The Death of Sulfonylureas?
A Review of New Diabetes Medications

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Objectives

- Review GLP-1 Agonists, DPP-IV Inhibitors and SGLT-2 Inhibitors
- Analyze new evidence supporting the use of liraglutide and empagliflozin
- Compare and contrast treatment algorithms from the American Diabetes Association and the American Association of Clinical Endocrinologists

Pretest Question

1. Which one of the following statements best describes your experience with GLP-1 agonists, DPP-IV inhibitors and/or SGLT-2 inhibitors?
   a) I routinely prescribe these medications
   b) I don't have much clinical experience with them
   c) I have never heard of these medications
   d) I haven't had enough coffee yet to answer this question

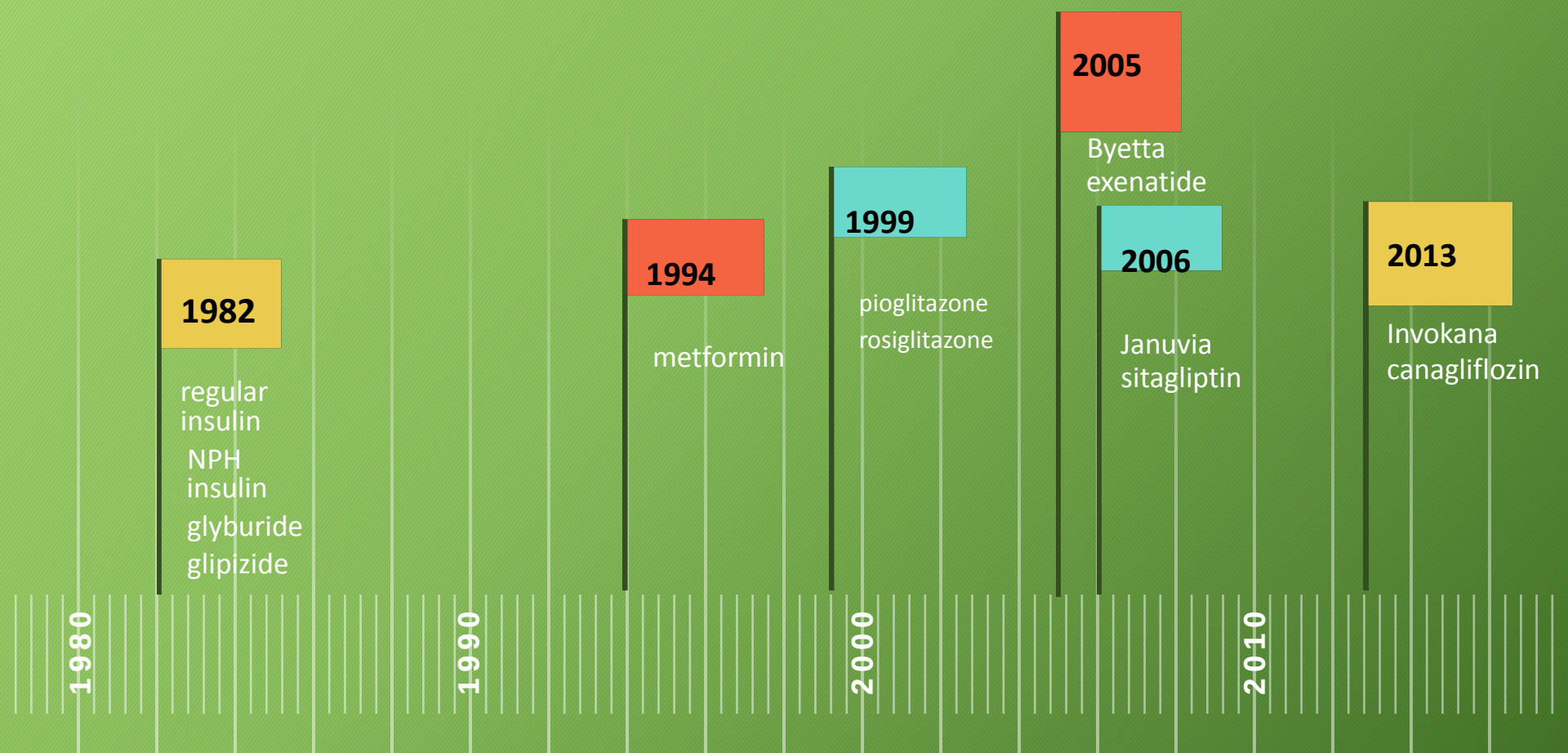
Pretest Question

2. Which one of the following medications have been shown to improve cardiovascular outcomes in high risk diabetic patients?
   a) exenatide (Byetta) and sitagliptin (Januvia)
   b) saxagliptin (Onglyza) and canagliflozin (Invokana)
   c) empagliflozin (Jardiance) and liraglutide (Victoza)

Pretest Question

3. Which of the following medications have been associated with euglycemic acidosis AND acute kidney injury AND bone fractures?
   a) canagliflozin (Invokana)
   b) empagliflozin (Jardiance)
   c) liraglutide (Victoza)
   d) exenatide (Byetta)

FDA Approvals of Diabetes Medications



GLP-1 Receptor Agonist

Generic (Brand Name)	Initial Dose	Usual Dose	Median AWP (per month)
Exenatide (Byetta)	5mcg sq bid	10mcg sq bid	$729
Exenatide (Bydureon)	2mg sq qwk	2mg sq qwk	$692
Liraglutide (Victoza)	0.6mg sq daily	1.2mg sq daily	$831
Albiglutide (Tanzeum)	30mg sq qwk	50mg sq qwk	$527
Dulaglutide (Trulicity)	0.75mg sq qwk	1.5mg sq qwk	$690
Lixisenatide (Adlyxin)	10mcg sq daily	20mcg sq daily	??

- MOA: ↑insulin secretion (glucose dependent), ↓ glucagon secretion, ↓ gastric emptying, ↑satiety
- Advantages: no hypoglycemia, weight loss, good A1c reduction (up to 1.5%)
- Disadvantages: nausea, injectable, medullary thyroid cancer (black box warning), high cost

DPP-IV Inhibitors

Generic (Brand Name)	Initial Dose	Usual Dose	Median AWP (per month)
Sitagliptin (Januvia)	100mg PO daily	100mg PO daily	$436
Saxagliptin (Onglyza)	2.5mg PO daily	5mg PO daily	$436
Linagliptin (Tradjenta)	5mg PO daily	5mg PO daily	$428
Alogliptin (Nesina)	25mg PO daily	25mg PO daily	$436

- MOA: ↑insulin secretion (glucose dependent), ↓ glucagon secretion
- Advantages: no hypoglycemia, weight neutral, well tolerated
- Disadvantages: minimal A1c reduction (0.4-0.7%), arthralgias/joint pain (FDA warning in 2015), ↑risk of HF-related admission, high cost

SGLT2 Inhibitor

Generic (Brand Name)	Initial Dose	Max Dose	Median AWP (per month)
Canagliflozin (Invokana)	100mg PO daily	300mg PO daily	$470
Dapagliflozin (Farxiga)	5mg PO daily	10mg PO daily	$470
Empagliflozin (Jardiance)	10mg PO daily	25mg PO daily	$470

- MOA: Blocks glucose reabsorption in the kidney
- Advantages: no hypoglycemia, weight loss, ↓blood pressure
- Disadvantages: GU infections, polyuria→ dehydration→ hypotension→ falls, many FDA warnings, high cost

SGLT2 Inhibitors- FDA Warnings

- Euglycemic ketoacidosis (all)
- Acute kidney injury (dapa and cana)
- Bone fracture (cana)
- Leg/foot amputations? (cana)

BENEFITS OF EMPAGLIFLOZIN AND LIRAGLUTIDE

DM Meds and CV Impact

- It can be argued that no DM med has ever demonstrated clear CV benefit
  - metformin/UKPDS study
    - 1970 data, post-hoc analysis in overweight pts
  - pioglitazone/PROactive study
    - 2^{o} endpoint only, offset by poor HF outcomes
- Since 2008 (and the rosiglitazone debacle), the FDA has asked for data evaluating CV outcomes with DM meds

Lancet 1998;352(9131):854-65
Lancet 2005;366(9493):1279-89

EMPA-REG Outcome- Cardiovascular

Study Design	Randomized, double-blind, placebo controlled trial (n=7020)
Treatment Arms	Empagliflozin 10mg or 25mg vs. placebo
Primary Endpoints	Death from CV/non-fatal MI or stroke, mean f/u 3.1 years
Efficacy Results	Empagliflozin superior to placebo in preventing death from CV/non-fatal MI or stroke (10.5% vs. 12.1%, HR 0.86 (95% CI 0.74-0.99, p=0.004 for superiority) [NNT 63 over 3 years]
Safety Results	Overall genital infections: NNH 22 (women: NNH 14) No difference in DKA, bone fracture, AKI
Notes	Average pt was a white, male in their 60's with A1c of 8% with CAD Death from CV causes: NNT 45 Hosp for HF: NNT 71 Death from any cause: NNT 39 Trend toward ↑stroke in empa group, but not statistically sig

NEJM 2015;373(22):2117-2128

EMPA-REG Outcome- Renal

Study Design	Randomized, double-blind, placebo controlled trial (n=6185)
Treatment Arms	Empagliflozin 10mg or 25mg vs. placebo
Primary Endpoints	Incident or worsening nephropathy, mean f/u 3.1 years
Efficacy Results	Empagliflozin superior to placebo in preventing incident or worsening nephropathy (12.7% vs. 18.8%, HR 0.61 (95% CI 0.53-0.70, p < 0.001) [NNT 16 over 3 years]
Safety Results	Higher incidence of genital infection Similar rates of overall/complicated UTI, fractures and AKI
Notes	Doubling of SCr: 1.5% empa/2.6% placebo RRT: 0.3% empa/0.6% placebo

NEJM 2016;375:323-344

LEADER Trial

Study Design	Randomized, double-blind, placebo controlled trial (n=9340)
Treatment Arms	Liraglutide 1.8mg (or max tolerated) daily or placebo
Primary Endpoints	Time to death from CV/non-fatal MI or stroke, mean f/u 3.8 years
Efficacy Results	Liraglutide superior to placebo in preventing death from CV/non-fatal MI or stroke (13% vs. 14.9%, HR 0.87 (95% CI 0.78-0.97, p = 0.01 for superiority), NNT 53 [66 over 3 years]
Safety Results	Most common adverse events were GI related (n/v/d/pain) Acute pancreatitis was lower in the lira group (non-sig) Benign/malignant neoplasms were higher in the lira group (non-sig)
Notes	Average pt was a white, male in their 60's with A1c of 8.7% with CVD Death from CV causes: 4.7% vs. 6%, NNT 77 Death from any cause: 8.2% vs 9.6%, NNT 71 (98 over 3 years)

NEJM 2016;375:311-322

Ongoing Cardiovascular Outcome Trials

- GLP-1 Agonists
  - HARMONY trial (albiglutide)
  - REWIND trial (dulaglutide)
  - EXSCEL trial (exenatide)
- DPP-IV Inhibitors
  - CAROLINA trial (linagliptin)
- SGLT2 Inhibitors
  - CANVAS trial (canagliflozin)
  - DECLARE-TIMI58 trial (dapagliflozin)

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	SU: Moderate/Severe; GLN: Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contrain-dicated if eGFR < 30 mL/min/1.73 m^2	Exenatide Not Indicated CrCl < 30; Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m^2; Genital Mycotic Infections; Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin); Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC* ASCVD		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect | * FDA indication to prevent CVD death in diabetes plus prior CVD events

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GUIDELINE UPDATES

ADA: Key Changes for 2017

- New recommendation to specifically consider the GLP-1 receptor agonist liraglutide and the SGLT-2 inhibitor empagliflozin in a high-risk population to lower the risk of death
  - More research is needed to confirm if the heart benefits are a class effect or if the benefits persist in patients without established CV disease.
- Also new data supporting the use of basal insulin + GLP1 receptor agonist vs basal insulin + rapid-acting insulin

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[¶]	or GLP-1-RA	or Insulin[¶]	or GLP-1-RA
or Insulin[¶]	or Insulin[¶]		or Insulin[¶]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

DM Care 2017;40(1)

Combination Injectable Therapy (See Figure 8.2)

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

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Post-test Question

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QUESTIONS?

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