New and Emerging Diabetes Medications

What do Advanced Practice Nurses Need to Know?

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Objectives

1) Describe the clinical indications on select emerging novel diabetes agents including the SGLT2 inhibitors, GLP-1 Receptor Agonists, and the ultra long acting insulin, Degludec.
2) Compare and contrast the recently FDA approved SGLT2, GLP1 and DPP-4 inhibitor agents
3) Explain the mechanism(s) of action in these new classifications of drugs
4) Describe three new and upcoming technological advances in diabetes

Today's Goal

- To gain a better insight into understanding new advances in diabetes management from 2014, to 2015 and beyond!

Focus Today

- Sodium-Glucose Cotransporter-2 Inhibitors
  - Canagliflozin (Invokana®)
  - Empagliglozin(Jardiance)
  - Dapagliflozin (Farxiga®)
- GLP-1 Receptor Agonists
  - Albiglutide (Tanzeum®)
  - Exenatide(Bydureon & Byetta)
  - Dulaglutide (Trulicty
- Insulin
  - Degludec (Tresiba®)
  - Insulin degludec and Liraglutide (IDegLira®)
- DPP-4 Inhibitors
  - Alogliptin (Nesina®)

Prevalence of Diabetes

Number of Persons with Diagnosed Diabetes,
United States, 1980-2012 (reported in 2014)

Diabetes is becoming more common in the United States. In 2000, about 12 million persons in the United States reported that they had diabetes. As the detailed tables show, people aged 65 years or older account for almost 40% of the population with diabetes. Between 1996 and 1997 an unusually large increase occurred in the number of people with diagnosed diabetes. Most of this increase is likely due to changes in the survey used to measure diagnosed diabetes.

2014 Estimates

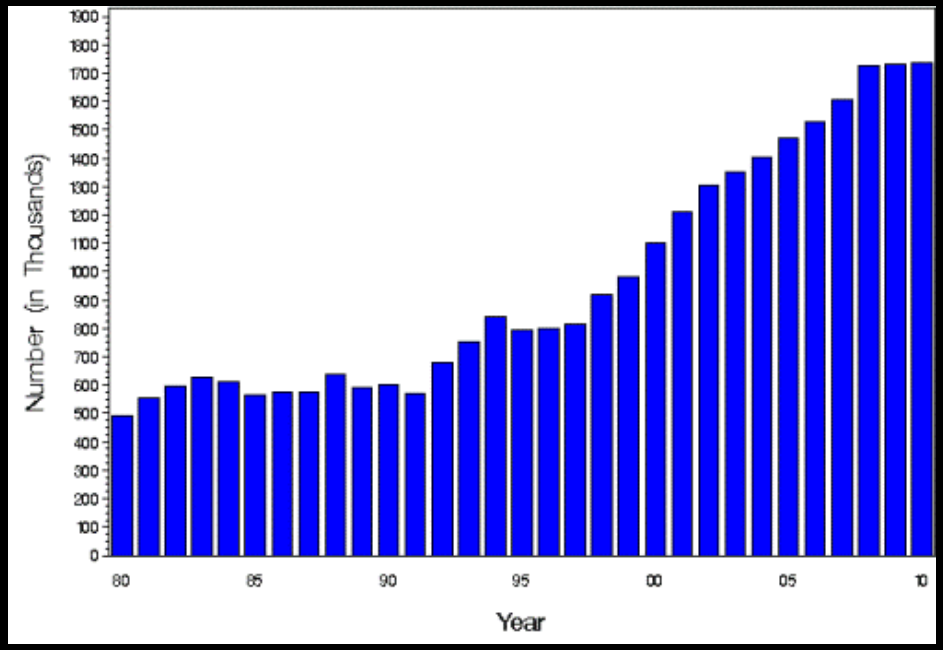
21.0 million diagnosed

8.1 million undiagnosed (27.8% of people with diabetes are undiagnosed)

9.3% of our population

29.1 million

Pre-diabetes = 86 million! *



* =age 20 and older

www.cdc.gov/diabetes

What color is a yield sign?

1. Red and white
2. Yellow and black
3. Orange and white
4. Orange and black
5. Black and white


YIELD


YIELD


YIELD
FreeFoto.com

The Foundation for Diabetes Management

- Education
- Nutrition
- Physical Activity
- Monitoring
- Medications

Population Group	Type and Amount of Activities	Observed Benefit
10,269 Harvard alumni	Walking at least 9 miles a week	22% lower death rate
	Climbing at least 55 flights of stairs a week	33% lower death rate[9]
1453 middle-aged Finnish men	At least 2.2 hours of leisure time/wk	69% lower risk for heart attack
73,743 American women aged 50-79	Walking for at least 2.5 hours per week	30% lower risk for cardiovascular events[12]
39,372 American female health professionals	Walking at least 1 hour/week	51% lower risk for coronary artery disease[13]
72,488 American female nurses	Walking at least 3 hours/week	35% lower risk for heart attack and cardiac death
30,640 Danish men and women aged 20-93	Spending 2-4 hours/week on light leisure time activity	32% lower mortality rate[15]
4311 British men aged 40-59	Performing light-to-moderate physical activity	35% to 39% lower mortality rate[16]
1404 female residents of Framingham, Massachusetts	Performing moderate physical activity	37% lower mortality rate[17]
802 Dutch men, aged 64-84	Walking or biking at least 1 hour/week	29% lower mortality rate[18]
707 retired Hawaiian men, aged 61-81	Walking at least 2 miles/day	50% lower mortality rate[19]
9518 older American women	Walking up to 10 miles/week	29% lower mortality rate[20]
229 postmenopausal women 10 yr study	Walking 1 mile/day or more	82% lower risk for heart disease[21]
7951 pairs of Finnish twins	Exercising 30 minutes 6 Days/Mont	43% lower mortality rate[22]
6017 Japanese men, aged 35-60	Walking (to work) for 21 minutes or more on work days	29% lower risk of developing hypertension[23]


Wonder what those are?
ADA EXPO 2012
Exhibi
Hey You at the bottom, why not try me?
Wow! None of those ADA attendees like us steps.

You have diabetes, which wafer should you purchase?

15 GRAMS SUGAR

O GRAMS SUGAR


15% Total Carbohydrate 18g 6%
10%
0% Sugars 15g
1% Protein 0g
SUGAR WAFERS
Poll on next slide
Nutrition Facts
Serving Size 3 wafers (31g)
Servings Per Container 5
SUGAR FREE
Amount Per Serving
Calories 170 Calories from Fat 90
% Daily Value*
Total Fat 10g 15%
Saturated Fat 1g 6%
Cholesterol 0mg 0%
Sodium 50mg 2%
Total Carbohydrate 19g
Dietary Fiber 0g 0%
Sugars 0g
Sorbitol 6g
Protein 1g
Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 4%

Keep it Simple

Preliminary Dietary recommendations at Diagnosis of Diabetes and Pre-Diabetes

- Food to Avoid!!!
  - Candy
  - Cookies
  - Cakes
  - Ice Cream
  - Pies
  - Honey
  - Sweet sodas
  - Juices
  - Muffins
  - Sugar free or no sugar added foods and drinks that have more than 60 – 80 calories per serving (e.g. sugar free ice cream, no sugar added muffins)
- Food Allowed!!!
  - Bread – In Moderation
  - Rice – In Moderation
  - Potatoes – In Moderation
  - Whole Fresh Fruit
  - Sugar free or no sugar added foods with no more that 10 calories per serving

What about Recommended Treatments for Pre-Diabetes from ADA and AACE for 2014?

THERE ARE NONE

Challenges in Diabetes Management

- In adequate Postprandial Glucose Control
- Significant Weight Gain
- Excessive Glucose Fluctuations
- Excessive Appetite
- Poor Satiety
- Excess Hepatic Glucose Release
- Impaired Gastric Emptying
- Clinical Inertial (Failure to Intensify Therapy)

Raskin P. Diabetes Metab Res Rev 2013; 29:347-56

Rosiglitizone is BACK!!!

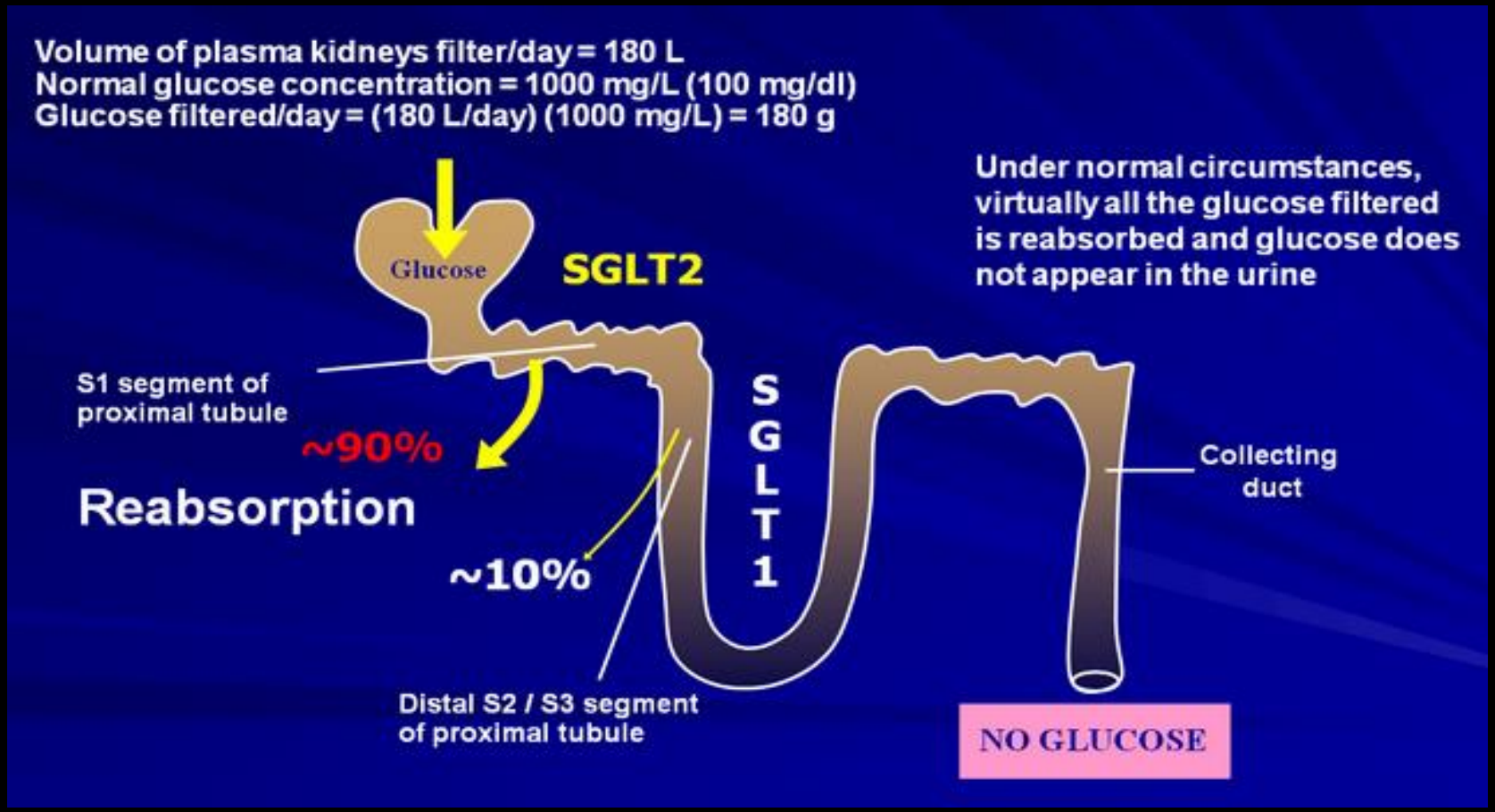
- Health regulators lift restrictions on the use of Avandia.
- Determined that it did not increase the risk of heat attacks.
- No longer require physicians to register Avandia patients into a Risk Evaluation and Mitigation Strategy (REMS) program.

SGLT2 Inhibitors

- Empagliflozin (Jardiance)
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Ipragliflozin (Suglat)

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors

Glucose Transportation at the Kidneys



Wright, EM. Am JH Renal Physiol 2001;280(1):F10-F18

Taylor SR, Harris KB. Pharmacotherapy 2013; 33(9): 984-99

SGLT2 Inhibitors

- Good safety profile if highly selective for SGLT2.
- Approved for monotherapy in early stage T2DM based on mechanism of action but use in combination currently recommended due to lack of sufficient data.
- Second line treatment.
- Minimal advantage if adequate glycemic control on current drug therapy.
- No concerns about development of insulin resistance or deterioration of β-cell function.

Development and potential role of type-2 sodium-glucose transporter inhibitors for management of type 2 diabetes. Timothy CH, Simon WD. Diabetes Ther. 2011 September, 2(3): 133-145.

SGLT2 Inhibitors

- HbA1C reduction of 0.5-0.9%
- Amount of glucose excretion in urine dependent on blood glucose concentration.
- Excretion of 80-90 g of glucose/day.
- Reduced hepatic glucose production.
- Enhanced insulin sensitivity in muscle & liver.
- Preserved pancreatic β-cell function.
- Increased glucose excretion leads to increased urinary flow (osmotic diuretic effect
- Reduced efficacy in kidney impaired patients.
- Do not use in stage IV nephropathy.

Sodium-Glucose Cotranspoerter-2 Inhibitors (Dapagliflozin-Farxiga® Canagliflozin-Invokana®)

What We Need to Know: Canagliflozini (Invokana®)

- Indication: Type 2 Diabetes
- Dosage 100 – 300 mg taken before the first meal of the day
- Assess renal function before starting Invokana®
- Hypotension can occur after initiation of therapy
- Hyperkalemia
- Increases in Genital Mycotic Infections
- Hypoglycemia
- Increases in LDL

What We Need to Know: Dapagliflozin (Farxiga®)

- Indication: Type 2 Diabetes
- Dosage 5 mg with or without food (can increase to 10 mg)
- Assess renal function before starting Farxiga®
  - Do not initiate with eGFR < 60 ml/min/1.73m^2
  - Discontinue if eGFR < 60 ml/min/1.73m^2
- Monitor for Genital mycotic infections UTI nasopharyngitis, and hypersensitivity
- Avoid use in patients with bladder cancers

Recommended Dosing in Patients with Renal Impairment

Canagliflozin

- Increase dose to 300 mg daily if eGFR >60 mL/min/1.73 m^2
- eGFR 45 to < 60 mL/min/1.73 m^2: Limit dose to 100 mg daily
- Do not initiate or discontinue if eGFR < 45 mL/min/1.73 m^2

Dapagliflozin

- Do not initiate or discontinue if eGFR < 60 mL/min/1.73 m^2

Canagliflozin [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.
Dapagliflozin [package insert].Princeton, NJ: Bristol-Myers Squibb Company; 2014.

Dapagliflozin® (Farxiga)

- SGLT2 Inhibitor Next is combination with Metformin
  - (5mg Dapagliflozin + 500 mg or 1000 mg metformin)
- NDA resubmission of Dapagliflozin triple combination with metformin and sulfonylurea.
  - Increased blood glucose lower compared with either agents alone in patients with newly diagnosed type 2 diabetes.
  - Significant drops in HbA1c and body weight at 24 weeks

Empagliflozin(Jardiance) Approved in August 2014

- Lowering HbA1c and weight independently of β-cell function or insulin resistance.
- Reduced HbA1c, fasting plasma glucose, and body weight for up to 90 weeks in T2DM when used as monotherapy (10 or 25 mg) or as an add-on to metformin
- Well tolerated at doses 10 & 25 mg over 90 weeks'
- > 90% of adverse events considered mild-moderate.

Take Home Messages: SGLT-2 Inhibitors

Pros

- Low Risk of Hypoglycemia
- A2c Lowering ~ 1%
  (Non inferior to Metformin)
- Fat Weight Loss 2.8 – 3.5 kg
  (> than metformin)
- Sustained Weight Loss up to 2 years
- FPG ~30 mg/dL
  (> than metformin)
- Improve Blood Pressure

Cons

- Renal Monitoring
- Renal Impairment
- Dosage Adjustments
- UTI Risks
- Mycotic Infections
- Can cause Hypotension
- Can cause Hyperkalemia

Which Statement is True Of the SGLT2 Inhibitors?

1) They have a Potent Long Term Effect on Fluid “Water” Weight

2) One side effect is hypotension

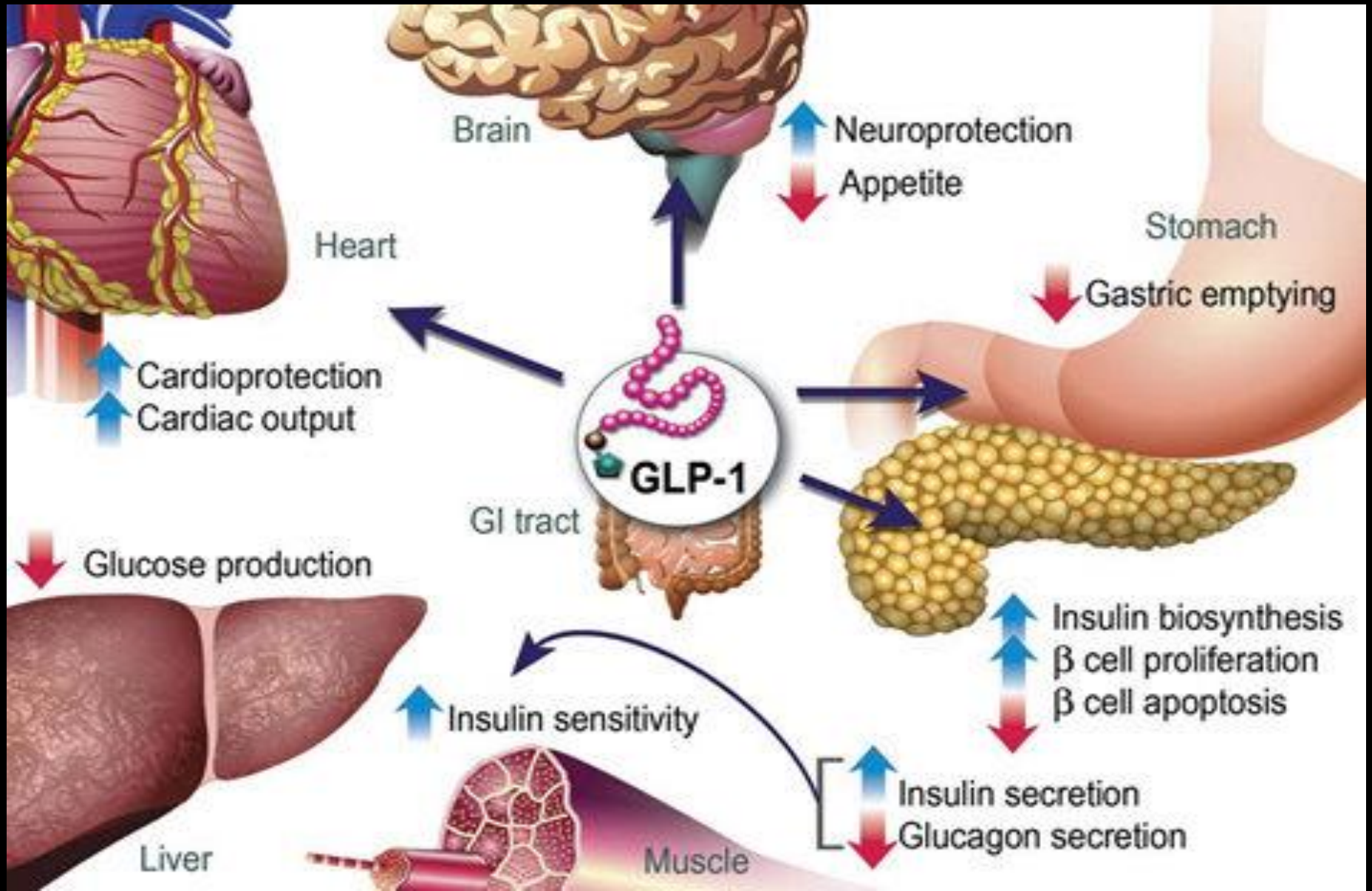
3) Only Canagliflozin Requires Renal Monitoring

4) SGLT2 Inhibitors decrease Fasting plasma glucose 30mg/dL(>than

GLP-1R Agonists

- APPROVED
  - Exenatide (BID) (Byetta®)
  - Exenatide (QW) (Bydureon®)
  - Liraglutide (QD) (Victoza®)
  - Albiglutide (QW) (Tanzeum®)
  - Dulaglutide(QW) (Trulicity)
- EMERGING
  - Lixisenatide (Lyxumia)
  - Semaglutide (Semaglutide or NN9535)

GLP-1 Actions Extend Beyond the Pancreas: Addresses 6 of 8 Aspects of the Ominous Octet + Improves Cardiac Function



Safety, Efficacy and Benefits

- Longer Dosing Intervals
- Gastrointestinal – mild, transient nausea
- Injection Site Reactions
- Low incidence of Hypoglycemia (increased with sulfonylurea or insulin)
- Improved weight related quality of life
- Higher Titer Antibodies
- Pancreatitis, Pancreatic cancers
- Thyroid Cancer

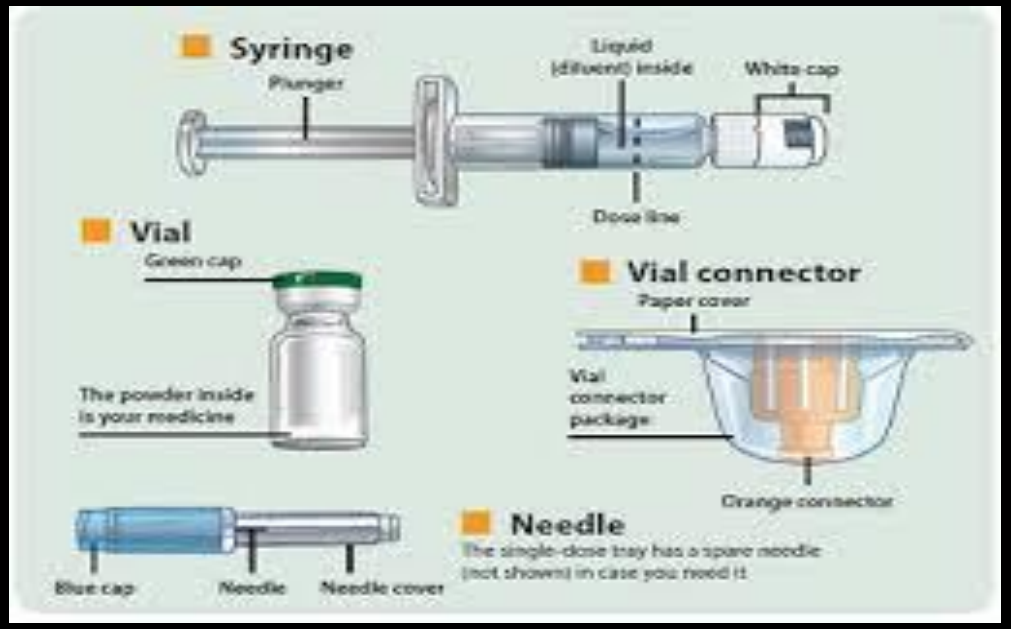
Samson SL, Garber A. Curr Opin Endocrinol Diabetes Obes 2013, 20:87-97

GLP-1 Agonists
Exenatide(Bydureon) and Liraglutide(Victoza)

- Recently approved for use by people with type 2 diabetes
- Exenatide is now approved for use with insulin glargine (Lantus®) in the US.
- Liraglutide is approved for use with detemir (Levemir®) in Europe.
- Hot topic among healthcare providers for several reasons:
- Study last year with exenatide in combination with glargine in type 2 diabetics confirmed:
  - Greater reductions in A1c and weight loss.

New Exenatide Syringe

From this



To this

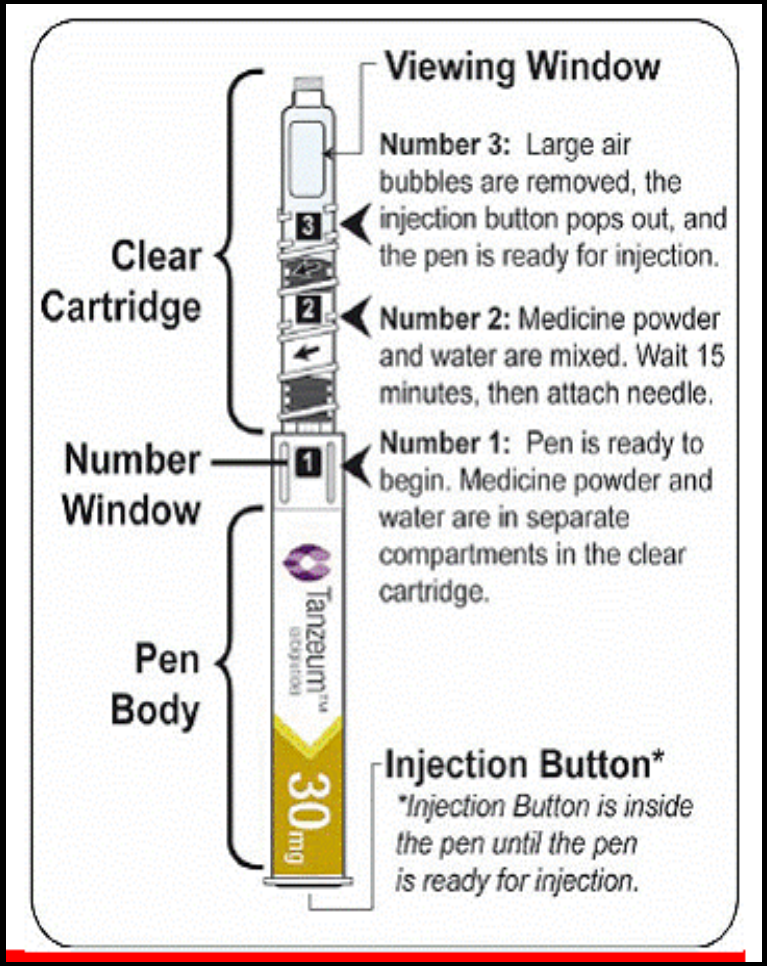
GLP 1 Receptor Agonists
Albiglutide (Tanzeum®)

Albiglutide (Tanzeum)GLP-1 Agonist

- Long-acting glucagon-like peptide agonist or GLP-1 agonist.
- Once-weekly dosing in type 2 diabetes.
- Half-life increased by fusion with albumin.
- Main outcome measure: Results:
  - Dose-dependent reduction in A1c in all albuglutide schedules.
  - Mean A1c reduced from baseline of 8%.
  - 24 mg/dL, Fasting glucose reductions.
  - Weekly dosing to be optimal therapy

Albiglutide (Tanzeum®)
How it works

- Inject at the same time weekly.
- The pen has medicine powder in one compartment and water in another compartment.
- You will need to mix them together by twisting the pen, then wait for 15 minutes for the medicine and water to fully mix.



Albiglutide (Tanzeum)

- Conclusion:
  - Administration of weekly albiglutide in type 2 diabetic patients:
  - Dosage:30mg SC once weekly (increase to 50mg once weekly) with or without food
  - No dosage adjustment for renal impairment
    - Improved glycemic control.
    - Elicited weight loss.
  - Favorable safety and tolerability profile.
  - Less gastrointestinal adverse events

Dulaglutide (Trulicity)

- Approved Sept. 2014
- Dulaglutide (Trulicty®) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) just approved by the FDA that offers adults with type 2 diabetes once-weekly dosing in the dulaglutide pen, which has a pre-attached, hidden needle and requires no reconstitution.

- Long acting GLP-1 agonist

- Once weekly injection.

- Reduced immunogenicity and limited renal clearance.

- Most common side effects: nausea and dyspepsia
- Significant weight loss

Lixsenatide (Lyxumia)

- GLP-1 agonist
- Currently approved in Europe
- Evaluation of lixisenatide in Acute coronary syndrome (ELIXA) study began in 2010.
- Early interim data has halted pharmaceutical company's decision to file an NDA application with the FDA this year.
- Phase III study of lixisenatide in combination with glargine remains on course for 2014.

DPP-4 Inhibitors

- Sitagliptin (Januvia®)
- Linagliptin (Tradjenta®)
- Saxagliptin (Onglyza®)
- Vildagliptin (Galvus®)
- **Alogliptin (Nesina®)**

DPP-4 inhibitors

- Alogliptin (Nesina®)
  - Approved in January 2013

Alogliptin (Nesina)

- Oral selective dipeptidyl peptidase IV inhibitor (DPP-4) as an adjunct to diet and exercise.
- Designed to slow the inactivation of incretin hormones, GLP-1 and GIP, which play a role in regulating blood glucose levels.
- Combinations
  - Alogliptin and metformin HCL
  - Alogliptin and pioglitazone

DPP-4 Inhibitor Agents: Alogliptin (Nesina®), Alogliptin/Metformin (Kazano®), Alogliptin/Pioglitazone (Oseni®)

Safety Concerns of Incretin Memetics (GLP-1R Agonists and DPP-IV Inhibitors)

Safety Concerns: Institute for Safe Medication Practices 2013

- 831 cases of pancreatitis
- 105 cases of pancreatic cancer
- 32 cases of thyroid cancer
- All 5 incretin mimetics taken together had rates of pancreatitis, which were > 25 times higher than in diabetes patients on other drugs.

Ephen D. BMJ 2013; 346:13680

What Do We Need to Know

- Warnings already published regarding postmarketing reports of acute pancreatitis (fatal and serious non-fatal cases)
- No conclusion that these drugs may cause or contribute to the development of pancreatic cancer
- Recent studies was unable to find the association
- Rate of pancreatitis is no different that that of sulfonylurea

http://wwww.fda.gov/drugs/drugsafety/ucm343187.htm Accessed June 3, 2014
Fallie JC, Arculay L, Patenaude V, Hillaire-Buys D, et al.
http://wwwbmj.com/content/348/bmi.g2780 Accessed June 3, 2014

Diabetes Drug Combinations in the Future

- From 1950 to 1995 only 1 oral medication available
- Expect to see other combinations with
  - SGLT-2 inhibitors
  - GLP-1 agonists
  - Metformin
  - TZD's
  - DPP-4's
  - Long acting insulin
- Possible combinations without duplications: 544,320

Insulin Degludec (Tresiba®);

Insulin Degludec (Tresiba®): BEGIN Studies

- The BEGIN studies have evaluated insulin degludec
  - Basal + bolus therapy for T1D and T2D
  - Basal + Oral Antidiabetic agents
- It can be dosed daily or three times weekly
- Its duration of action is up to 40 hours compared to 18 to 26 hours (glargine and detemir)

Gough SCL, Harris S, Woo V, et al. Diabetes, Obesity and Metabolism, 2013 (15): 301-9

Degludec (Tresiba) Basal Insulin

- 21% fewer hyperglycemic events especially at night.
- Requires less frequent dosing
- Requires less insulin
- Offers a more consistent insulin release
- Submitted to FDA in July, 2014.
- Equivalent glycemic control as insulin glargine.

What We Need to Know: Insulin Degludec

Pros

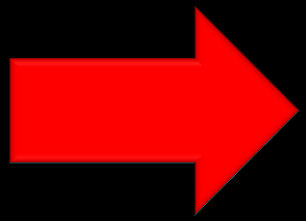
- Less risk of hypoglycemia
- Nocturnal hypoglycemia is reduced
- FPG is lower
- Flexible Dosing

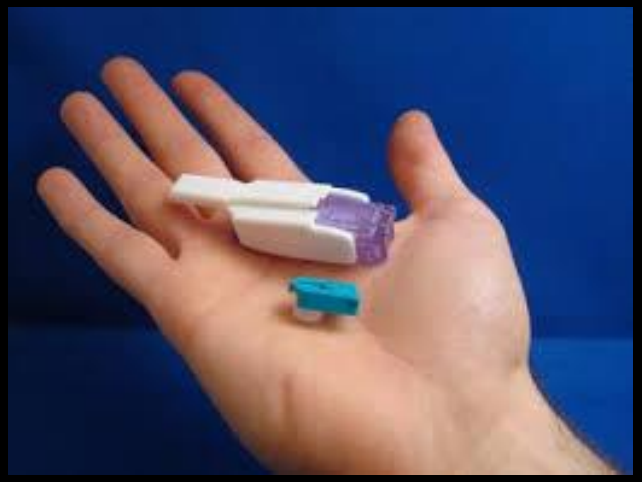
Con

- Similar HbA1c
- Non inferior with regard to weight gain
- May increase the risk of cardiovascular death, no-fatal heart attacks and strokes and unstable angina, compared to standard insulins

Gough SCL, Harris S, Woo V, et al. Diabetes, Obesity and Metabolism, 2013 (15): 301-9

Inhaled Insulin?

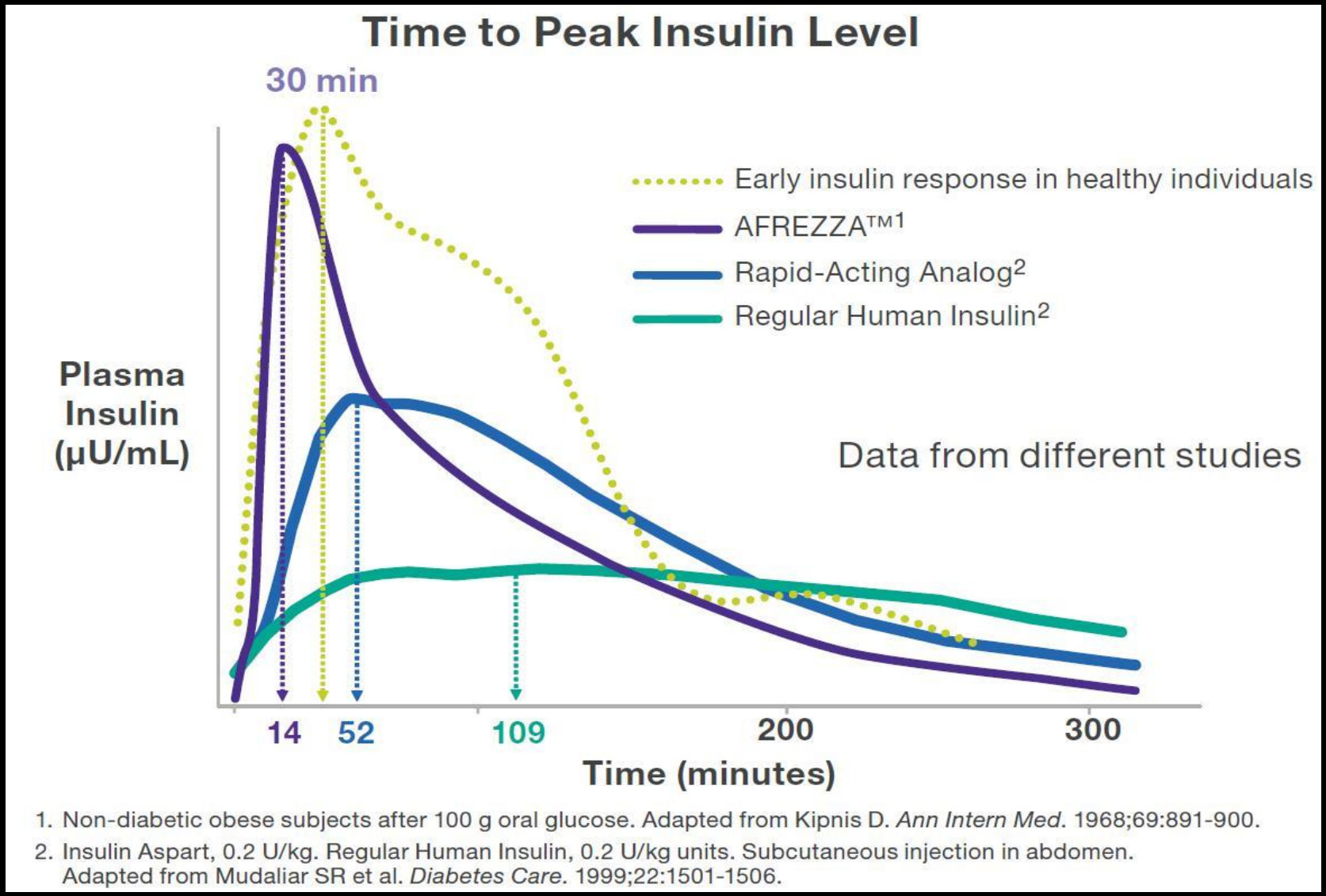




2014

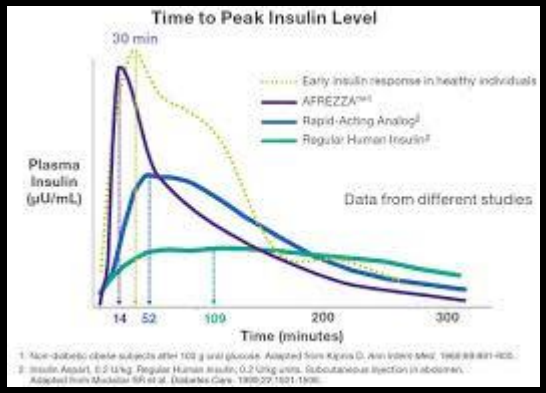
Sept 2007 – Oct. 2007

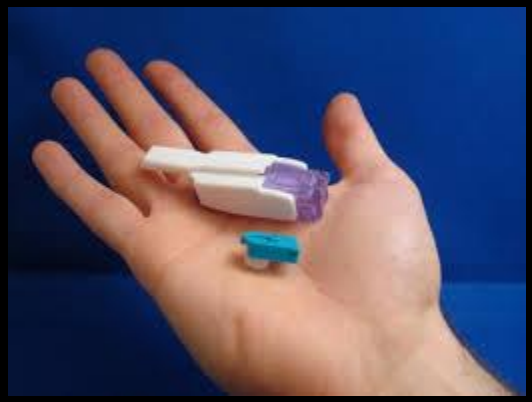
(insulin human) Inhalation Powder



1. Non-diabetic obese subjects after 100 g oral glucose. Adapted from Kipnis D. *Ann Intern Med.* 1968;69:891-900.
2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. *Diabetes Care.* 1999;22:1501-1506.

(insulin human) Inhalation Powder (Afrezza®)





- FDA approved in June 2014
- Clinical trials comparing insulin human inhalation powder to current insulin treatment has shown:
  - Reduction in post-meal glucose fluctuations.
  - Achievement of comparable levels of overall glucose control.
  - Lower fasting glucose levels.
  - Lower risk of hypoglycemia.
  - Less weight gain
- FDA requesting two more studies to be conducted to test tine insulin device's effectiveness in patients with type 1 and type 2 diabetes.

- **Upcoming Devices and Technology**

BIOD-123

- Ultra-rapid acting recombinant human insulin.
- BIO-D123 met the primary efficacy endpoint for non-inferiority in change in A1c vs. Humalog.
- Biod-123 trends in secondary endpoints:
  - ~34% less hypoglycemia vs Humalog.
  - Better postprandial glucose
  - More weight loss

Glargine U300 + Lixisenatide Lyxumia (GLP-1)

- Combines insulin gargine {rDNA origin} + GLP-1 (lixisenatide)
- Phase III trials begin early 2014.
- Synergistic effect of the combination
- First fixed-ratio combination of basal insulin and GLP-1 in the US.
- Insulin glargine in sales was $6.6 billion and the patent expires in 2015.

Medical Devices for Diabetes

- Insulin detemir [rDNA origin] injection pen with low injection force

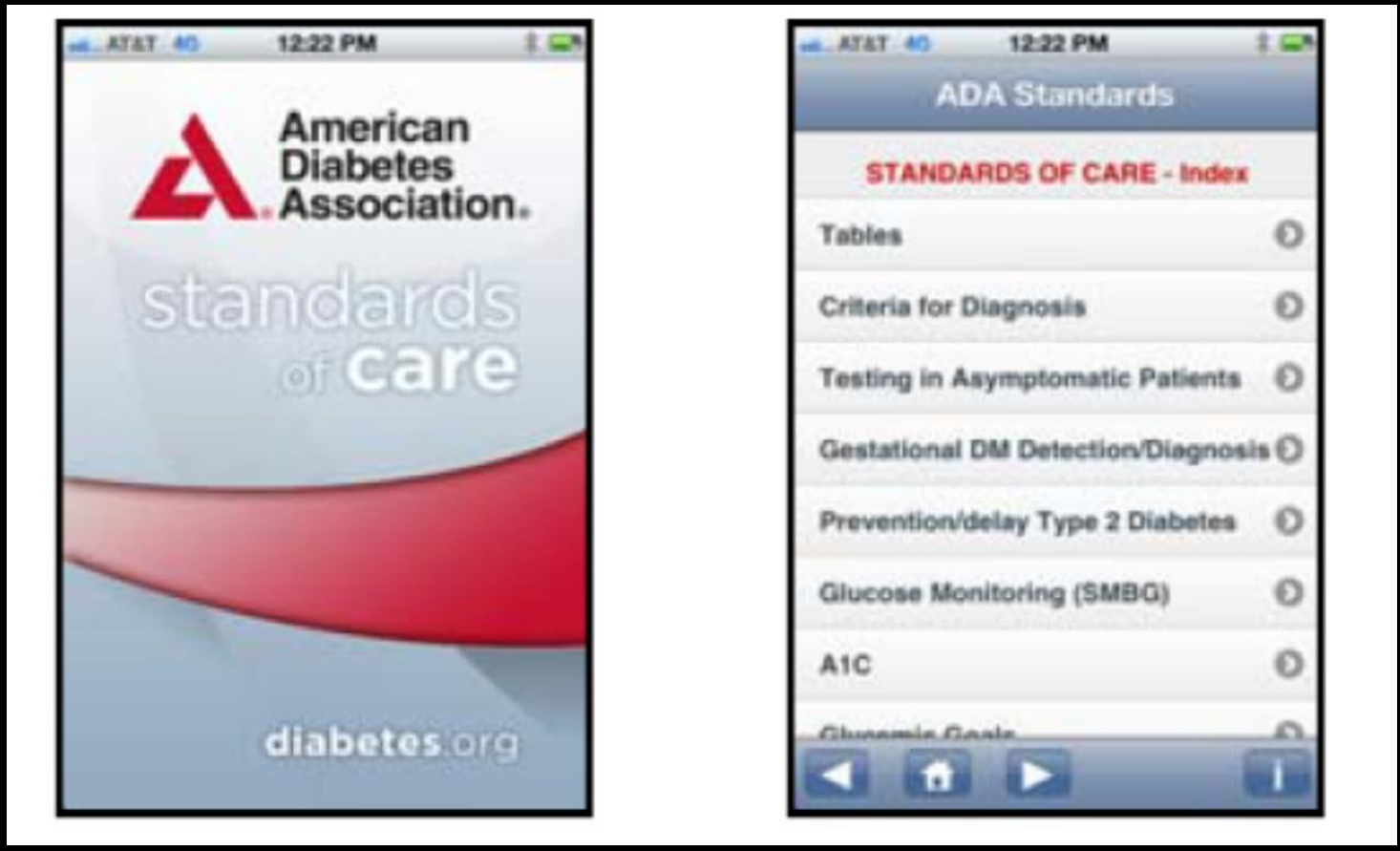
Automatic Shield Pen Needle (BD Duoshield®)

- The automatic shield Pen Needle automatically protects patients from both ends of a pen needle which become contaminated after use.
- This prevents used needle exposure for anyone who may come into contact after the pen needle is removed from the pen.
- The small 5 mm size allows for a safer, no “pinch up”, single-handed injection technique with patients of BMI’s (20-49).
- It has been rigorously tested for fit, function, and dose accuracy with all pens on the market.

Diabetes Apps

- Glucose Buddy®
- Record blood glucose (BG), insulin injections, and view trend graphs.
- Record exercise and diet.
- Can sync with the website (glucosebuddy.com)
- Free, available on iPhone, iPod Touch, iPad.
- 4.5/5 stars based on 704 reviews (itunes.apple.com)

Standards of Care App for Clinicians

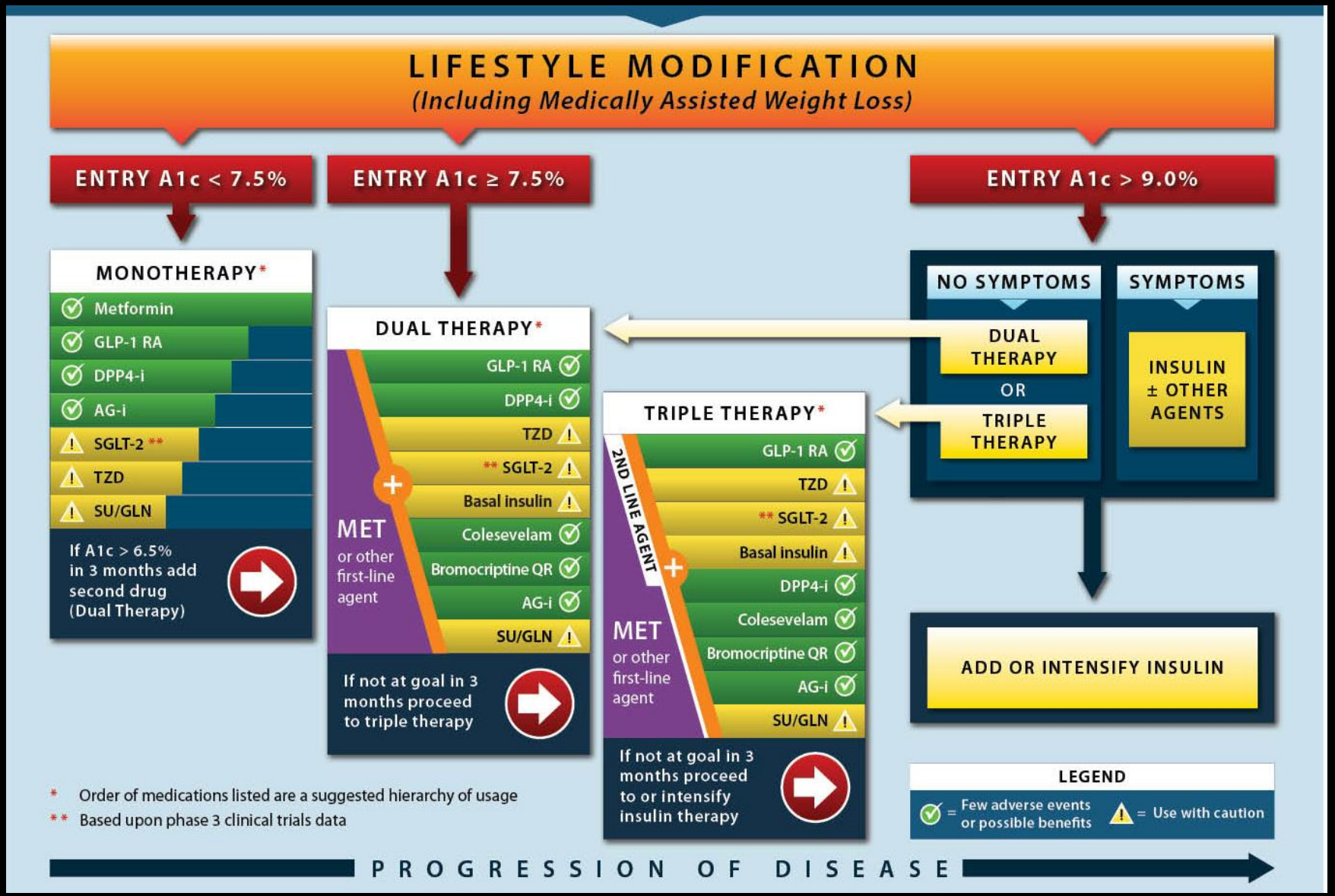


Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits — Use with caution — Likelihood of adverse effects

Glycemic Control Algorithm



Diabetes Apps

Track3 Diabetes Planner

- Log BFG, insulin, view trend graphs
- Track exercise routing, food intake
- Has calorie and carb values for 80,000+ foods
- $6.99 for Android & $4.99 for iPhone
- 3.5/5 stars on Android based on 29 ratings (appbrain.com)
- 4.5/5 stars on iPhone based on 218 ratings (itunes.apple.com)

Diabetes Apps

VREE for Diabetes 2.0

- Merck launched new mobile application for people with type 2 diabetes, available on the Apple Store.
- VREE is a comprehensive set of easy-to-use tools developed to help people with type 2 diabetes track their blood sugar, medications, nutritional intake and activity level, with helpful features such as progress charts and live reminders.
- 3.5/5 stars from 20 ratings (itunes.apple.com)

www.medicalsmartphone.com/2010/11/mobile-application-for-diabetes-from.html

Diabetes Apps

Blendr: Diabetes Awareness Advisory

- Available as an app on Facebook, the iPhone, iPad, and iPod touch
- 2.5/5 stars on iPhone based on 660 ratings on all versions (itunes.apple.com)
- Geo-social network for everyone to discover, meet, interact with people nearby.

PR_Newswire@PRNewswire.com
Itunes.apple.com/us/app/blendr/id434528779?mt=8

Monitor Your Blood Sugars While You Drive??

Ford Motor Company has teamed up with a CGMS company to develop a prototype device that will allow people with diabetes to monitor their blood glucose levels as they drive. Using Bluetooth technology the system will connect readings from a CGMS continuous glucose monitor to Ford's onboard communications system, called "Sync".

Is it over yet?

Conclusion

"With all the knowledge, treatments and technology available, there is no reason why anyone should have elevated blood sugars above normal"

THANK YOU!

QUESTIONS?

References

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