the American Diabetes Association.
Formerly Step Out: Walk to Fight Diabetes and America's Walk for Diabetes, the event has raised more than $200 million to Stop Diabetes.

In 2014, more than 100,000 walkers participated in 105 Step Out events across the country to raise nearly $24 million.

ADA Tour de Cure

2017 Milwaukee Tour de Cure July 22nd, 2017 @ Hoyt Park

2017 Madison Tour de Cure 9/16/2017
@ American Family Corporate Headquarters

- The first Tour de Cure events were held at five pilot sites, including Buffalo, NY; New Jersey; New Hampshire; Napa, CA; and St. Louis, MO in 1991.
- The Tour de Cure is a series of fundraising cycling events held in 44 states.
- In 2014, 89 Tour de Cure events attracted more than 61,000 cyclists who raised more than $26 million to support the mission of the American Diabetes Association.

1993-Tight Glucose Control Shown to Reduce Complications in Type 1 Diabetes

The New England
Journal of Medicine

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Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Abstract *Background.* Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts

The Diabetes Control and Complications Trial (DCCT) showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve complications caused by diabetes. In fact, it demonstrated that any sustained lowering of blood glucose helps, even if the person has a history of poor control. This landmark study, along with the later UKPDS study showing similar outcomes for tight blood glucose control in type 2 diabetes, and continuing long term followup reports have effectively ended the debate on the link between tight control of blood glucose and improved health outcomes for people with diabetes.

1997-New Diabetes Terminology and Diagnostic Levels Adopted

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

- **The terms "insulin-dependent diabetes" (IDDM) and "non-insulin-dependent diabetes" (NIDDM) were no longer to be used.**
- **The terms type 1 diabetes and type 2 diabetes were adopted to define diabetes by cause rather than by treatment.**
- **In addition, the fasting glucose level for diagnosing diabetes was lowered from 140 mg/dl to 126 mg/dl to better reflect the point at which diabetes complications begin to develop.**

1998-Tight Control of Blood Glucose Shown to Reduce Complications in Type 2 Diabetes

UKPDS

- The United Kingdom Prospective Diabetes Study (UKPDS) showed that people with type 2 diabetes who practice tight control of blood sugar levels and blood pressure levels reduce their risk of complications, similar to the results of the DCCT in people with type 1 diabetes
- The UKPDS trials demonstrated the importance of the management of hypertension, dyslipidemia as well as hyperglycemia.

2013- Safe at School Landmark Ruling Issued

The California Supreme Court ruled in a landmark case that non-medical school staff can administer insulin to students in the state's public schools.
The ADA led the fight, which helped prevent students from being denied access to insulin at school.

Thank You