Trends in Diabetes Medication Management

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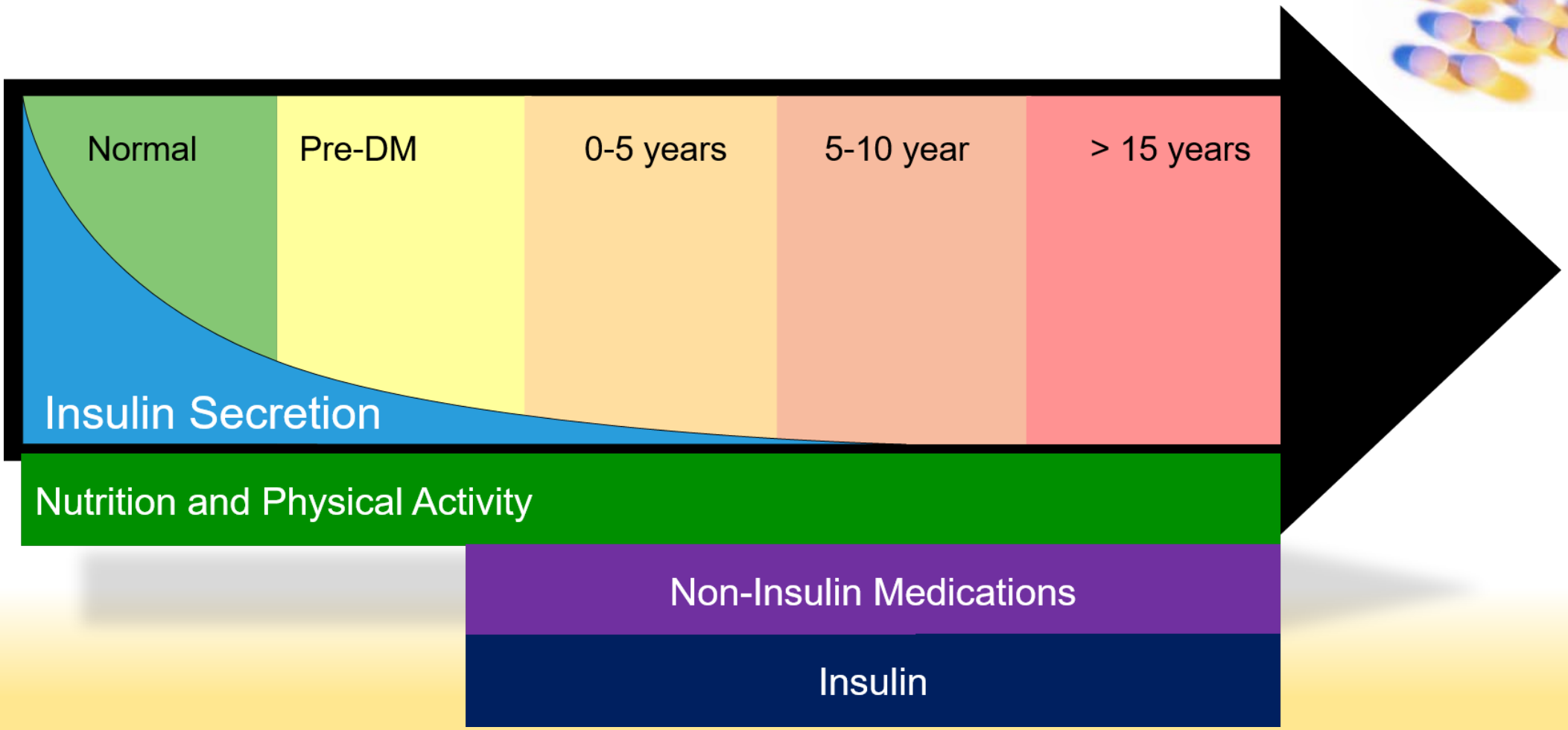
Objectives

- At the end of this presentation, participants will be able to:
  - Describe the changes in treatment goals for type 2 diabetes mellitus.
  - Explain the pros and cons of commonly prescribed glucose lowering medications.
  - Synthesize reasons for selecting glucose lowering medications.
  - Reinforce the importance of assessing for medication adherence among people with type 2 diabetes mellitus.

Diabetes is a Progressive Disease



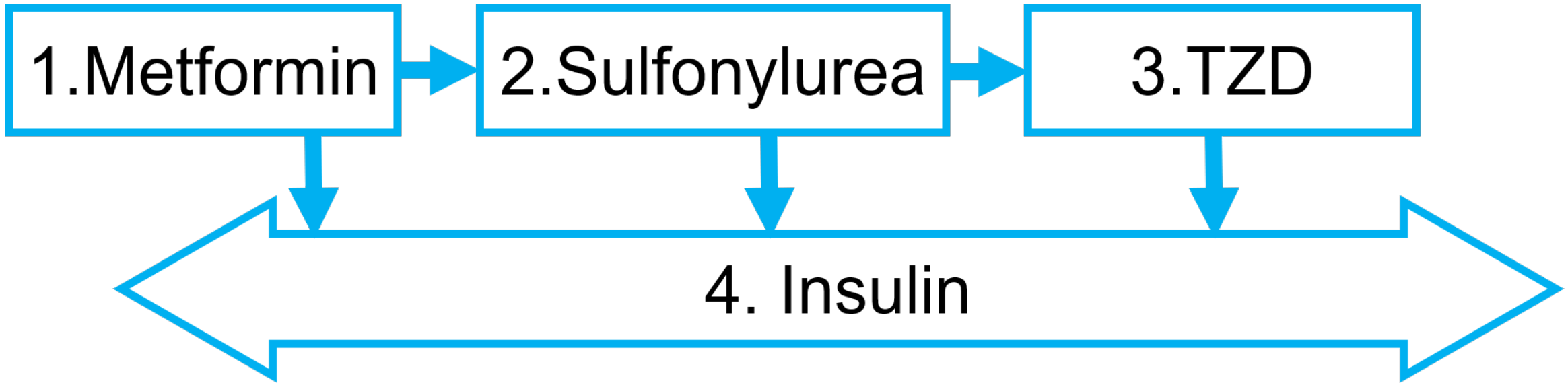
Changes in Treatment Targets

	2007	2017
A1C	<7%	Individualize targets (Many <7%)
BP	<130/80	<140/90
LDL	<100mg/dL	Statin if at risk of ASCVD
Aspirin	Age >40 yrs	If at risk of ASCVD

A1C Targets

Situation	A1C Target
Pregnancy	<6.5%
Early Disease	<6.5%
Most non-pregnant Adults	<7%
Clinically Complex Adults	<8%
Very Complex or Adults in Poor Health	<8.5%

Selecting Medications (circa 2007)



More Medication Options

Alpha Glucosidase Inhibitors

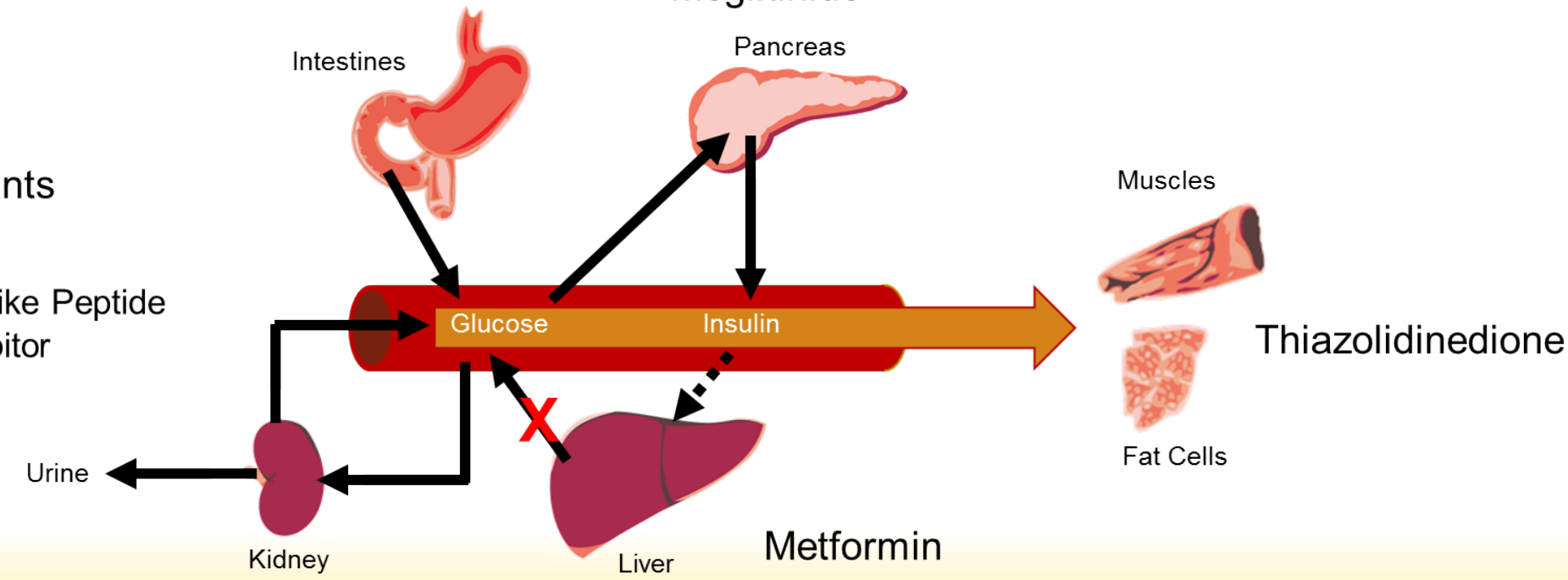
Amylin Analog

Bile Acid Sequestrants

Incretin Mimetics

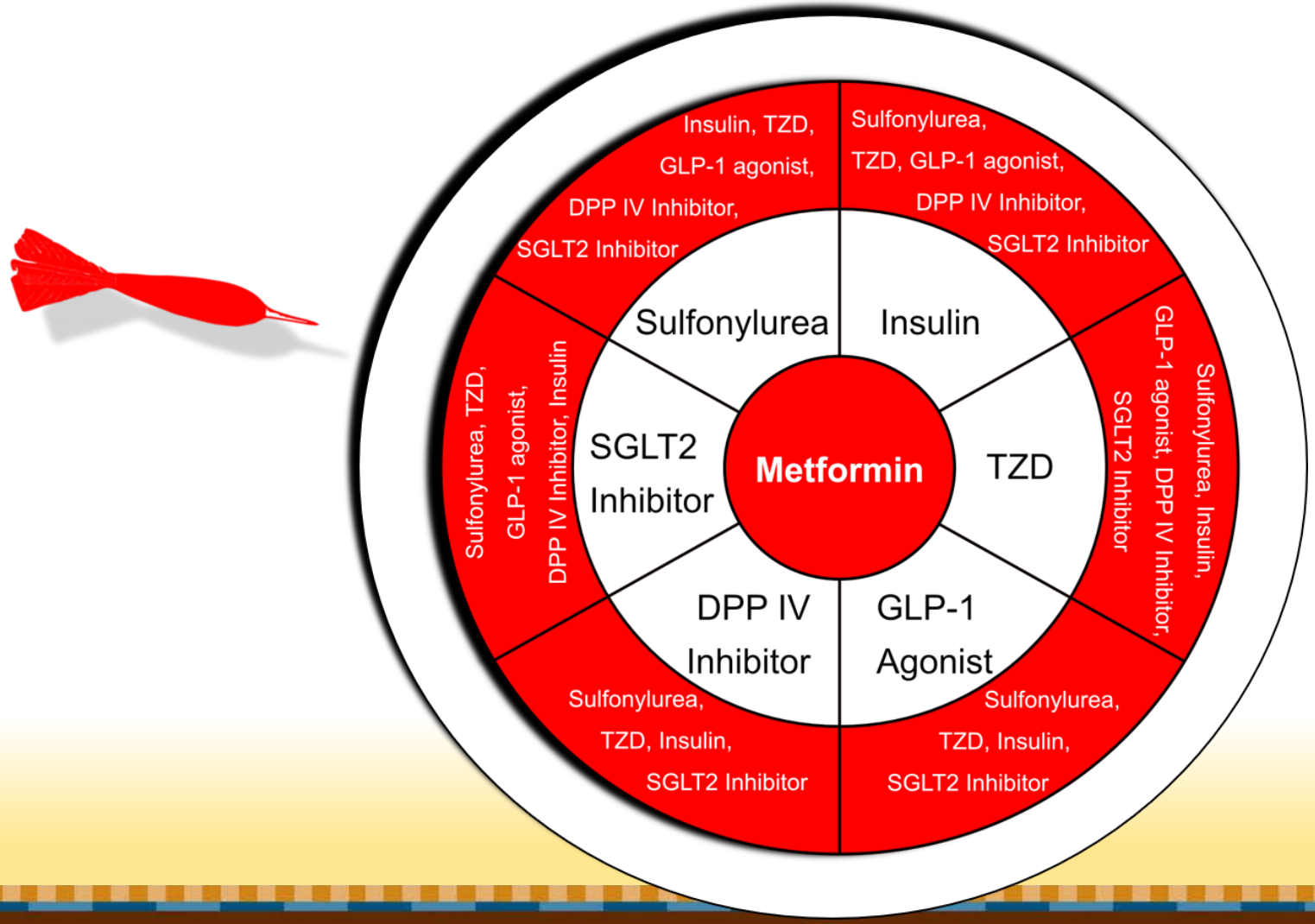
Glucagon Like Peptide

DPP-4 Inhibitor



SGLT-2 Inhibitors

Medication Selection in 2017



Step 1: Metformin

- A1C <9% Metformin monotherapy
- A1C 9-10% Metformin + second agent
- A1C >10% Consider insulin therapy +/- Metformin

Metformin

Decrease A1C 1-2%

Decrease Weight

Low Risk of Hypoglycemia

Taste Disturbances

Monitor B12

GI Upset

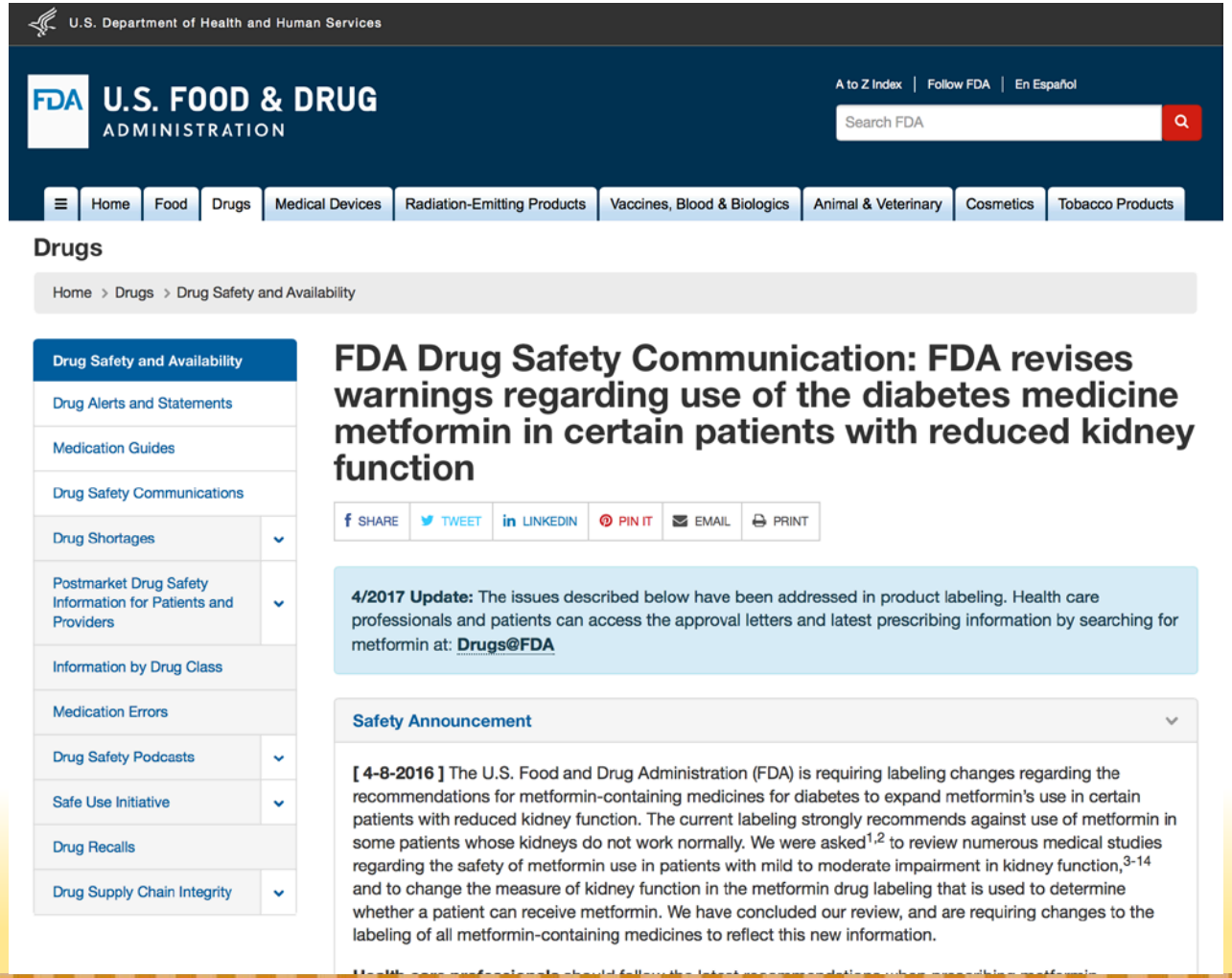
Metformin Dosing

- Start with 500mg once a day with largest meal of the day.

- Regular Release
  - Increase to 1 tablet 2 times a day for at least 1 week.
  - Increase by 1 tablet weekly if able.
  - Maximum dose 2500mg per day (5 tablets)

- XR (Extended Release)
  - Increase to 2 tablets with largest meal for at least 1 week.
  - Increase by 1 tablet weekly if able.
  - Maximum dose 2000mg per day (4 tablets)

Metformin Dosing (cont.)



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FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

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4/2017 Update: The issues described below have been addressed in product labeling. Health care professionals and patients can access the approval letters and latest prescribing information by searching for metformin at: **Drugs@FDA**

Safety Announcement

[4-8-2016] The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. We were asked[1,2] to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function,[3-14] and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. We have concluded our review, and are requiring changes to the labeling of all metformin-containing medicines to reflect this new information.

Metformin Contraindications and Cautions

- Lactic Acidosis
  - **Contraindications**
    - Severe renal impairment: eGFR < 30 mL/min
    - Acute or chronic metabolic acidosis
  - **Temporarily discontinue**
    - Radiologic studies using iodinated contrast media
    - Hold for non-minor surgery – restart when eating and renal function normal
  - **Cautions**
    - Hypoxia (shock, CHF, AMI)
    - Hepatic dysfunction
    - Excessive alcohol intake
    - Severe renal impairment: eGFR 30-45 mL/min

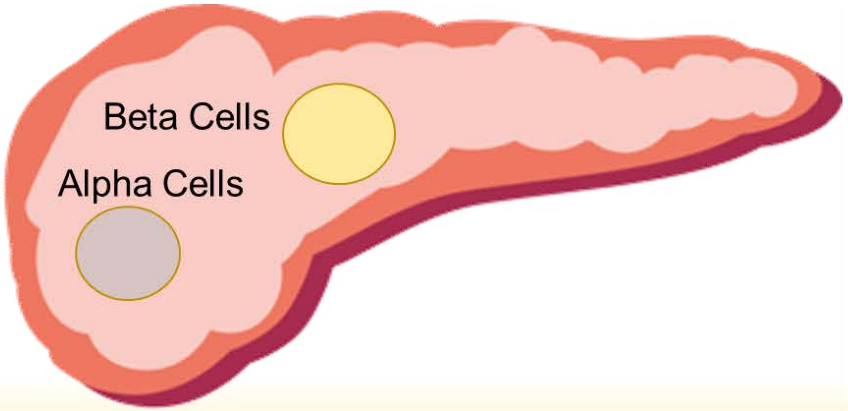
Step 2: Add Another Agent

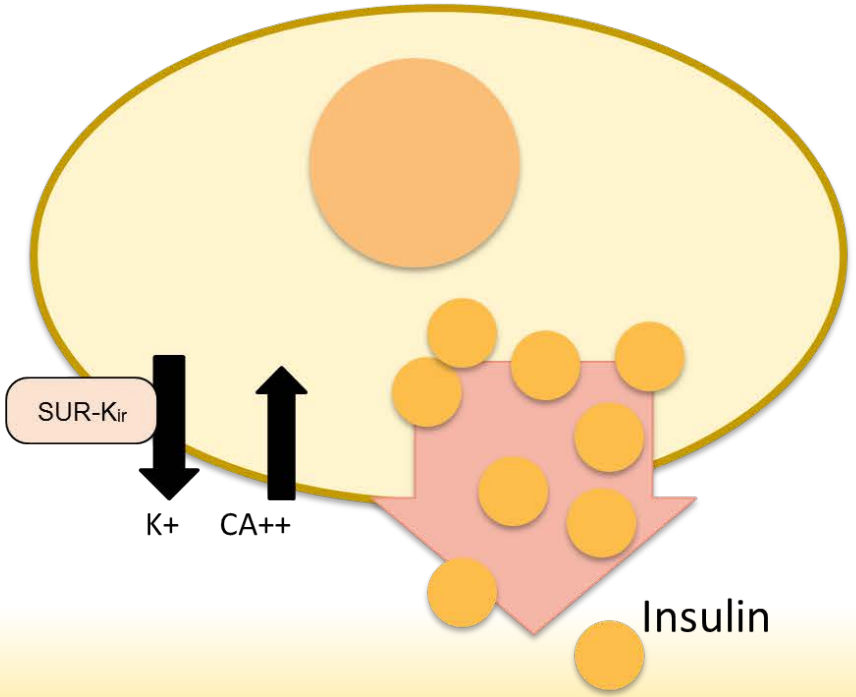
	Sulfonylurea	TZD	DPP-4 Inhibitor	SGLT2 Inhibitor	GLP-1 Agonist	Insulin
A1C Lowering	↓↓	↓↓	↓	↓	↓↓	↓↓↓
Hypoglycemia risk*	↑↑	↓↓	↓↓	↓↓	↓↓	↑↑
Weight gain	↑↑	↑↑	-	↓	↓	↑↑
Cost	low	low	high	high	high	low-high

* when used alone

Sulfonylureas

- Stimulates insulin release
  - Requires functional pancreas and ability to create insulin



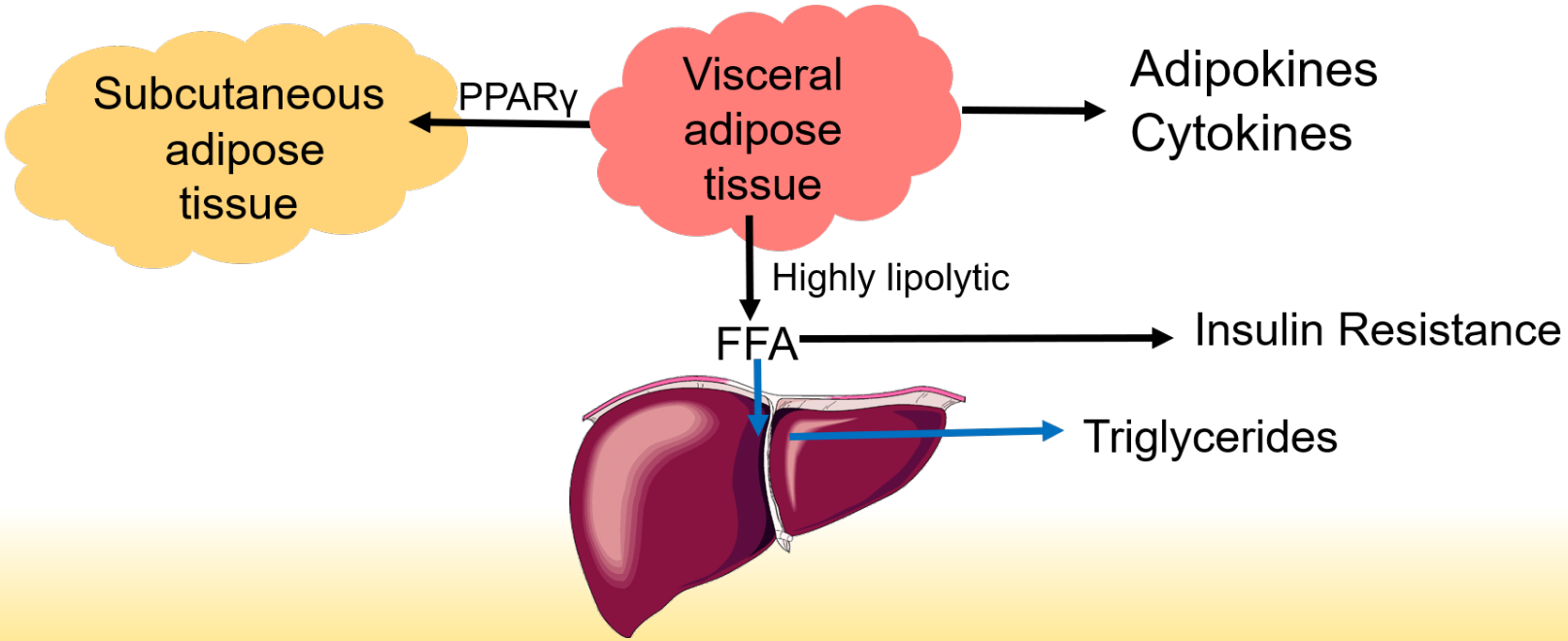


Sulfonylureas (cont.)

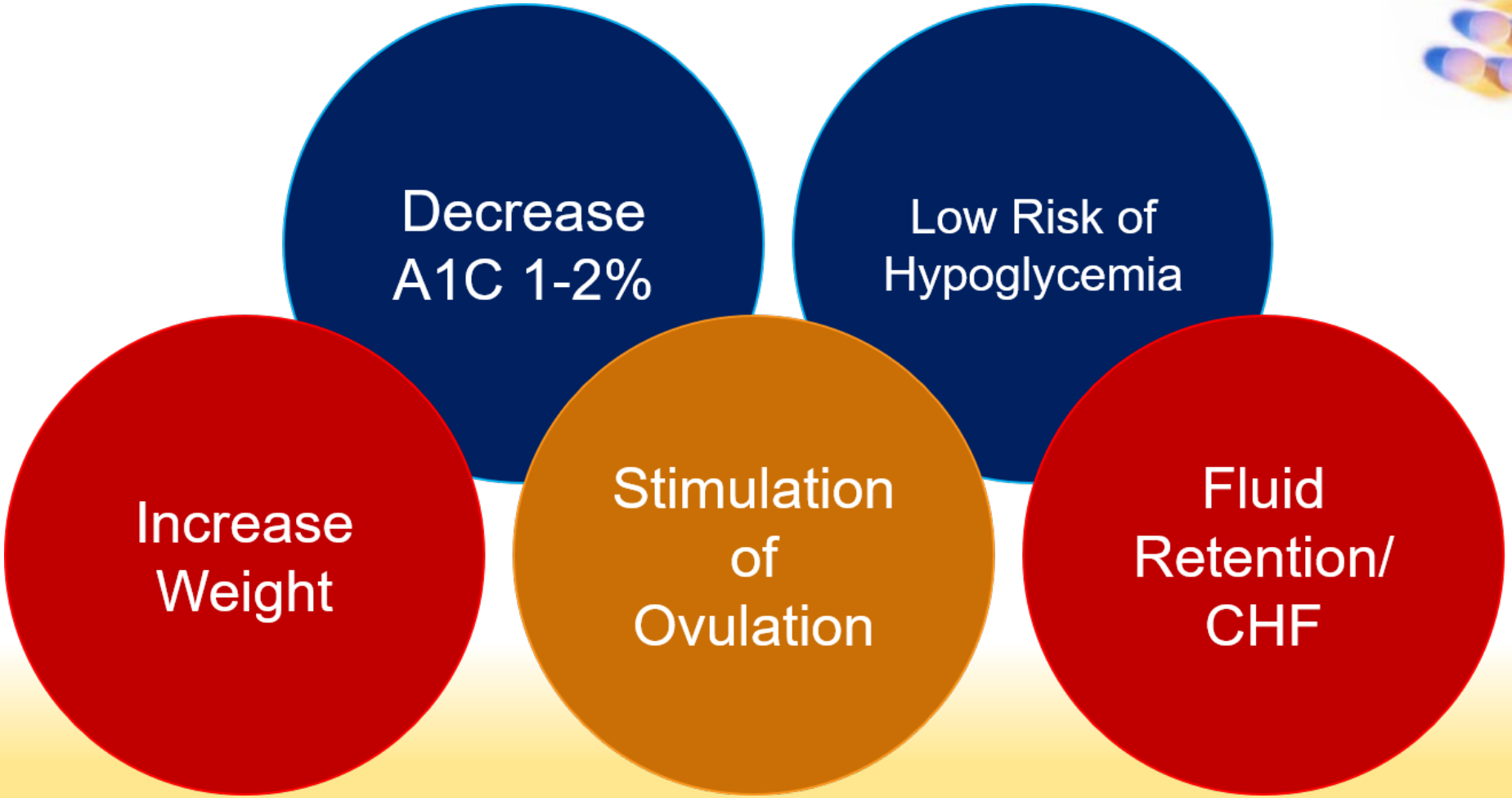
Drug	Starting Dose	Max Dose	Duration	Comments
Glyburide (Diabeta®, Micronase®)	1.25-10mg daily (single or divided dose)	20mg daily	24 hours	Metabolized by the liver. Excreted in urine and bile.
Glyburide (Glynase®)	0.75-12mg daily	12mg daily		
Glipizide (Glucotrol® Glucotrol XL®)	**2.5-20mg daily (single or divided dose)**	**40mg (20mg if XL)**	**12-16 hours**	**Metabolized by the liver. Excreted in the urine. Take on empty stomach.**
Glimepiride (Amaryl®)	1-4mg daily	8mg daily	24 hours	2 major metabolites. Hepatic & renal elimination. Take with first main meal

Thiazolidinediones

- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)



Thiazolidinediones (cont.)



Thiazolidinediones (more)

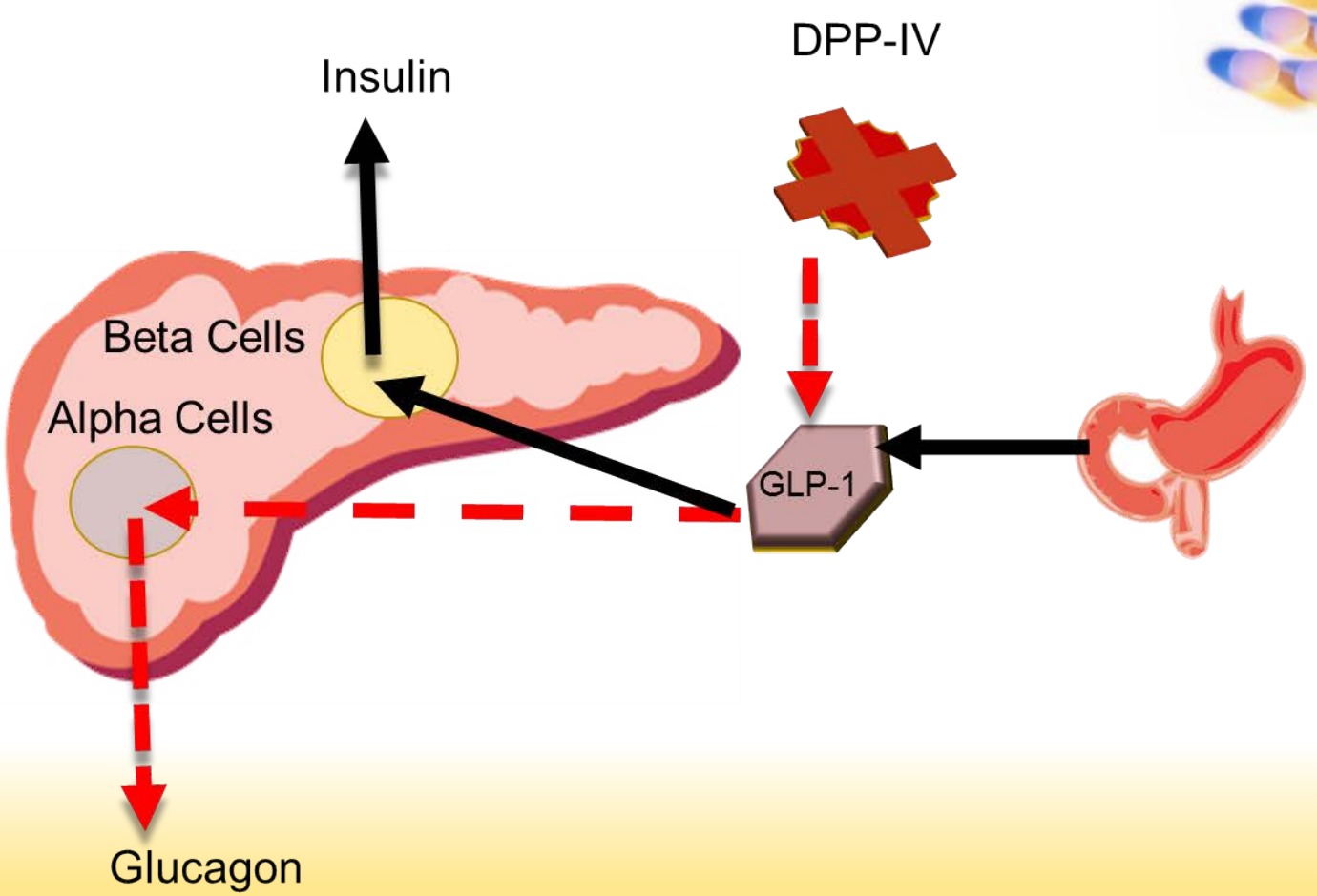
Drug	Starting Dose	Max Dose	Comments
Pioglitazone (Actos®)	15-45 mg daily	45 mg daily	Metabolized by the liver. LFTs every 2 months x first year then periodically.
Rosiglitazone (Avandia®)	2-8 mg daily	8 mg daily	Metabolized by the liver. LFTs every 2 months x first year then periodically.

4mg rosiglitazone daily = 15mg pioglitazone

8mg rosiglitazone daily = 30mg pioglitazone

4mg rosiglitazone BID = 45mg pioglitazone daily

GLP-1 Agonists (1)



GLP-1 Agonists (2)

- Exenatide (Byetta®, Bydureon®)
- Liraglutide (Victoza®)
- Albiglutide (Tanzeum®)
- Dulaglutide (Trulicity®)
- *Liraglutide (Saxenda®)*

GLP-1 Agonist Dosing

Medication	Starting Dose	Maximum Dose
Exenatide	5 mcg Q12 hours 60 minutes before meals	Increase to 10 mcg after 1 month
Exenatide Weekly	2 mcg weekly	
Liraglutide	0.6 mg daily x 7 days	1.2 mg daily
Albiglutide	30 mg weekly	Increase to 50 mg weekly
Dulaglutide	0.75 mg weekly	Increase to 1.5 mg weekly

GLP-1 Agonists (3)

- HS is a middle aged man with Type 2 Diabetes diagnosed just over 6 years ago. He has been taking Albiglutide 50mg every Monday morning for about 9 months. He calls you on Thursday stating that he forgot to take his medication on Monday and wonders if it is OK to take it now or should he just wait until next Monday?

GLP-1 Agonists (4)

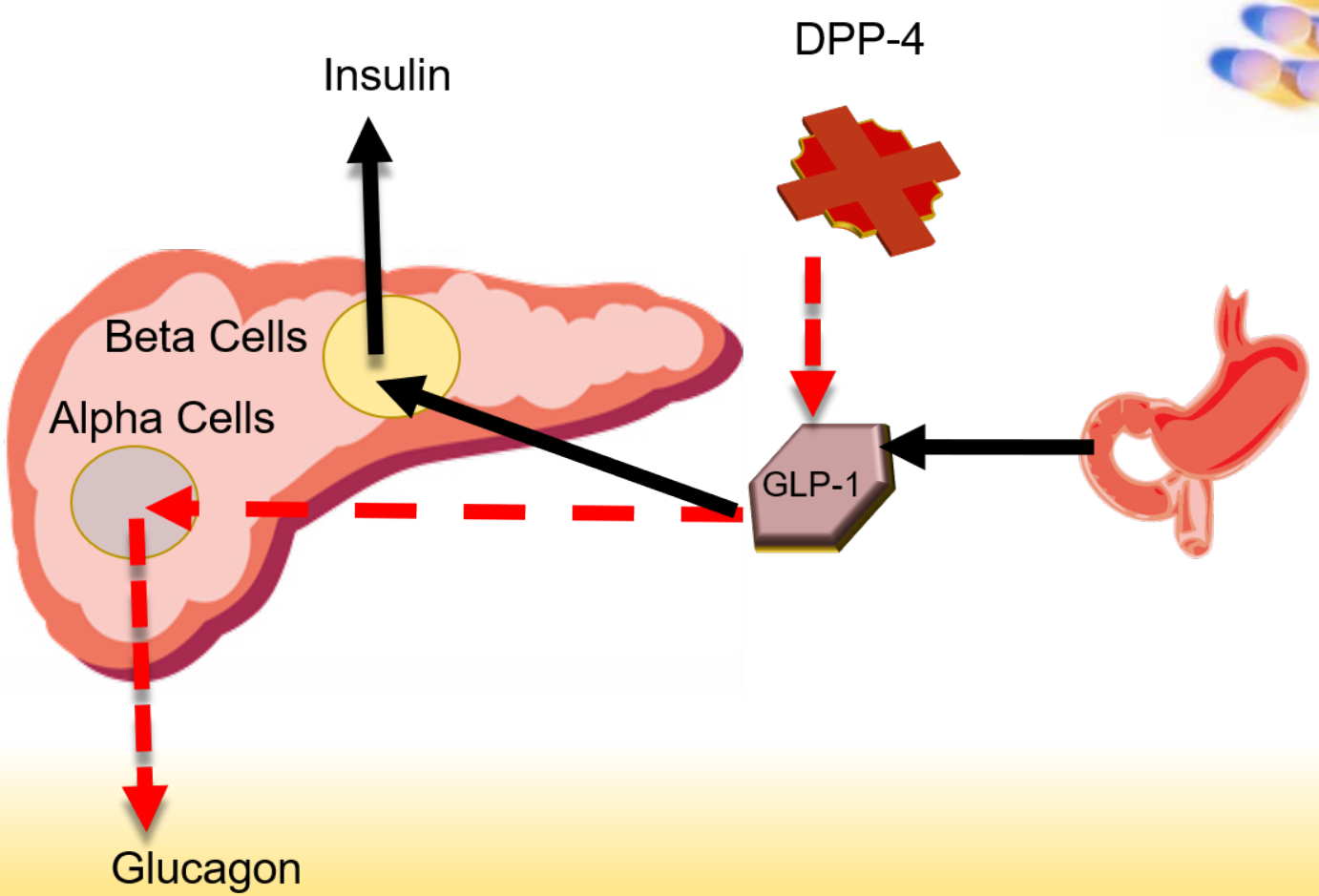
- Missed weekly doses: take when remembered if ≤ 3 days of the next dose

MON TUE WED THUR FRI SAT SUN MON

- Switching days: after at least 4 days of last dose

MON TUE WED THUR FRI SAT SUN MON

DPP-4 Inhibitors



DPP-4 Inhibitors (cont.)

- Sitagliptin (Januvia®)
- Saxaglipitin (Onglyza®)
- Alogliptin (Nesina®)
- Linagliptin (Tradjenta®)

Saxagliptin

Dosing: 5mg daily

2.5mg daily if CrCL≤50ml/min or

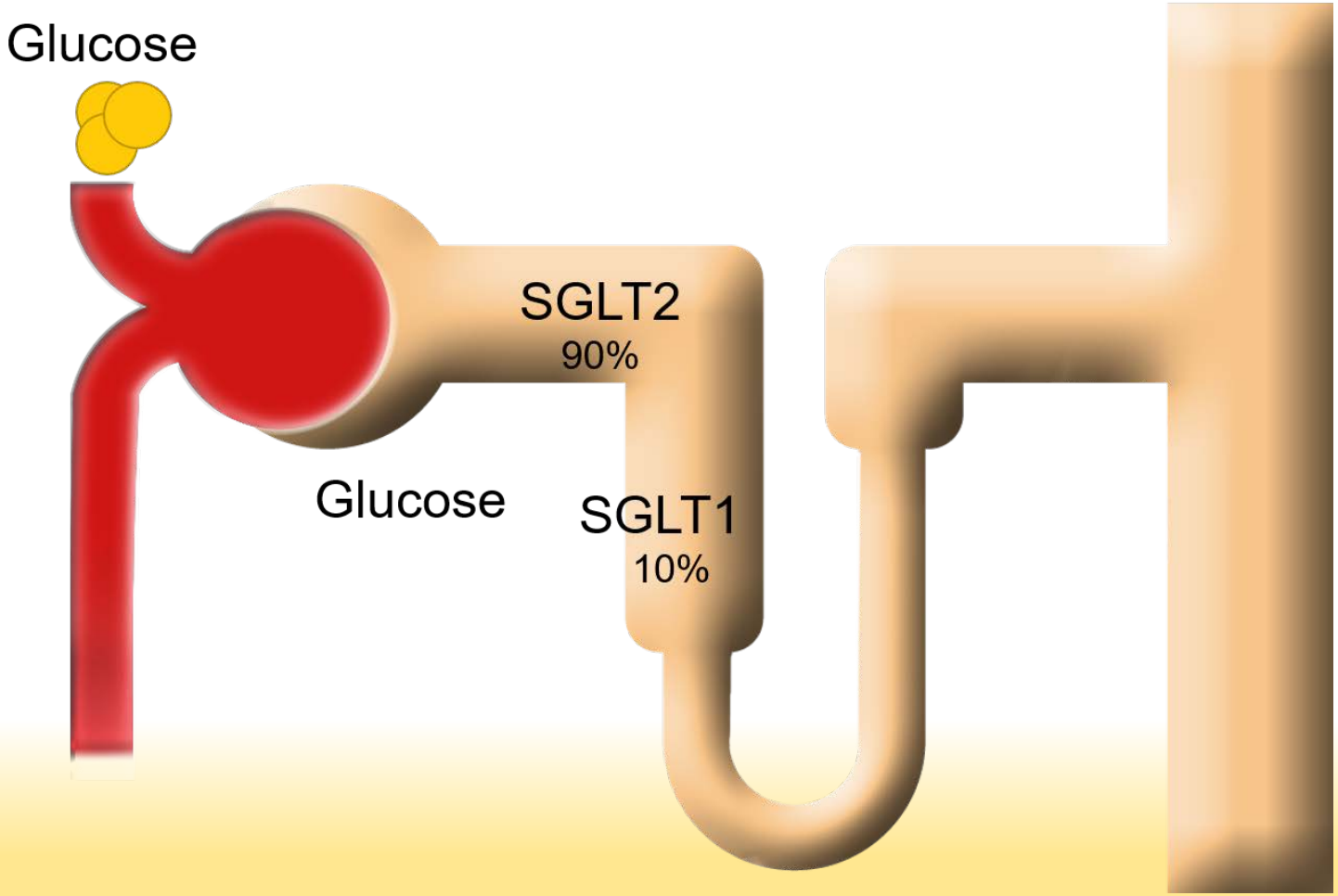
strong CYP3A4/5 Inhibitor

Heart failure risk - Heart failure occurred in:

3.5% of patients taking saxagliptin

2.7% of patients taking placebo

SGLT-2 Inhibitors



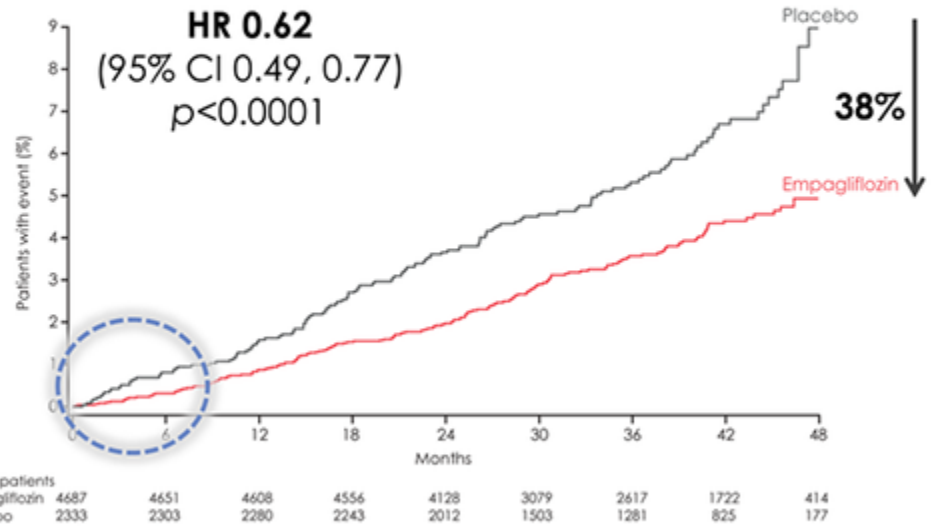
SGLT-2 Inhibitors (cont.)

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

Medication	Starting Dose	Maximum Dose
Canagliflozin	100mg daily before the first meal	300mg daily
Dapagliflozin	5mg daily with or without food	10mg daily
Empagliflozin	10mg daily with or without food	25mg daily

SGLT-2 Inhibitors: CVD Benefit

CV death



Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

Zinman B *et al. N Engl J Med* 2015;373:2117-28

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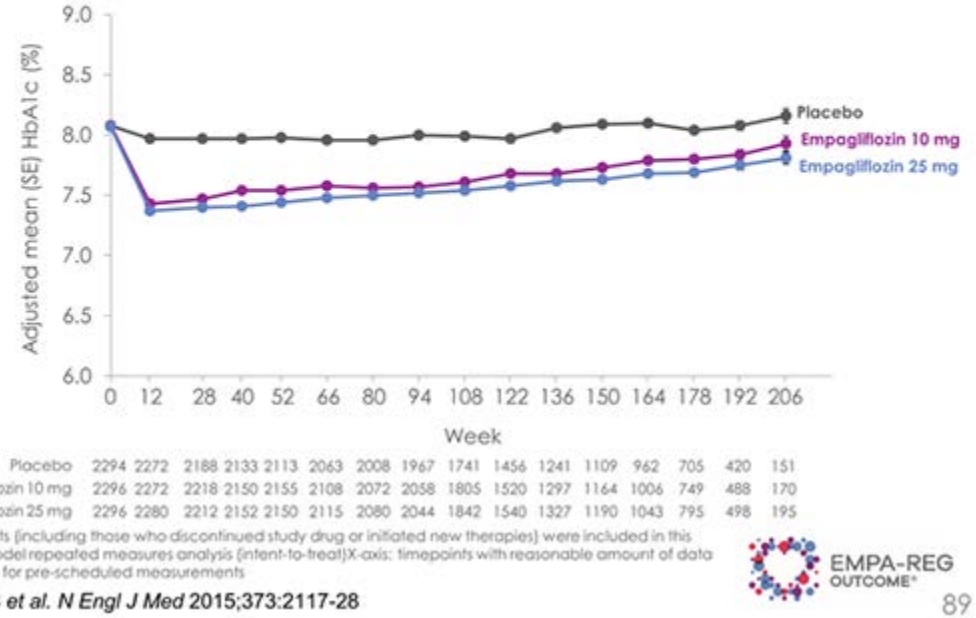
HbA1c



All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

EMPA-REG OUTCOME®

Zinman B *et al. N Engl J Med* 2015;373:2117-28

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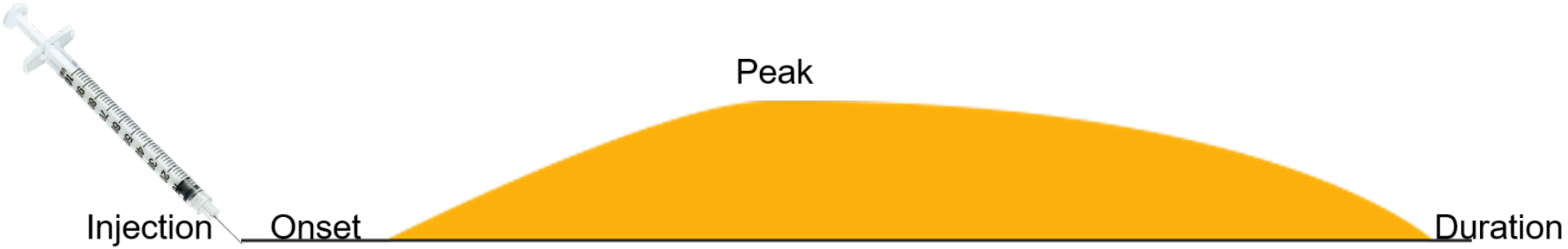
Basal Insulin

- Intermediate Acting
  - NPH
- Long Acting
  - Glargine
  - Detemir (Levemir®)
- Ultra Long Acting
  - Glargine U300 (Toujeo®)
  - Degludec (Tresiba®)

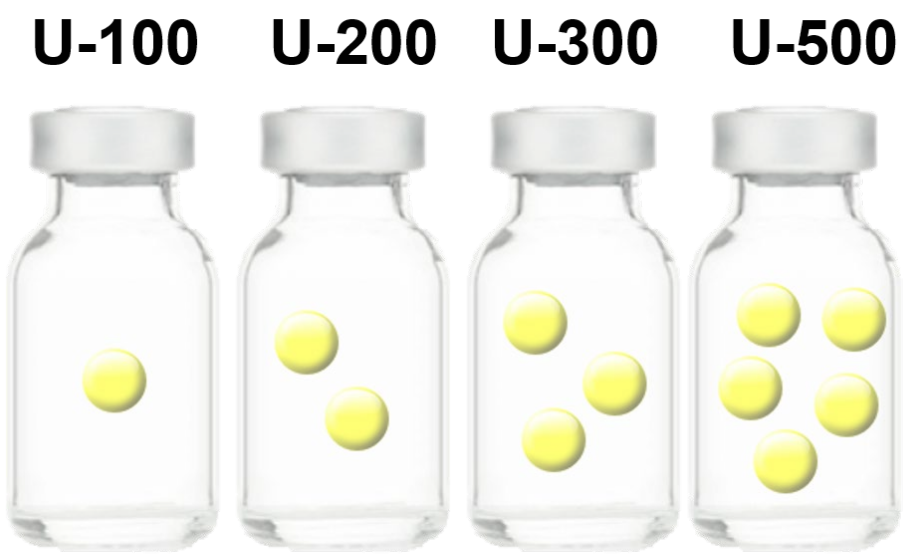
What Makes Insulin Different?

- How long it takes to work (onset)?
- When (if) the insulin spikes (peak)?
- How long it works (duration)?



- How concentrated is the insulin?

Insulin Concentrations



- 1mL U-100 contains 100 units of insulin
- 1mL U-200 contains 200 units of insulin
- 1mL U-300 contains 300 units of insulin
- 1mL U-500 contains 500 units of insulin

Intermediate Acting Insulin

Type of Insulin	Onset	Peak	Duration
NPH	1-2 hours	4-12 hours	12-16 hours

Long-Acting Insulin

Type of Insulin	Onset	Peak	Duration
Glargine (Basaglar®, Lantus ®)	1-2 hours	None	20-26 hours
Detemir (Levemir®)	1-2 hours	6-8 hours	18-24 hours

Ultra-Long-Acting Insulin

- Steady insulin levels for over 24 hours
- Injected once daily
- May be combined with short-acting insulin to cover meals

Type of Insulin	Onset	Peak	Duration
Glargine U300 (Toujeo®)	1-2 hours	None	Up to 36 hours
Degludec (Tresiba®)	30-90 min	None	>42 hours

Insulin Glargine U300 (Toujeo®)

- Concentrated insulin
  - 1ml of Glarine U100 contains 100 units
  - 1ml of Glargine U300 contains 300 units

  - 3ml of Glargine has the same amount of insulin as 1ml of Glargine 300U

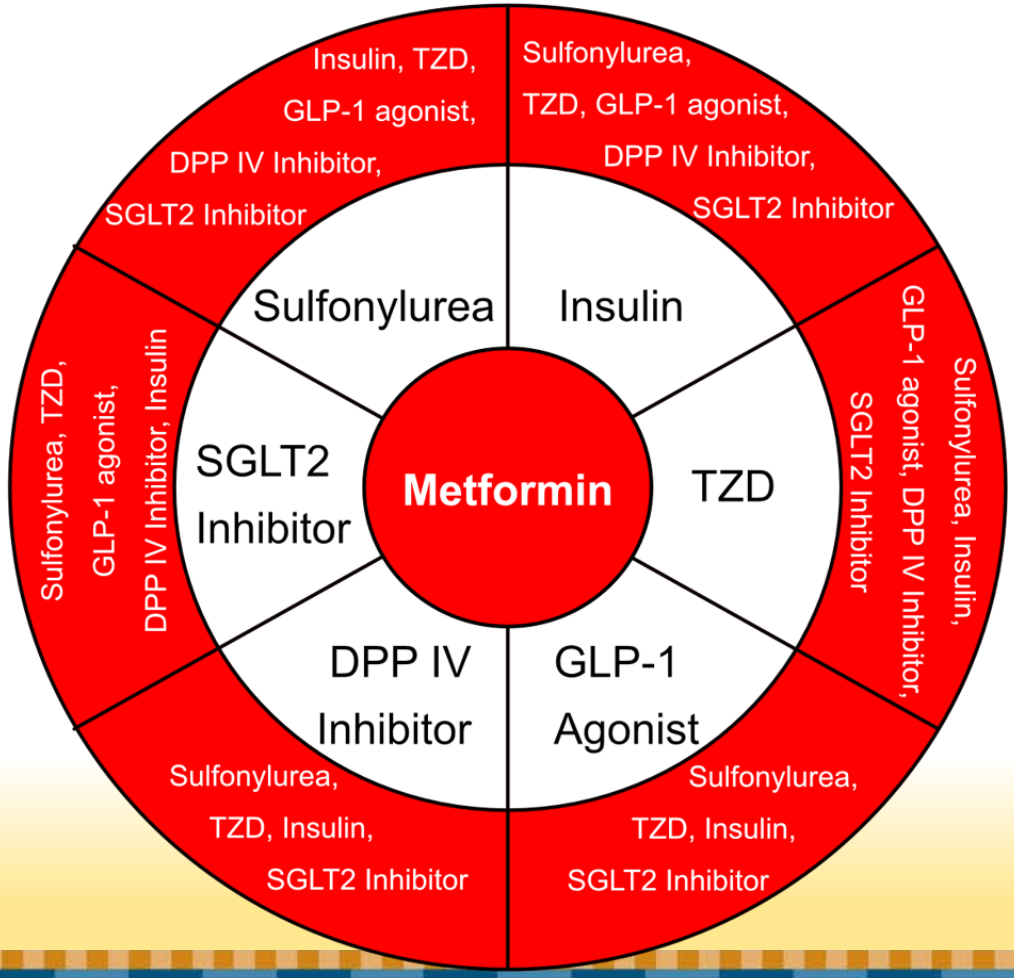
Insulin Degludec (Tresiba®)

- Available as:
  - U100 (100 units/mL)
  - U200 (200 units/mL)
- Good for 8 weeks after opening

Step 2: Add Another Agent

	Combination with Metformin
Sulfonylurea	Good A1C lowering; risk of hypoglycemia
Thiazolidinedione	Insulin sensitizers
GLP-1 Agonist	Good A1C lowering
DPP-4 Inhibitor	May lessen GI Side effects
SGLT2 Inhibitor	Synergistic mechanisms of action
Insulin	Good A1C lowering; risk of hypoglycemia

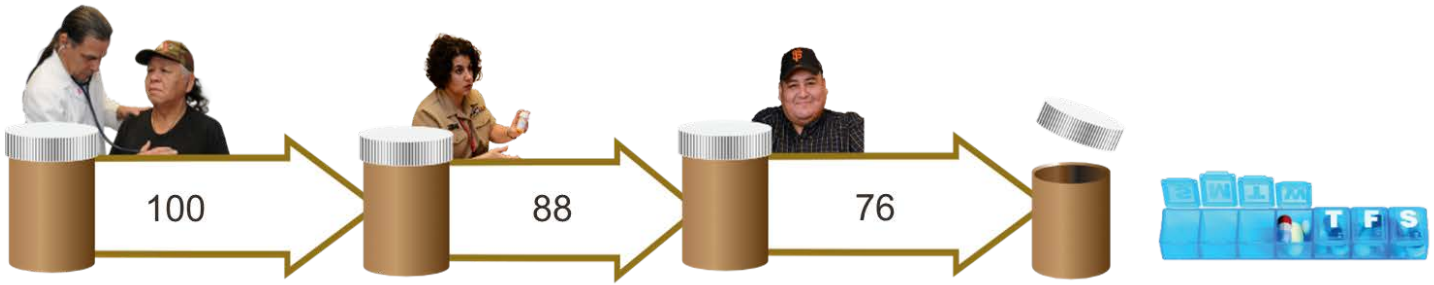
Step 3: Add Additional Agent



Drugs don’t work if….

….people don’t take them!

Medication Adherence



100 Prescriptions written

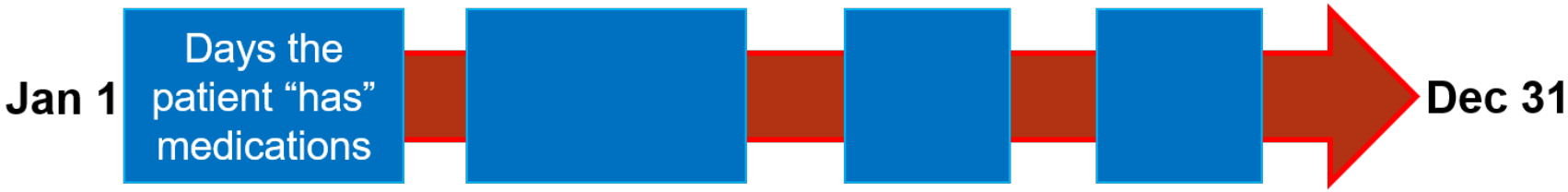
88 are filled at the pharmacy

76 are taken by the patient

49 are refilled after the prescription runs out

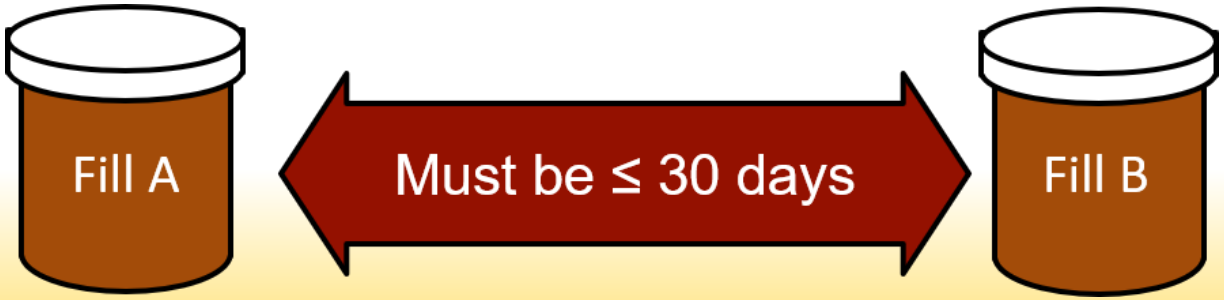
Medication Adherence (cont.)

- Proportion of Days Covered (PDC)

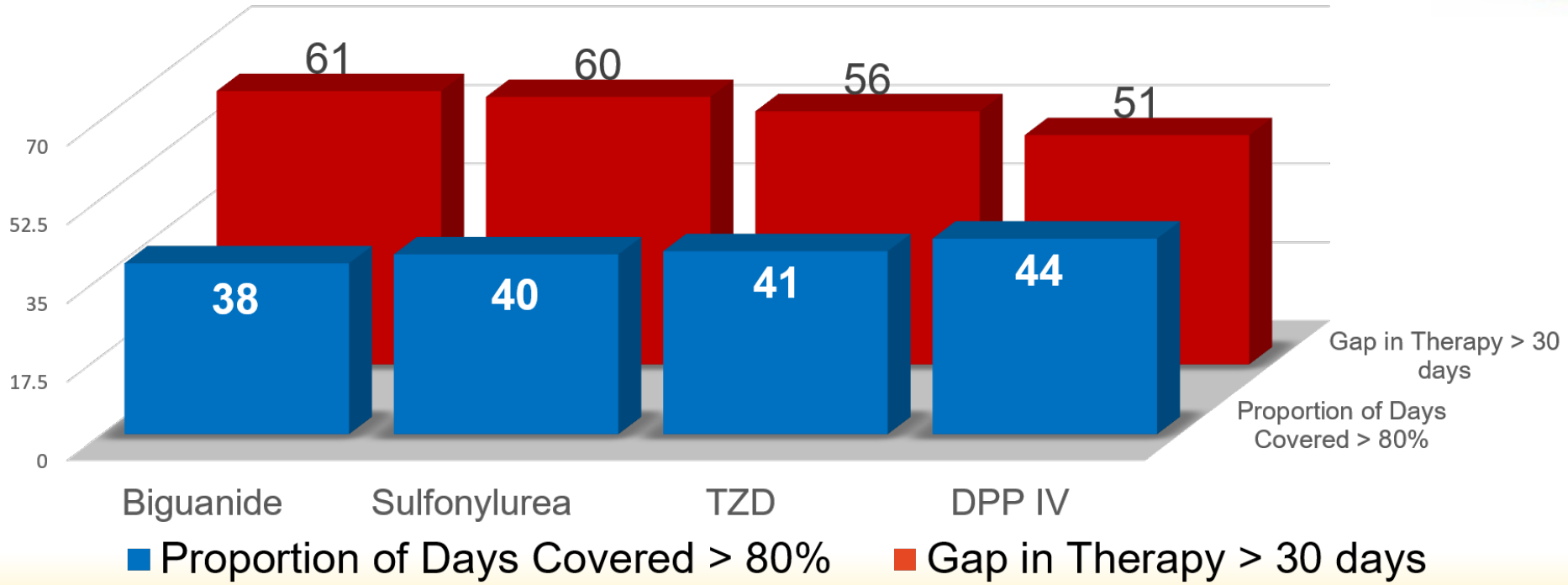


Total days must be ≥ 80% (> 292 days supply)

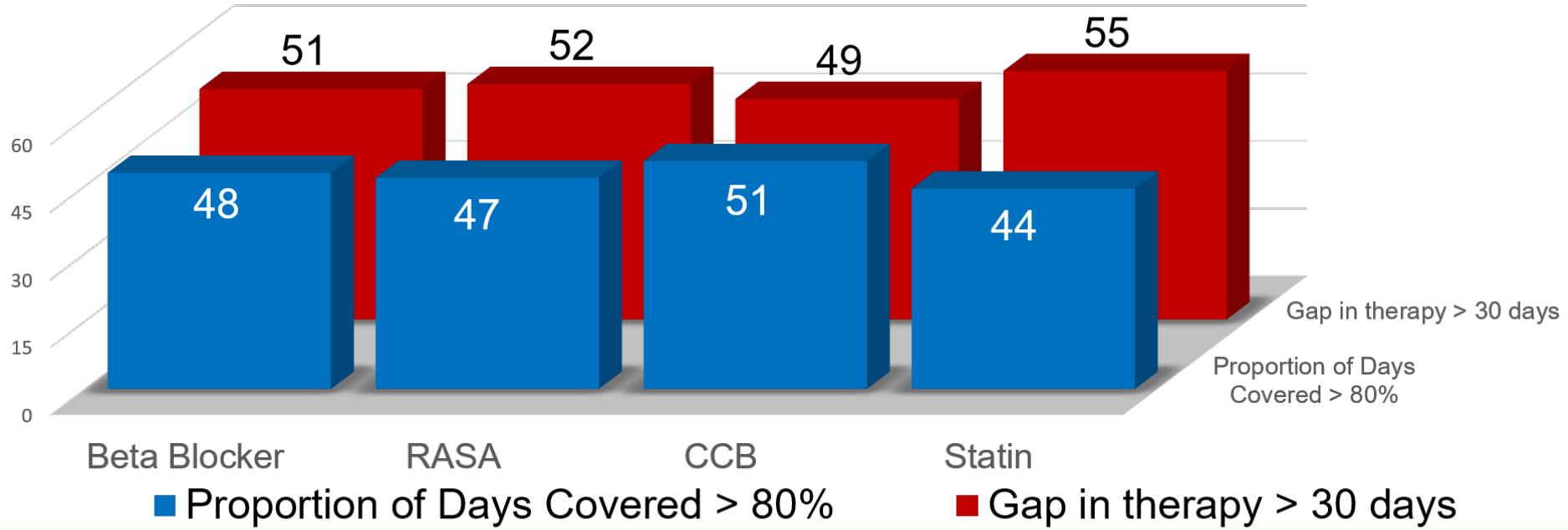
- Gaps in Therapy



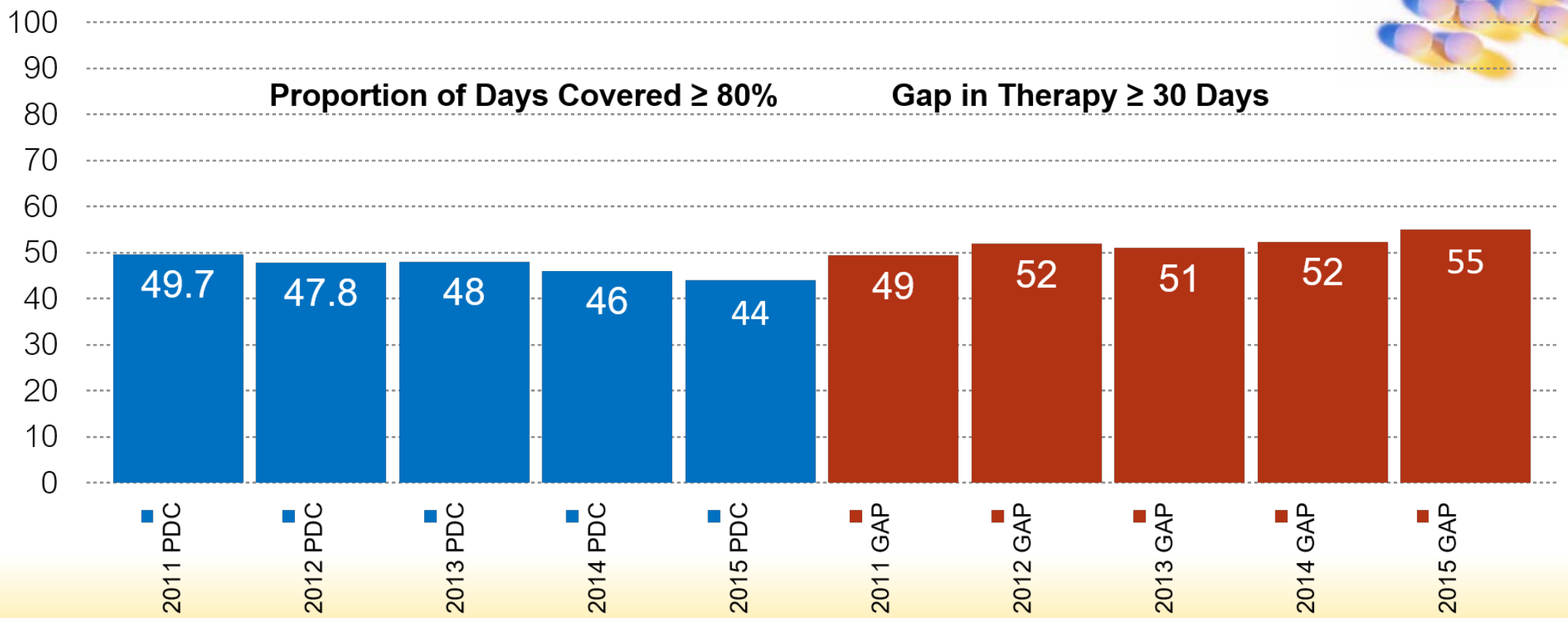
Diabetes Medications



Cardiovascular Medications



Adherence to Statin Medications 2011-2015



Addressing Adherence

- Simplify the regimen
- Impart knowledge
- Modify patient beliefs and human behavior
- Provide communication and trust
- Leave the bias
- Evaluate adherence

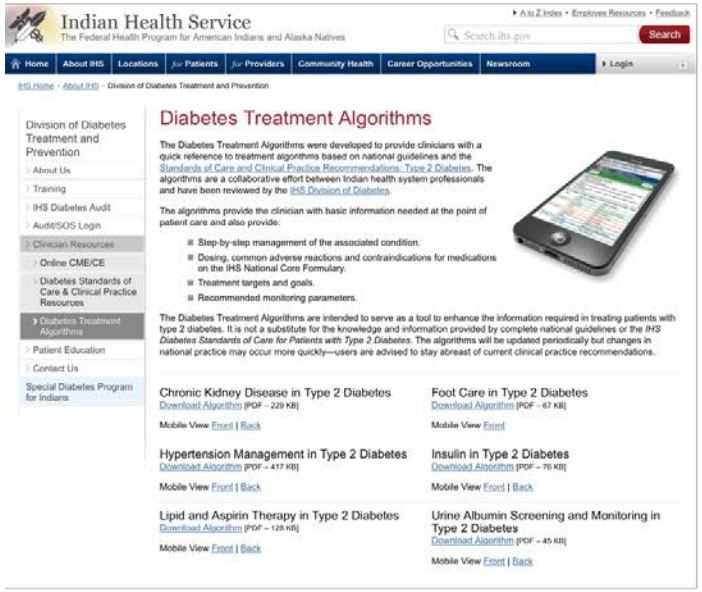
Step 4: Add Basal/Bolus Insulin

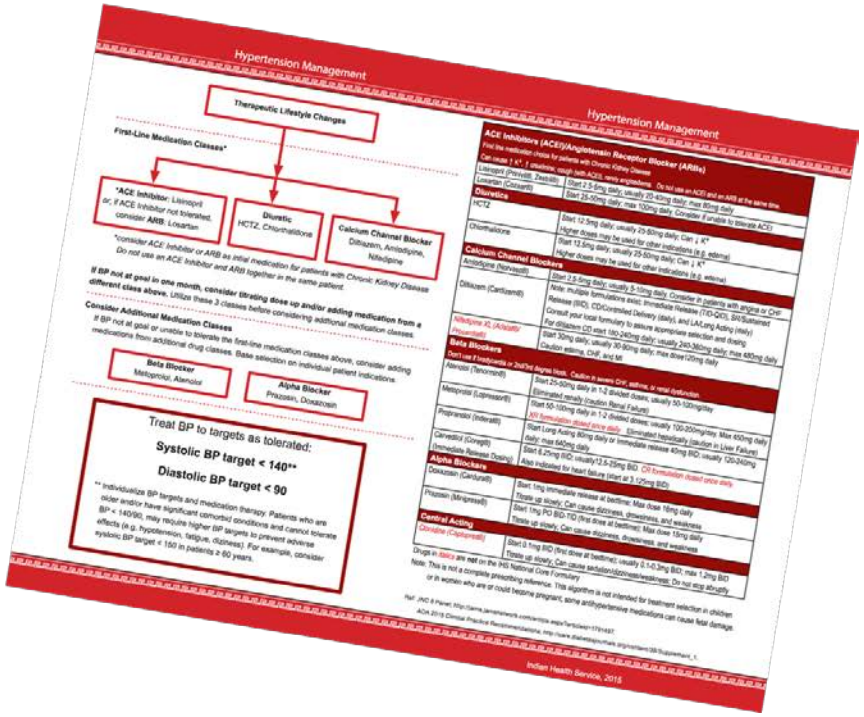
What to do with other medications when starting Insulin?

What to do with other medications when starting Insulin? (cont.)

- **Metformin**: Recommend that it be continued
- **Sulfonylureas**: questionable benefit
- **TZD**: May increase risk of edema and weight gain; may reduce insulin resistance
- **SGLT2 Inhibitors**: Lower risk of hypoglycemia compared with other agents and less weight gain
- **DPP4 Inhibitors**: Modest A1C lowering; may be weight neutral
- **GLP-1 Agonist**: Can reduce A1c and body weight; longer acting have more effect than shorter acting; low risk of hypoglycemia

Diabetes Algorithms



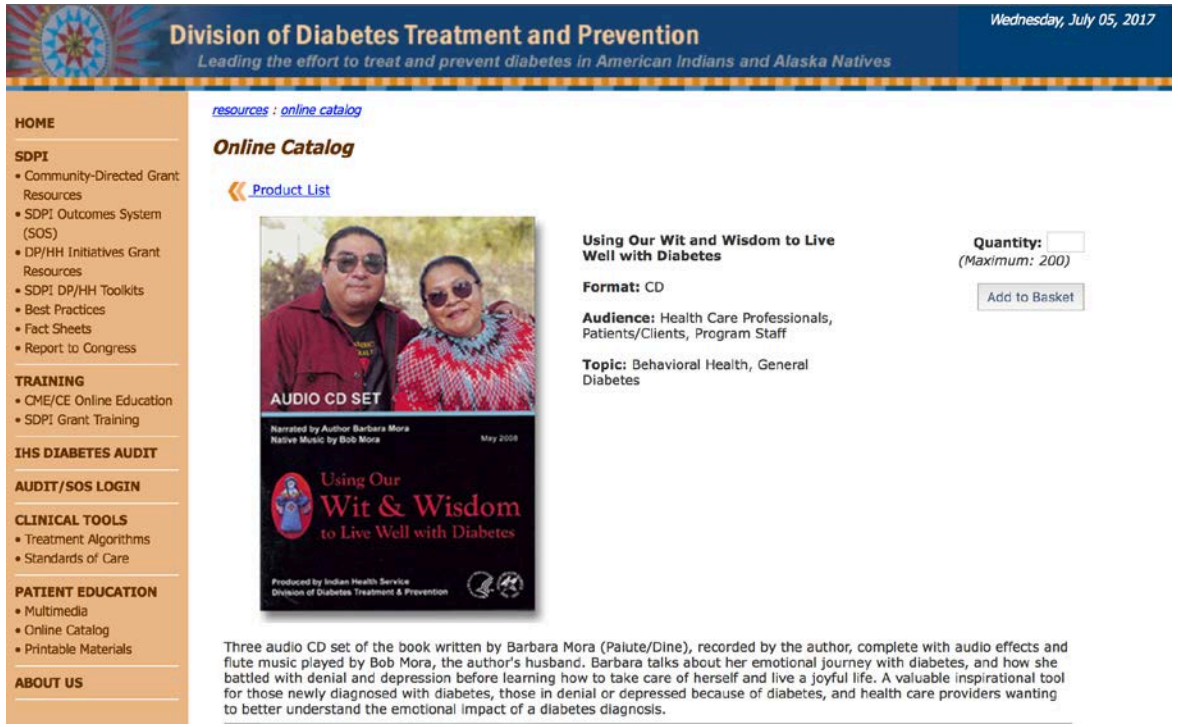


https://www.ihs.gov/diabetes/clinician-resources/dm-treatment-algorithms/

Trends in Diabetes Management:

- Individualize treatment targets and care plans based on the patient's needs and choices.
- Target treatments that may also enhance health beyond blood glucose lowering.
- Improve the delivery of medications to increase medication acceptance and adherence.

Conclusion



https://www.ihs.gov/MedicalPrograms/Diabetes/RESOURCES/Catalog/index.cfm?module=productDetails&productID=126

Thank you!

Chris.Lamer@ihs.gov

Regular Insulin U500

	U-100	U-500
50 units	0.5mL	0.1 mL
100 units	1 mL	0.2 mL
200 units	2 mL	0.4 mL
400 units	4 mL	0.8 mL