WHAT IS NEW IN 2013/2014 FOR TREATING DIABETES

Anne Peters, MD
Professor, USC Keck School of Medicine
Director, USC Clinical Diabetes Programs

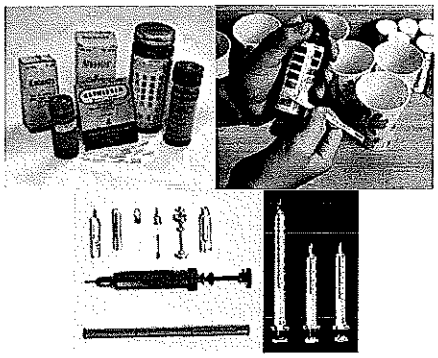
Disclosure of Financial Relationships

Consultantship
Medtronic Minimed
Roche
Sanofi
BD
Janssen
Medscape
Lilly
Abbott Diabetes Care

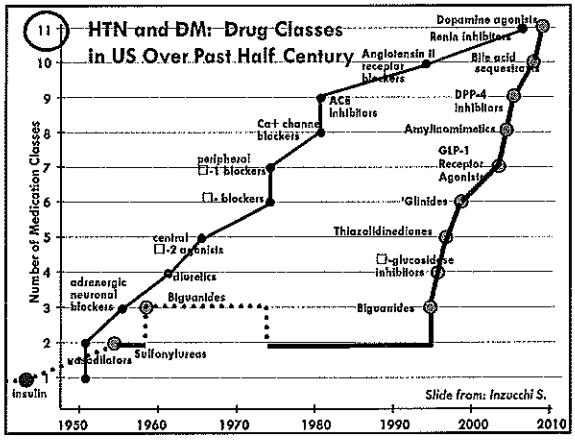
Honoraria
Takeda

Speakers Bureau
BMS/AstraZeneca
NovoNordisk

Diabetes Care in the 1970s



HTN and DM: Drug Classes in US Over Past Half Century



Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

American Diabetes Association.

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

EASD

The New ADA/EASD Position Statement on Management of Hyperglycemia in Type 2 Diabetes

ADA

Richard M. Bergenstal MD
Int'l Diabetes Center, Minneapolis, MN
John B. Buse MD, PhD
University of North Carolina, Chapel Hill, NC
Anne L. Peters MD
Univ. of Southern California, Los Angeles, CA
Richard Wender MD
Thomas Jefferson University, Philadelphia, PA
Silvio E. Inzucchi MD (co-chair)
Yale University, New Haven, CT

EASD

Michaela Diamant MD, PhD
VU University, Amsterdam, The Netherlands
Ele Ferrannini MD
University of Pisa, Pisa, Italy
Michael Nauck MD
Diabetes zentrum, Bad Lauterberg, Germany
Apostolos Tsapas MD, PhD
Aristotle University, Thessaloniki, Greece
David R. Matthews MD, Dphil
Oxford University, Oxford, UK

Management of Type 1 Diabetes Across the Age Spectrum

A Position Statement of the American Diabetes Association (ADA)

Chiang J, Kirkman S, Laffel L, Peters A for the ADA

American Diabetes Association.

Diabetes Care 2014—soon!!!

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

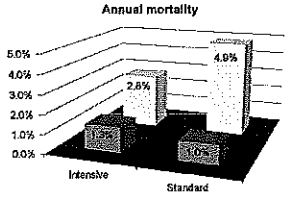
Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Kendall DM, Bergenstal RM. © International Diabetes Center 2009
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med.* 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med.* 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moore T. *N Engl J Med* 2009;361:1024)

Initial Trial
Long Term Follow-up
* In T1DM

Lessons from Accord Severe Hypoglycemia and Mortality Risk

	ACCORD		ADVANCE		VADT	
Severe Hypo (%/ year)	Intensive 3.1%	Standard 1.1%	Intensive 0.7%	Standard 0.4%	Intensive 12.0%	Standard 4.0%



Bonds et al. BMJ 2010;340:b4909

Severe Hypoglycemia in ACCORD

- "Patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death, regardless of the intensity of glucose control."
- "The increased risk of death seen in the ACCORD trial among participants in the intensive glycaemia control arm cannot be attributed to the increased rate of severe hypoglycaemia in intensive arm participants."

Bonds et al. BMJ 2010;340:b4909

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

ANTI-HYPERGLYCEMIC THERAPY

- **Glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - **Individualization** is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

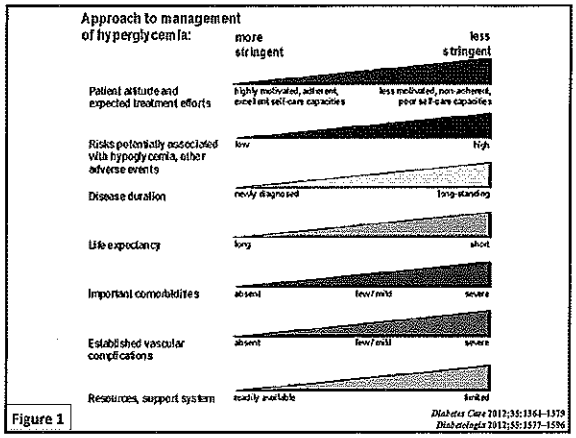


Figure 1

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

iBG Star

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

1. Patient-Centered Approach

"...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions."

- Gauge patient's preferred level of involvement.
- Shared decision making – final decisions re: lifestyle choices ultimately lies with the patient.
- Explore, where possible, therapeutic choices.
- Utilize decision aids.

Diabetes Care 2012;35:1364–1379

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

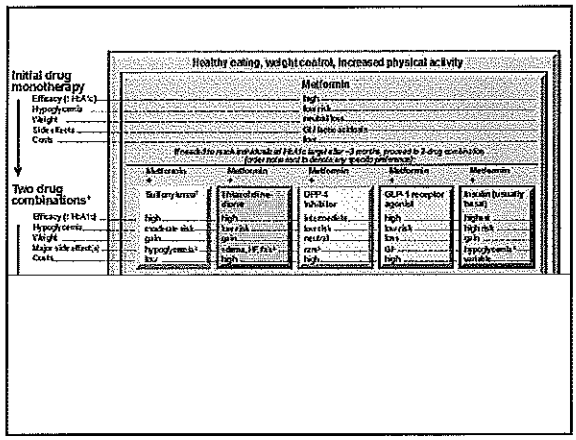
ANTI-HYPERGLYCEMIC THERAPY

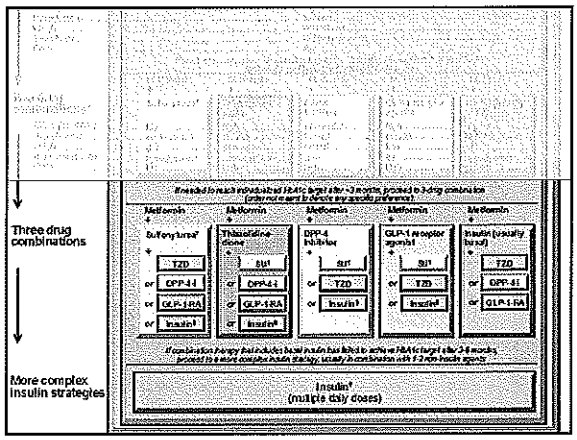
- Therapeutic options:

Oral agents & non-insulin injectables

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

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596





Metformin

The Only Choice in Type 2 DM?

- Most commonly used therapy for T2 DM (2/3rds of patients)
- Clinical effects
  - Lowers A1C 1-2% (especially at high baseline A1C), no weight gain
  - Maximal clinical effect at 1500-2000 mg/day
- Possible side effects and precautions
  - GI side effects common – less well tolerated by up to 10%
  - Not advised if significant renal or liver disease, heart failure (~20%)
- Other features
  - Lower CV risk in obese patients (UKPDS)
  - Extensive clinical experience and lower cost
  - ? Favorable impact on cancer risk and mortality

Sulfonylureas and the Secretagogues

How Do We Use Them Now?

- Most common (traditional) 2nd agent in T2 DM
  - Stimulate insulin release – during hyperglycemia and post-meal
- Clinical Use
  - Inexpensive and commonly used, rapid glucose lowering
  - Limited dose effect and limited "durability" of effect
- Side effects
  - Associated with weight gain and risk of hypoglycemia
- Precautions and contraindications
  - Associated with risk of severe hypoglycemia (elderly, renal disease)
  - Highest risk of hypoglycemia with GLYBURIDE

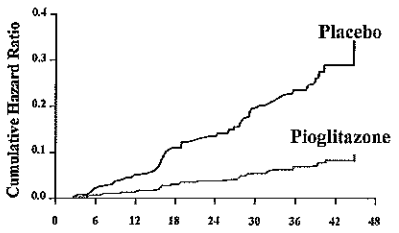
Thiazolidinediones (TZDs)

Do We Target Insulin Resistance?

- Clinical application
  - Targeted patients with clinical markers of insulin resistance
    - Dyslipidemia, HTN, established CVD, central obesity
  - May limit CVD risk and alter progression of diabetes
- Adverse effects and considerations
  - Significant weight gain and increase risk of edema and HF
  - Increased risk of long-bone fractures
  - Possible increase in MI risk with rosiglitazone (complex data)
- Patient selection
  - Higher CVD risk – particularly with dyslipidemia, est. CVD
  - Those at lower risk for fracture and with central obesity, NASH

Gray A et al. J Clin Endocrinol Metab. 2007;92:1305-1310.

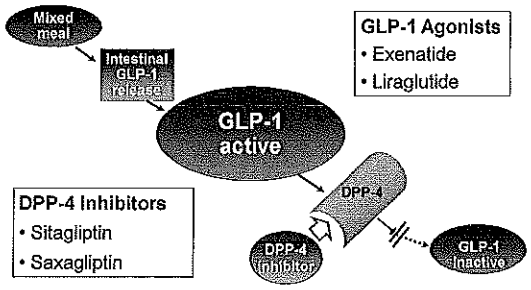
ACT-NOW Study



At Risk, n								
Placebo	299	259	228	204	191	134	83	17
Pioglitazone	303	262	244	228	218	140	87	24

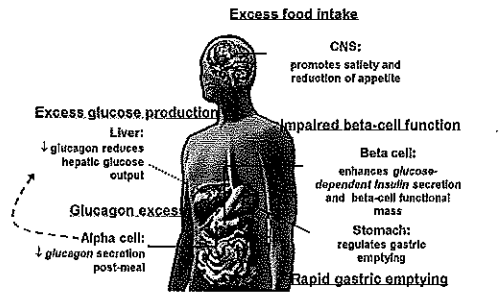
Hazard ratio, 0.25 (95% CI, 0.16-0.49); P<.001.
DeFronzo RA et al. *N Engl J Med.* 2011;364(12):1104-1115.

GLP-1 Secretion and Inactivation



Adapted from Rothenberg P, et al. *Diabetes.* 2000;49(suppl 1):A39.

The Therapeutic Potential of GLP-1 and GIP

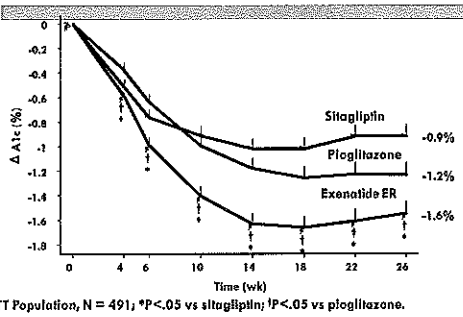


Flint A, et al. *J Clin Invest.* 1998;101(3):515-520. Larsson H, et al. *Acta Physiol Scand.* 1997;160(4):413-422. Nauck MA, et al. *Diabetologia.* 1996;39(12):1546-1553. Drucker DJ. *Diabetes.* 1998;47(2):159-169.

DPP-4 Inhibitors: Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta) and Alopgliitin (Nesina)

- Clinical Use
  - Moderate effectiveness (A1C reduction ~0.5-0.8%)
  - Use in both combo and mono therapy
- Unique Features
  - Limited side effect profile, very well tolerated
  - Weight neutral, no significant weight loss, no hypoglycemia
  - Variable clinical response (A1C reduction 0.2-1.1%)
- Reduced dosing in chronic kidney disease (except for linagliptin)

A1c Reduction of Sitagliptin vs Pioglitazone vs Exenatide ER

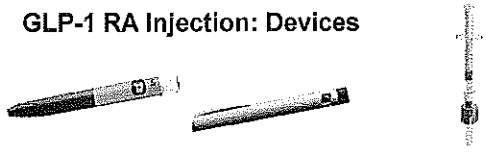


ITT Population, N = 491; *P<.05 vs sitagliptin; †P<.05 vs pioglitazone.
Sitagliptin; baseline = Pioglitazone; baseline = 8.5 Exenatide ER; baseline = 8.6
Bergenstal RM, et al. Lancet. 2010;376:431-439.

Overview: GLP-1 Receptor Agonists

- Excellent improvement in A1C
  - Head-to-head studies versus other classes suggest similar or greater efficacy of GLP-1 receptor agonists
- Moderate weight loss
- Modest improvement in blood pressure
- Other potential benefits
- Adverse events largely gastrointestinal (GI)
- Safety concerns (eg, renal failure, pancreatitis, cancer)

GLP-1 RA Injection: Devices



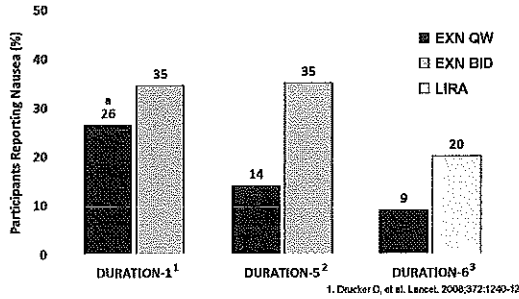
Exenatide BID Pen[1]
- 5 mcg – orange, 10 mcg – yellow
- Inject within 60 min of 2 main meals
- Start with 5 mcg
- Increase to 10 mcg after 1 month

Liraglutide Pen[2]
- Adjust to deliver dose (0.6, 1.2, or 1.8 mg)
- Inject once daily, any time
- Start with 0.6 mg
- Increase after 1 week to 1.2 mg
- May increase to 1.8 mg, if needed

Exenatide ER Syringe[3]
- Inject single 2-mg dose once weekly, any time
- Inject immediately after mixing
- Prior exenatide BID treatment not required
- Inject missed dose only if next dose is ≥ 3 days away

1. http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=01460100;
2. http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=57558000
3. http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=01460085

Nausea: Exenatide QW Versus Exenatide BID and Exenatide QW Versus Liraglutide

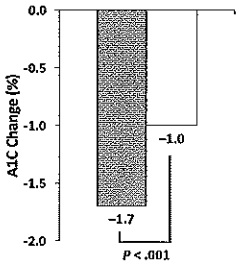


a - Significantly lower vs EXN BID

1. Drucker D, et al. Lancet. 2008;372:1240-1250.
2. Blevins T, et al. J Clin Endocrinol Metab. 2011;96:1301-1310.
3. Buse J, et al. EASD 47th Annual Meeting. 2011;75

Exenatide BID Added to Insulin Glargine

EXN BID or PBO Added to GLAR
30-week trial (N = 259)



Outcome	PBO	EXN BID	P-Value
Δ FPG (mg/dL)[a]	−27	−29	.63
Δ Insulin dose (U/d)[b]	20	13	.03
Δ Weight (kg)	1.0	−1.8	< .001
Hypoglycemia[c] (events/patient-y)	1.2	1.4	0.49
Discontinuation due to AEs (% of patients)	1	9	< .01

[a] Baseline FPG: 149 and 142 mg/dL for PBO and EXN BID groups, respectively.
[b] Baseline insulin: 47.4 and 49.5 U/d for PBO and EXN BID groups, respectively.
[c] 1 reported event of major hypoglycemia (PBO group).

Buse JB, et al. *Ann Intern Med*. 2011;154:103-112.

GLP-1 Receptor Agonists in Development

Compound	Company	Administration, formulation
Albiglutide (Syncria)	GSK / Sanofi-Aventis	Subcutaneous, once weekly, fusion of human albumin and GLP-1
Lixisenatide (Lyxumia)	Zealand Pharma / Sanofi	Subcutaneous, once daily
Semaglutide / NN9535	Novo Nordisk	Subcutaneous, once weekly
NN9924	Novo Nordisk / Emisphere/Merrion	Oral, once weekly, using the Eligen or GIPET technology to facilitate GLP-1 absorption from the gut
MAR701	Marcadia Biotech	GLP-1 and GIP receptor agonist
GLP-1 Fc / LY2189265 / Dulaglutide	Eli Lilly	Subcutaneous, once weekly, a von proteinconstruct of a DPP-4 protected GLP-1R agonist linked to a fragment of immunoglobulin G4
LX4211	Lexicon Pharmaceuticals	Dual inhibitor of sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2) increasing circulating GLP-1 and PYY
CJC-1131	ConjuChem	Subcutaneous, once weekly, human GLP-1R agonist conjugated to recombinant human albumin
Albugon	GSK / Human Genome Sciences	Recombinant GLP-1 fused with human albumin
Glymera / PB1023	Phase Bio Pharmaceuticals	Subcutaneous, once weekly, recombinant GLP-1R agonist using elastin-like biopolymer technology
ZP2929	Zealand Pharma	GLP-1R/glucagon R agonist
GLP-1 PEG / LY2428757	Eli Lilly	Polyethyleneglycol (PEG)-modified GLP-1 compound
TTP054	TransTech Pharma	Orally available, non-peptide agonist of GLP-1R
GLP-1R PAM / ADX91866	Addex pharmaceutical's	Orally available, small molecule therapeutic agent - works by positive allosteric modulation of the GLP-1R
Exenatide (nasal)	AmyRad MORNA (Nastech)	Nasal spray formulation of exenatide
AC3174	Eli Lilly	Exenatide with leucine substituted methionine at position 14
CJC-1134-PC (PC-DAC Exendin-4)	ConjuChem	Subcutaneous, once weekly, exendin-4 conjugated to recombinant human albumin
ITCA 650	Intarcia Therapeutics	Continuous subcutaneous delivery, exenatide-based
ORV0-0801	Orexed Pharmaceuticals	Oral, GLP-1R agonist, exenatide-based
ViaDer-GLP1R Agonist	TransPharma Medical	Transdermal, once daily, exenatide-based
VRS 859 / Exenatide once monthly	Eli Lilly	Subcutaneous, once monthly, fusion protein of exenatide and a long hydrophilic tail of sialic acids
PF-04603829	Pfizer	Combination of exendin-4 fused to human transferrin

Adapted by Filip K. Knop, MD, PhD (Copenhagen, Denmark) from Sivertsen J, et al. *Nat Rev Cardiol*. 2012;9:209-222.

SGLT-2 Inhibitors—Canagliflozin (Invokana)

Dapagliflozin (resubmitted FDA, PDUFA date 1/2014)(Forxiga in Europe); Empagliflozin (PDUFA date 3/2014)

Clinical Effects

- Novel mechanism of action
- Most will respond—action independent of beta-cell function
- A1C reduction ~1% with 2-3 kg weight loss

Possible Side Effects and Precautions

- Mycotic genital infections
- Findings due to volume depletion
- Don't use if eGFR <45%

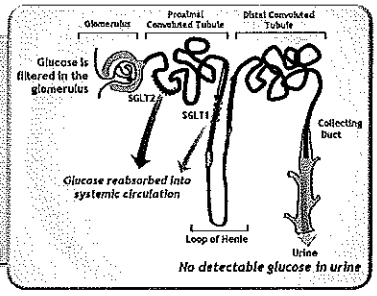
Other Features

- Lowers BP slightly
- Raises LDL cholesterol

Jardiance LV, et al. *Br J Clin Pharmacol.* 2009;68:549-558. Invokana PI, et al. *Br J Clin Pharmacol.* 2007;64:817-827.

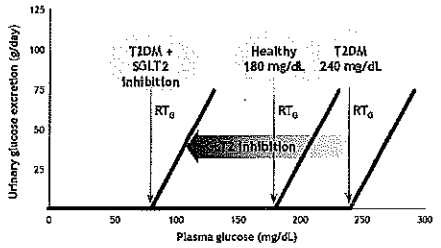
Sodium-Glucose Co-transporters (SGLTs) and Normal Renal Handling of Glucose

- 180 g/day/1.73 m² is filtered glucose load[1]
- SGLT2 transports 90% of filtered glucose out of the tubular lumen[1-4]
- SGLT1 transports the remaining 10% of filtered glucose[1-4]
  - SGLT1 is the primary SGLT in the small intestine[1,3]



SGLT = sodium-glucose co-transporter.
1. Wright EM et al. *J Intern Med.* 2007;261(1):32-43. 2. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 3. You G et al. *J Biol Chem.* 1995;270(49):29365-29371. 4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion (RT_G)

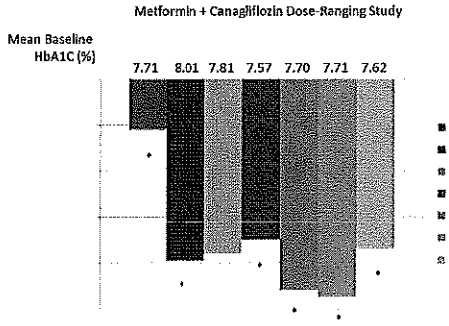


Adapted with permission from Abdul-Ghani MA, DeFronzo RA.
T2DM = type 2 diabetes mellitus.
1. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract.* 2008;14(6):782-790. 2. Katz S, Wilding JP. *J Clin Endocrinol Metab.* 2010;95(1):34-42.

RS2

Canagliflozin: Effects on HbA1c

Metformin + Canagliflozin Dose-Ranging Study

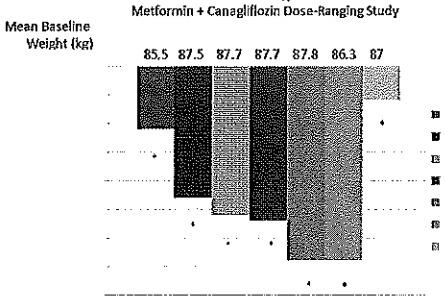


Rosenstock J, et al. *Diabetes Care* 2012;35:1232-1238. *P <0.001 vs. placebo calculated using LS means

RS3

Weight Loss with Canagliflozin

SGLT2 Inhibition for Type 2 Diabetes: Metformin + Canagliflozin Dose-Ranging Study



Rosenstock J, et al. *Diabetes Care* 2012;35:1232-1238. *P <0.001 vs. placebo calculated using LS means

Volume Depletion-related AEs (DS3)

	Non-CANA N=3282 n (%)	CANA 100 mg N=3092 n (%)	CANA 300 mg N=3085 n (%)
Any adverse events (AEs)	78 (2.4)	99 (3.2)	141 (4.6)
Serious AEs	11 (0.3)	12 (0.4)	6 (0.3)
Specific AE Terms			
Blood pressure decreased	1 (<0.1)	2 (0.1)	2 (0.1)
Dehydration	13 (0.4)	6 (0.2)	13 (0.4)
Dizziness postural	24 (0.7)	26 (0.8)	33 (1.1)
Hypotension	20 (0.6)	47 (1.5)	60 (1.9)
Hypovolemia	1 (<0.1)	0	0
Hypovolemic shock	0	0	1 (<0.1)
Orthostatic hypotension	6 (0.2)	8 (0.3)	27 (0.9)
Orthostatic intolerance	1 (<0.1)	1 (<0.1)	1 (<0.1)
Presyncope	9 (0.3)	4 (0.1)	3 (0.1)
Syncope	13 (0.4)	12 (0.4)	20 (0.6)
Urine output decreased	1 (<0.1)	0	0

CANA: canagliflozin
Data on file, Janssen Pharmaceuticals, Inc.

Prepared by Janssen Scientific Affairs, LLC | April 2013 | 25

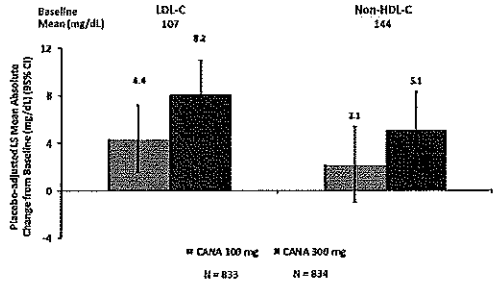
Risk Factors: Volume Depletion-related AEs (DS3)

	Non-CANA %	CANA 100 mg %	CANA 300 mg %
eGFR (mL/min/1.73m²)			
<60	2.5	4.7	8.1
60 to <90	1.5	2.4	2.9
≥90	1.2	1.3	2.4
Age (years)			
<75	1.4	2.2	3.1
≥75	2.6	4.9	6.7
Use of loop diuretics			
No	1.2	2.2	2.9
Yes	4.7	3.2	8.8

CANA: canagliflozin; eGFR: estimated glomerular filtration rate.

Invokana [prescribing information]. Janssen Pharmaceuticals, Inc., Titusville, NJ: 2013; Data on file. Janssen Pharmaceuticals, Inc.

Fasting LDL-C and Non-HDLC Absolute Change (DS1)



CANA: canagliflozin

Invokana [prescribing information]. Janssen Pharmaceuticals, Inc., Titusville, NJ: 2013; Data on file. Janssen Pharmaceuticals, Inc.

RS4

RS5

Goal: HbA1c Reduction

CLASS	HbA1c reduction
Insulin	+++
Sulfonylureas/glinides	++
Thiazolidinediones	++
GLP-1 receptor agonists	++
SGLT-2 inhibitors	++
Biguanides	++
DPP4 inhibitors	+
Colesevelam	+
Bromocriptine QR	+
α-Glucosidase inhibitors	+
Amylin mimetics	+

Inzucchi SE et al. Diabetes Care 2012; 35:1364-1379. Majumdar SK & Inzucchi SE Endocrine. 2013 Jan 25. [Epub ahead of print]

RS6

Goal: Avoiding hypoglycemia

CLASS	Risk of hypoglycemia
Insulin	Yes
Sulfonylureas/glinides	Yes
Amylin mimetics	Yes*
Biguanides	Neutral
Thiazolidinediones	Neutral
GLP-1 receptor agonists	Neutral
SGLT-2 inhibitors	Neutral
DPP4 inhibitors	Neutral
Colesevelam	Neutral
Bromocriptine QR	Neutral
α-Glucosidase inhibitors	Neutral

AACE

RS7

Goal: Weight loss or avoidance of weight gain

CLASS	Weight change
Secretagogues	↑
Insulin	↑ or ↑↑
Thiazolidinediones	↑↑
Metformin	↓ or ↔
GLP-1 receptor agonists	↓
SGLT-2 inhibitors	↓
Amylin mimetics	↓
DPP-4 inhibitors	↔
Colesevelam	↔
Bromocriptine quick-release	↔
α-Glucosidase inhibitors	↔

Haines S Diabetes & Inzucchi SE Endocrine. 2013 Jan 25. [Epub ahead of print]

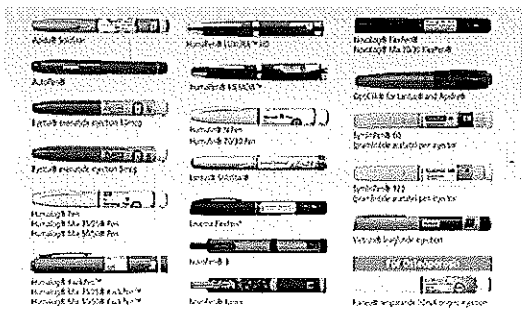
RS8

Goal: Reducing cardiovascular risk factors

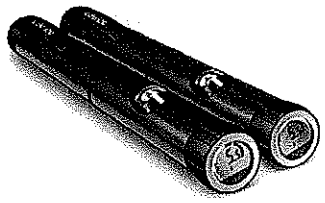
Therapies with positive effects on:	
Blood Pressure	Lipids
GLP-1 receptor agonists	GLP-1 receptor agonists
~~DPP4 inhibitors~~	~~DPP4 inhibitors~~
SGLT-2 inhibitors	Colesevelam
Thiazolidinediones	Pioglitazone

Inzucchi SE et al. *Diabetes Care* 2012;35:1364-1379; Singh S *Curr Cardiol Rep* 2013;15:327-35.

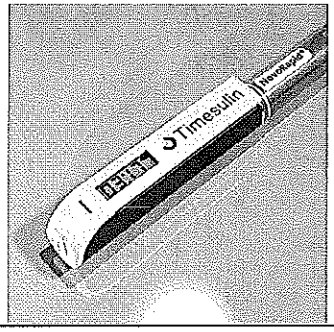
Pen Delivery of Injectibles



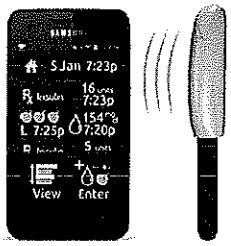
Echo Pen (not just for kids…)



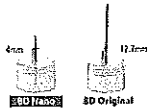
Timesulin



GoCap



Shorter Pen Needles



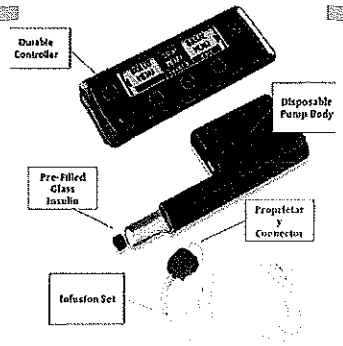
ADA Statement on CSII Therapy

Most people with type 1 diabetes should be treated with MDI injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII).
Evidence category A

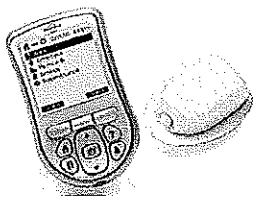
Standards of Medical Care-2014, Diabetes Care 37 (suppl 1), 2014

TSlim

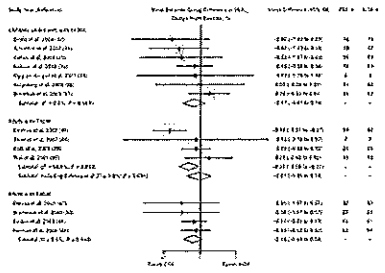
Asante Snap



Pumps: Omnipod

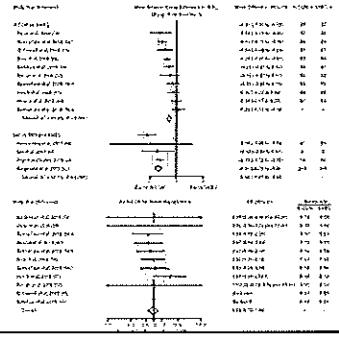


AHRQ Review Insulin Pumps--Mean Between-group Difference in the Change from Baseline HbA1c: CSII vs MDI

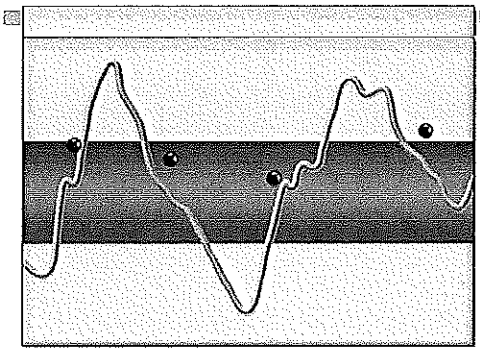


Ann Int Med 157:336-347, 2012

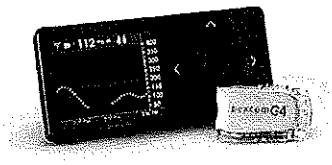
AHRQ Review Insulin Pumps—Sensor Augmented Pump (SAP) vs MDI + SMBG



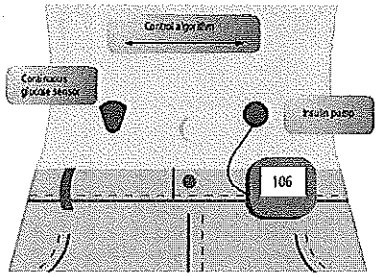
The Value of Continuous Glucose Monitoring



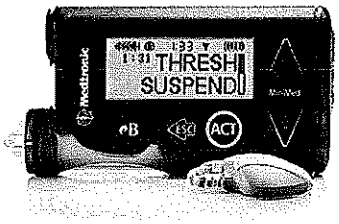
CGM: Dexcom Gen 4



Closed loop "automatic" systems (pump-sensor)



First Step to Closing the Loop



MiniMed 530G system

The Threshold Suspend feature automatically stops insulin delivery when sensor glucose values reach a preset low threshold.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

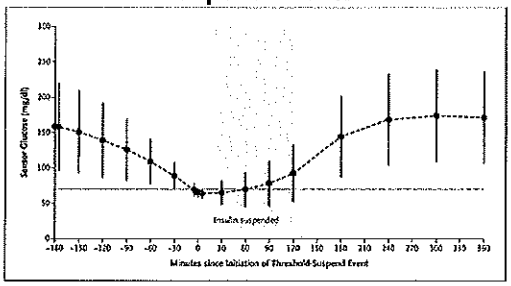
Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*

ABSTRACT

BACKGROUND

The threshold-suspend feature of sensor-augmented insulin pumps is designed to minimize the risk of hypoglycemia by interrupting insulin delivery at a preset sensor glucose value. We evaluated sensor-augmented insulin-pump therapy with and without the threshold-suspend feature in patients with nocturnal hypoglycemia

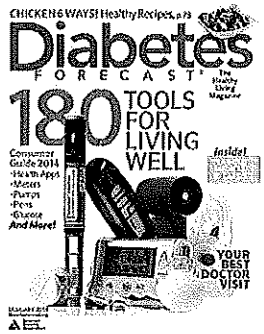
Sensor Glucose Values during Threshold-Suspend Events



Bergenstal RM et al. N Engl J Med 2013;369:224-232

NEJM 369:224-232, 2013

Devices Resource Guide



THANK YOU