



# Trends in Diabetes Medication Management

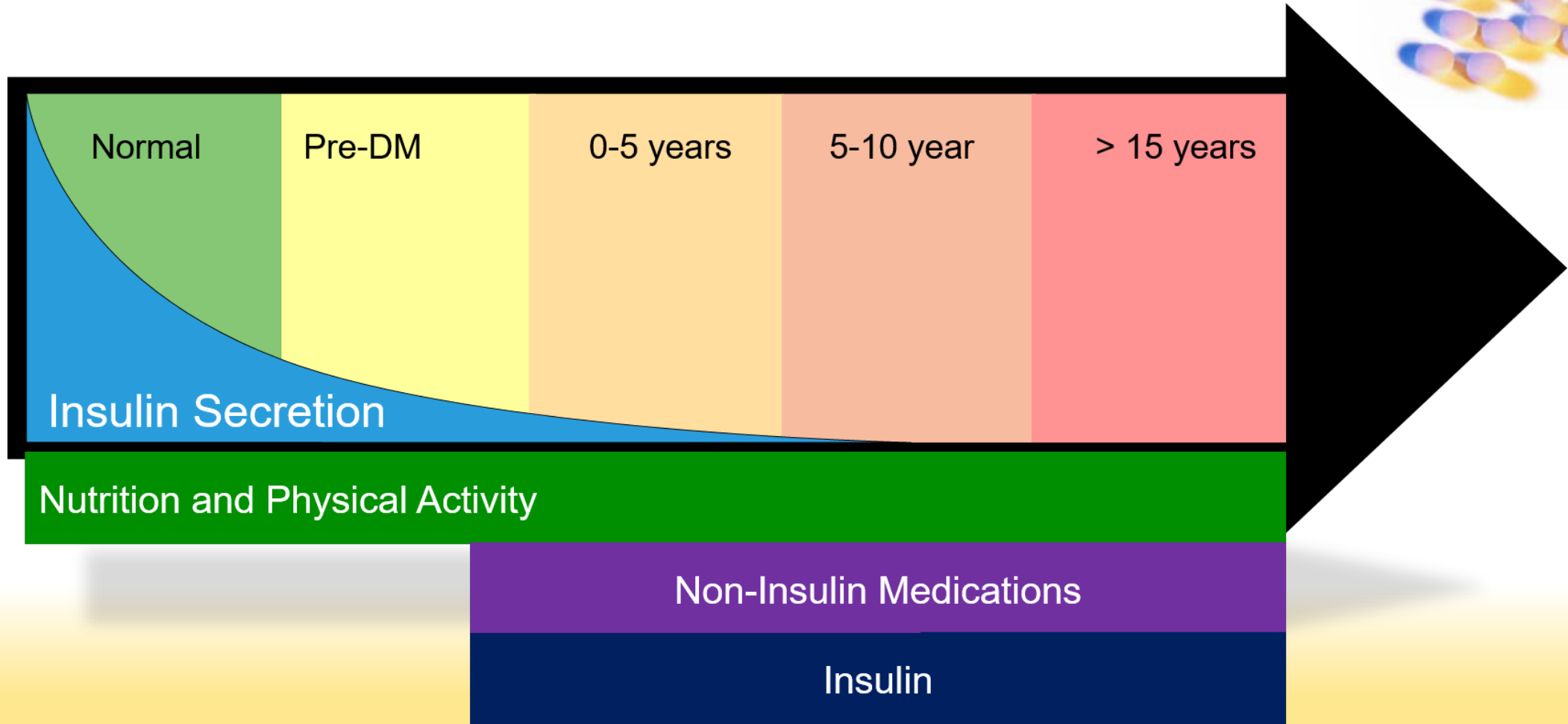
CAPT Christopher Lamer, PharmD, MHS, BCPS, CDE

# 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



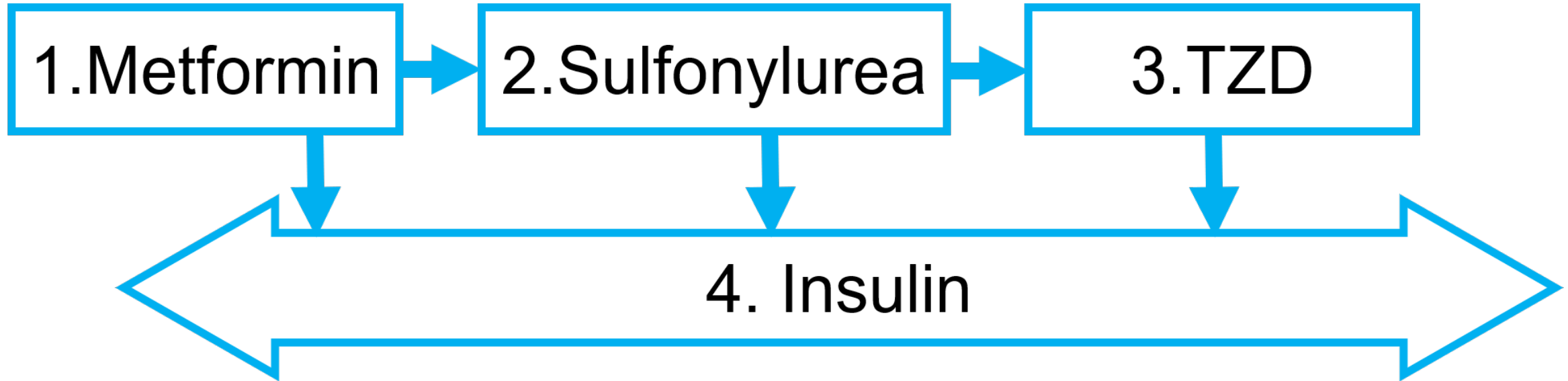
	2007	2017
<b>A1C</b>	<7%	Individualize targets (Many <7%)
<b>BP</b>	<130/80	<140/90
<b>LDL</b>	<100mg/dL	Statin if at risk of ASCVD
<b>Aspirin</b>	Age >40 yrs	If at risk of ASCVD

# 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

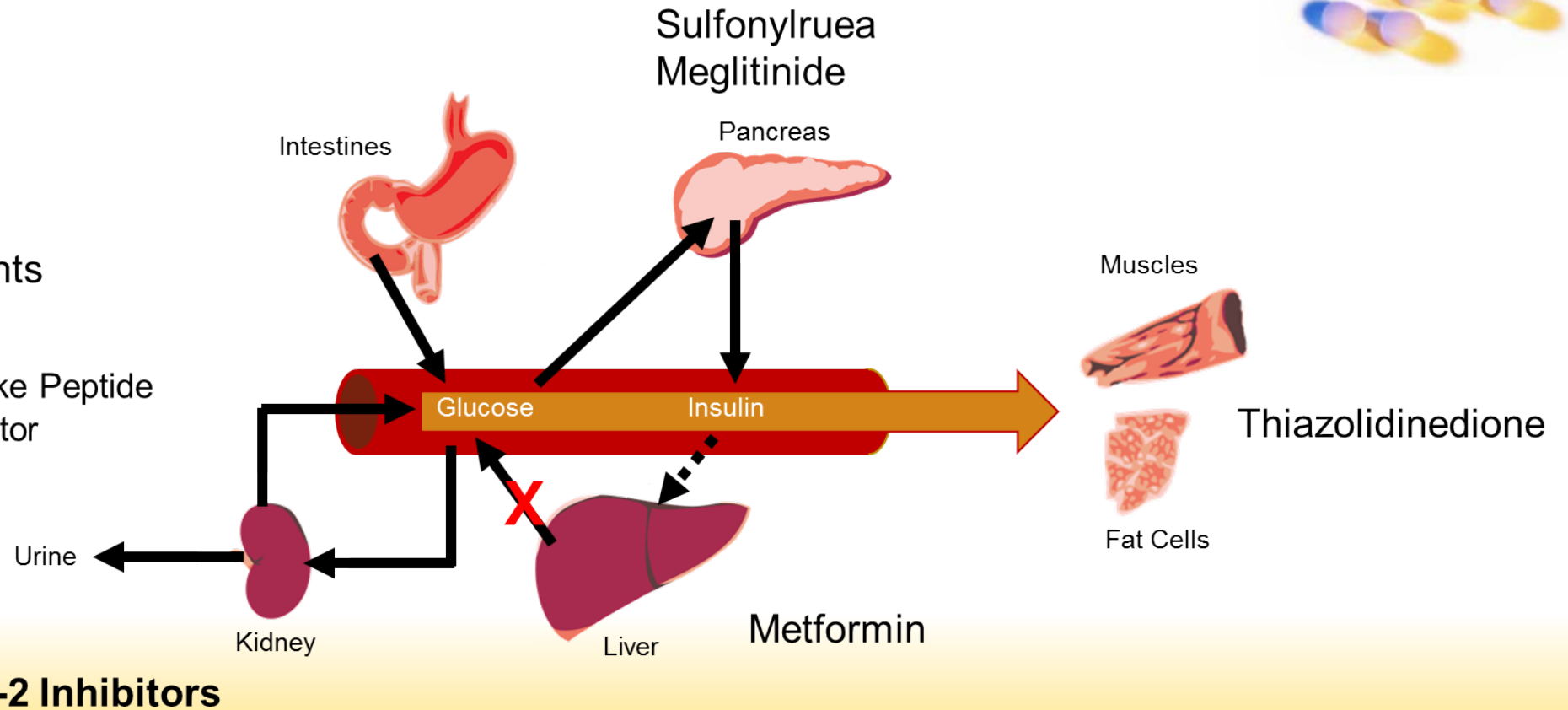
Alpha Glucosidase Inhibitors

Amylin Analog

Bile Acid Sequestrants

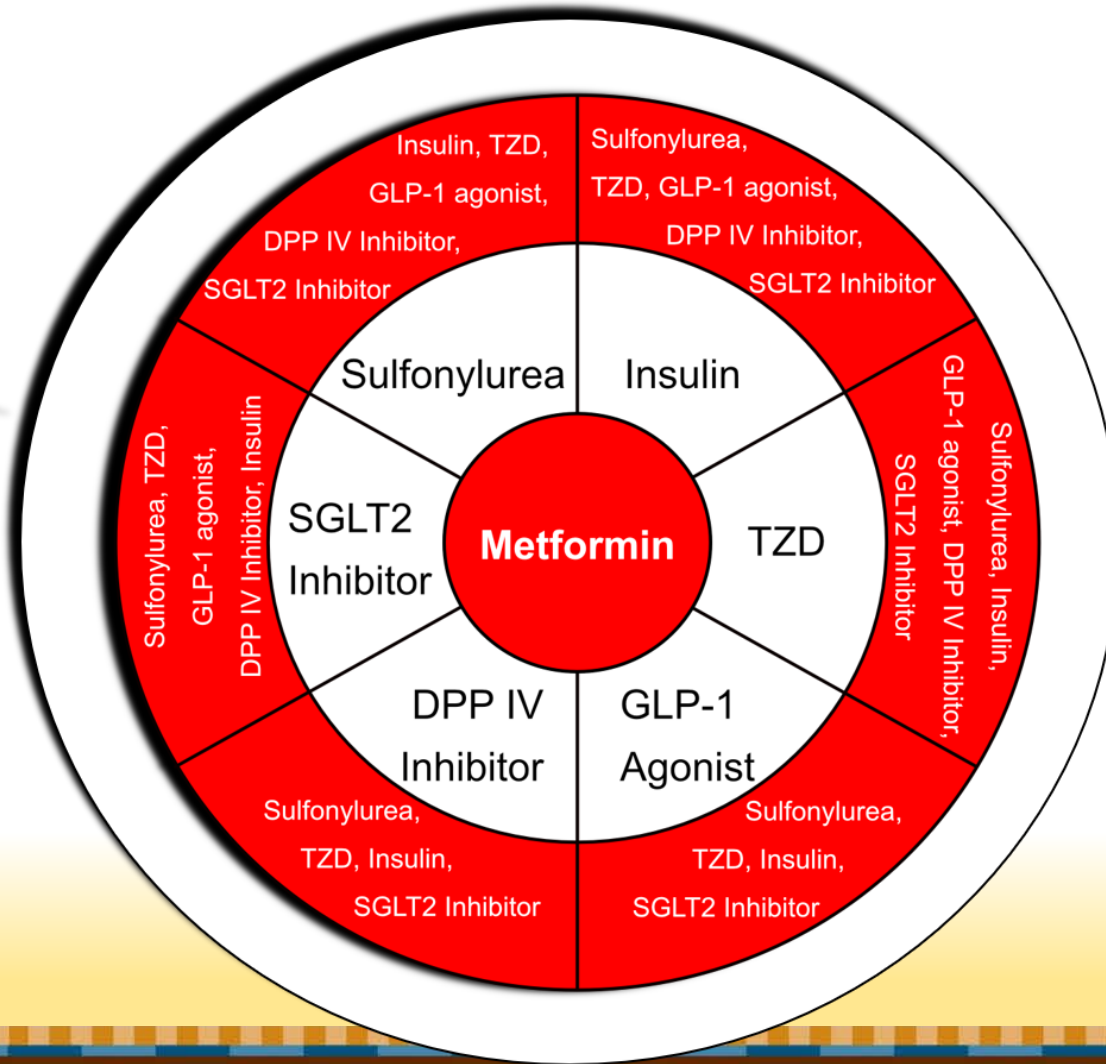
Incretin Mimetics

Glucagon Like Peptide  
DPP-4 Inhibitor





# 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.)



U.S. Department of Health and Human Services

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## Drugs

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**Drug Safety and Availability**

- Drug Alerts and Statements
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Supply Chain Integrity

### 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](mailto: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<sup>1,2</sup> to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function,<sup>3-14</sup> 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.

Health care professionals should follow the latest recommendations when prescribing metformin.

# 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



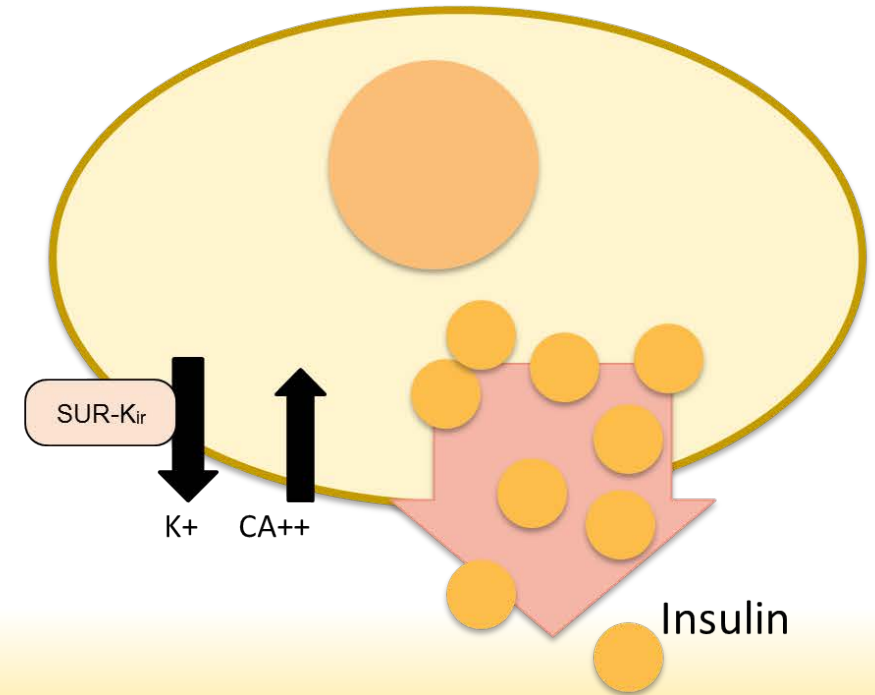
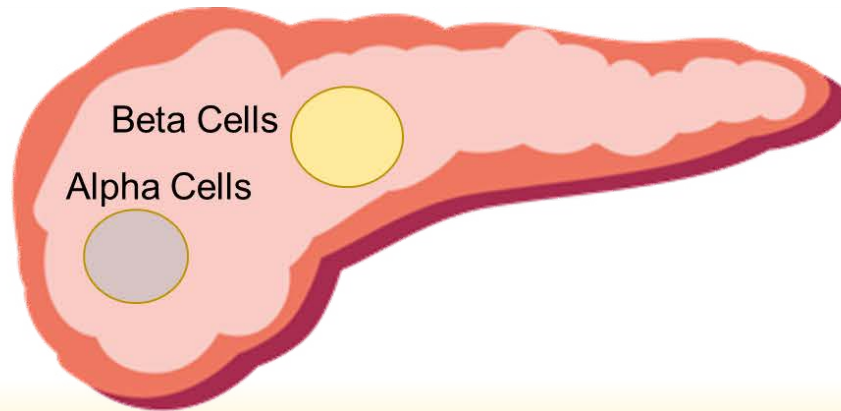
	Sulfonylurea	TZD	DPP-4 Inhibitor	SGLT2 Inhibitor	GLP-1 Agonist	Insulin
A1C Lowering	↓↓	↓↓	↓	↓	↓↓	↓↓↓
Hypoglycemia risk*	↑↑	↓↓	↓↓	↓↓	↓↓	↑↑
Weight gain	↑↑	↑↑	-	↓	↓	↑↑
Cost	low	low	high	high	high	low-high

\* when used alone



# Sulfonylureas

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



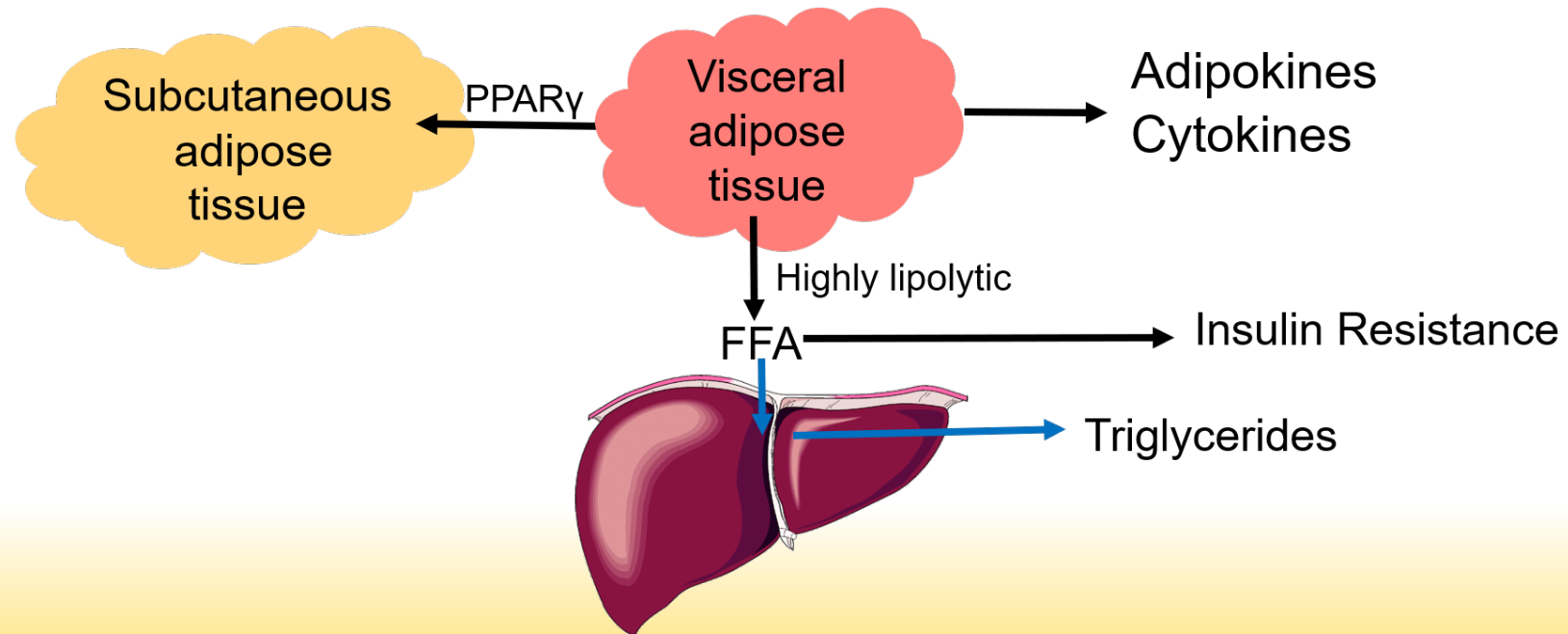
# Sulfonylureas (cont.)



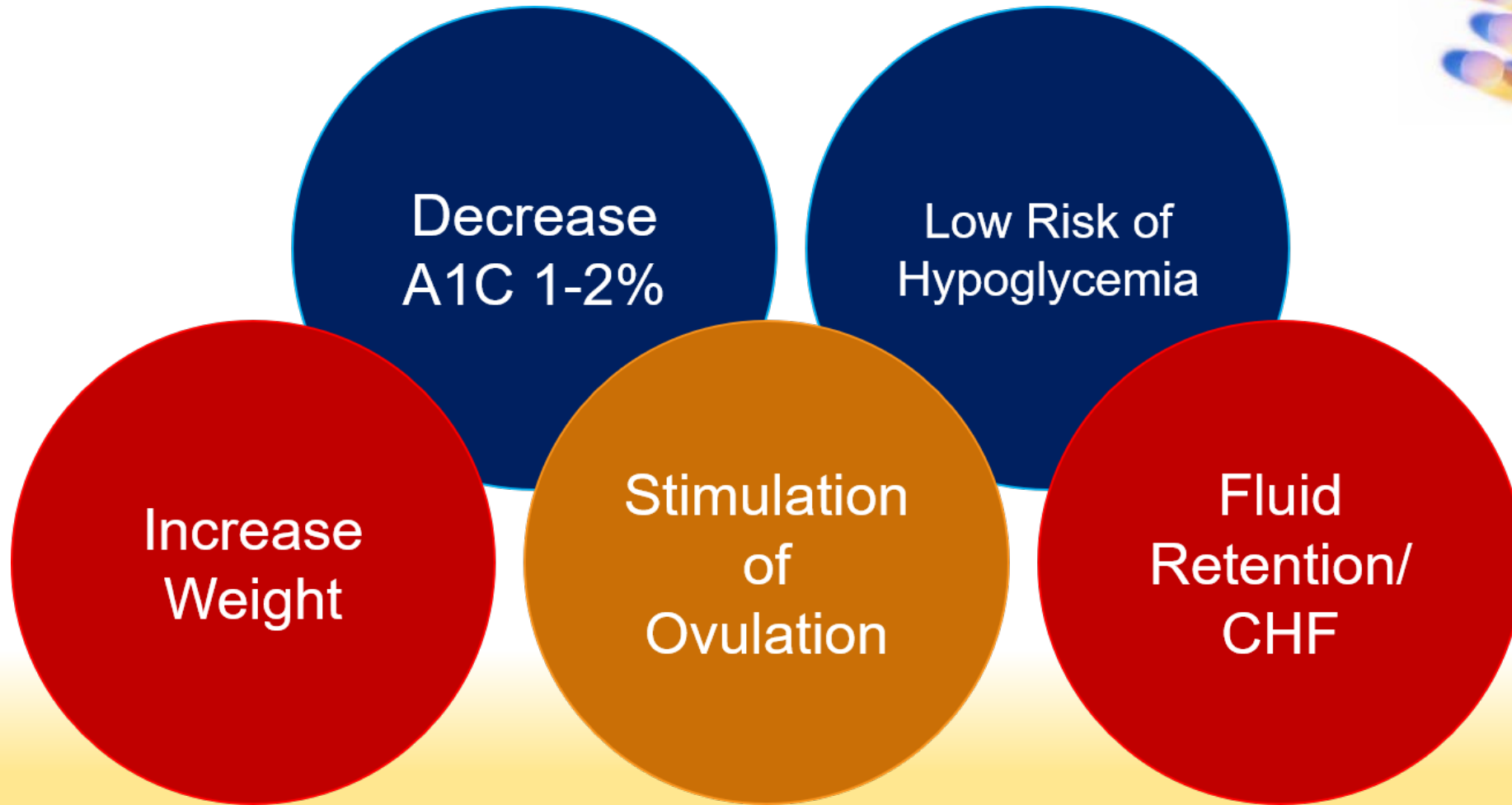
Drug	Starting Dose	Max Dose	Duration	Comments
Glyburide (Diabeta®, Micronase®)	1.25-10mg daily (single or divided dose)	20mg daily	24 hours	Metabolized by the liver. Excreted in urine and bile.
Glyburide (Glynase®)	0.75-12mg daily	12mg daily		
<b>Glipizide (Glucotrol® Glucotrol XL®)</b>	<b>2.5-20mg daily (single or divided dose)</b>	<b>40mg (20mg if XL)</b>	<b>12-16 hours</b>	<b>Metabolized by the liver. Excreted in the urine. Take on empty stomach.</b>
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 (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)



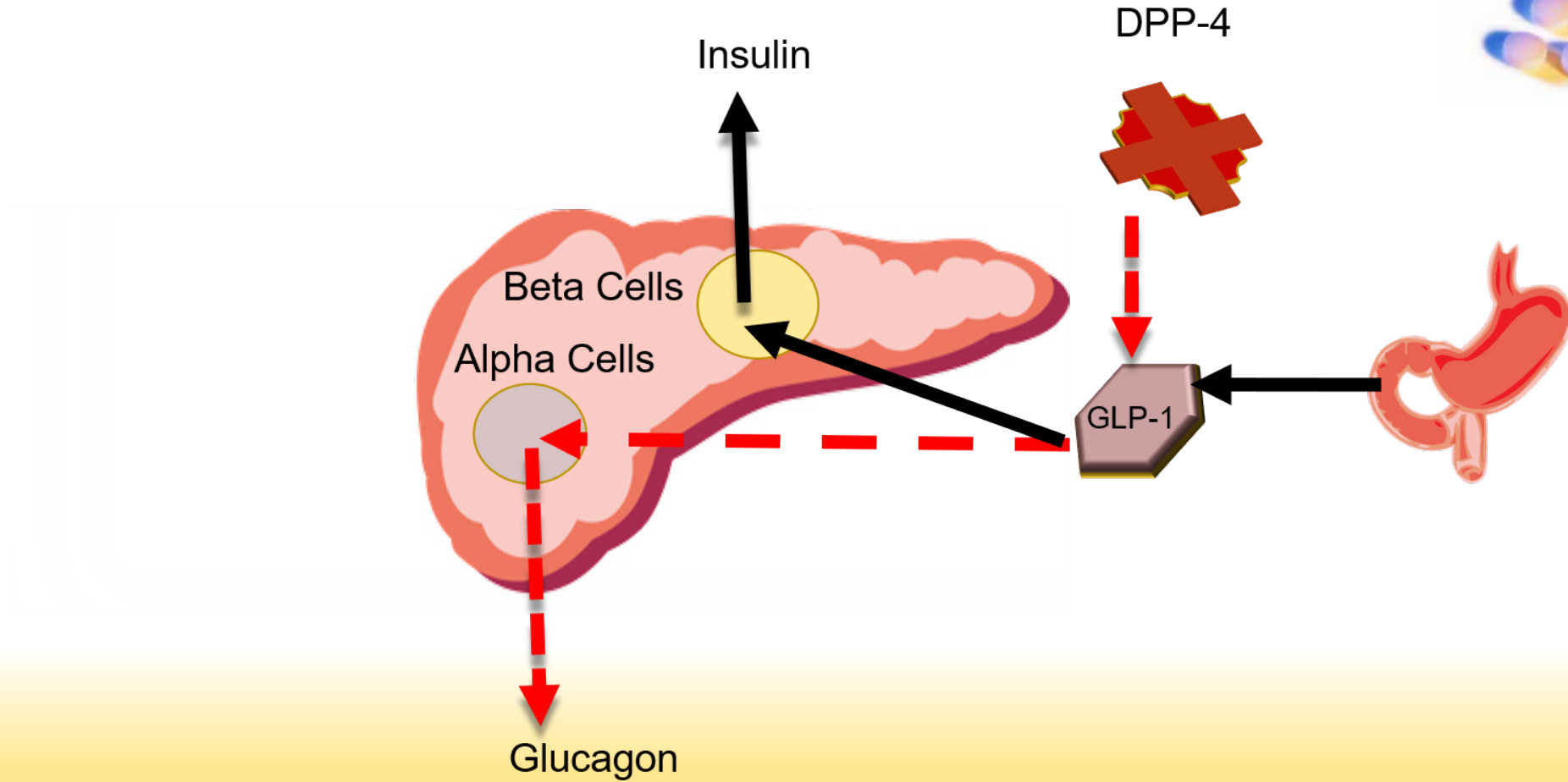
- Missed weekly doses: take when remembered if  $\leq 3$  days of the next dose



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



# DPP-4 Inhibitors





# DPP-4 Inhibitors (cont.)



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



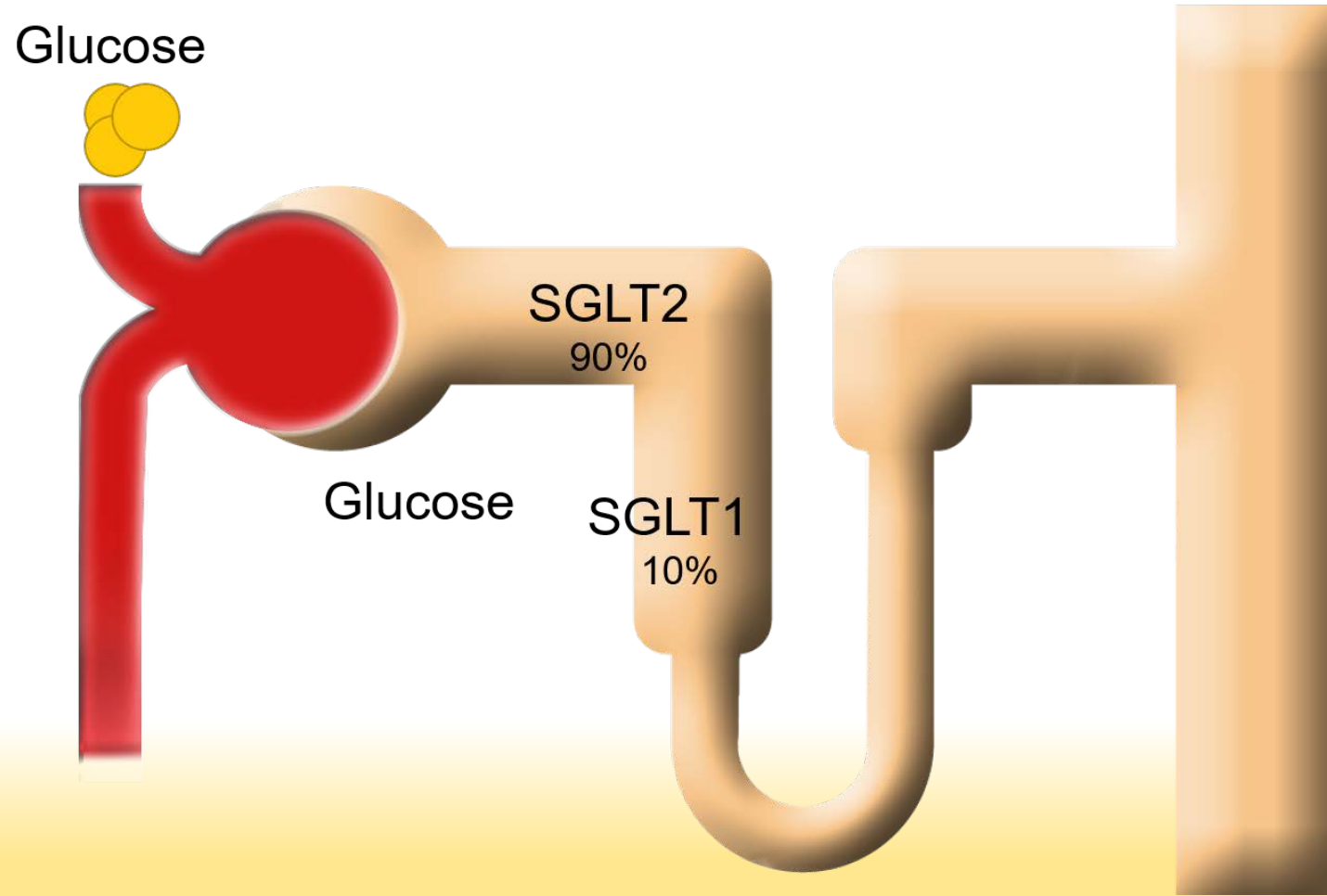
# Saxagliptin

Dosing: 5mg daily  
2.5mg daily if  $\text{CrCL} \leq 50 \text{ml/min}$  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)

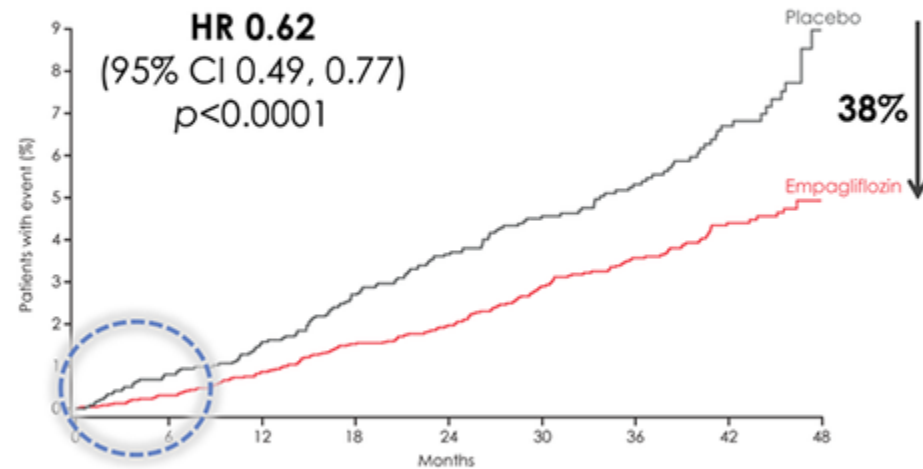


Medication	Starting Dose	Maximum Dose
Canagliflozin	100mg daily before the first meal	300mg daily
Dapagliflozin	5mg daily with or without food	10mg daily
Empagliflozin	10mg daily with or without food	25mg daily

# SGLT-2 Inhibitors: CVD Benefit



## CV death



No. of patients	4687	4651	4608	4556	4128	3079	2617	1722	414
Empagliflozin	2333	2303	2280	2243	2012	1503	1281	825	177
Placebo									

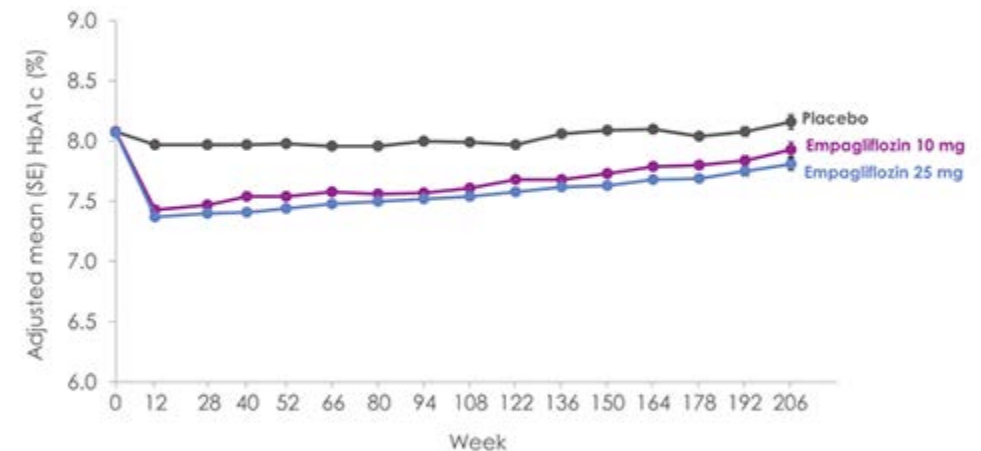
Cumulative incidence function, HR, hazard ratio



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

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## HbA1c



Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

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



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

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# Basal Insulin

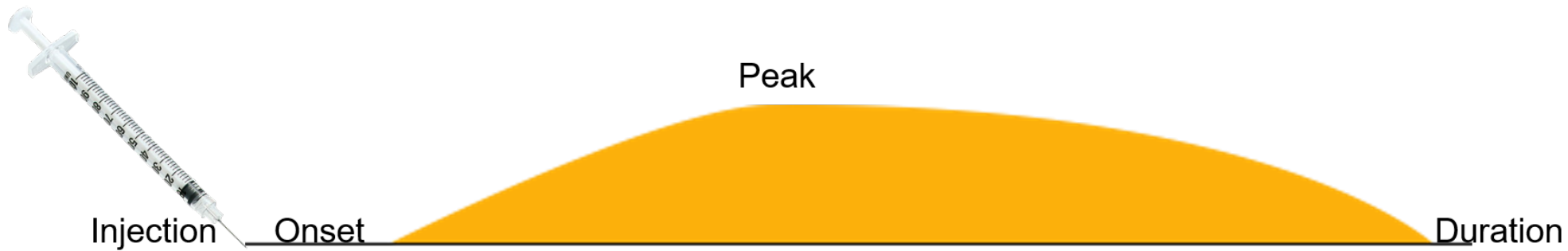
- Intermediate Acting
  - NPH
- Long Acting
  - Glargine
  - Detemir (Levemir®)
- Ultra Long Acting
  - Glargine U300 (Toujeo®)
  - Degludec (Tresiba®)





# 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



**U-100**

**U-200**

**U-300**

**U-500**



- 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



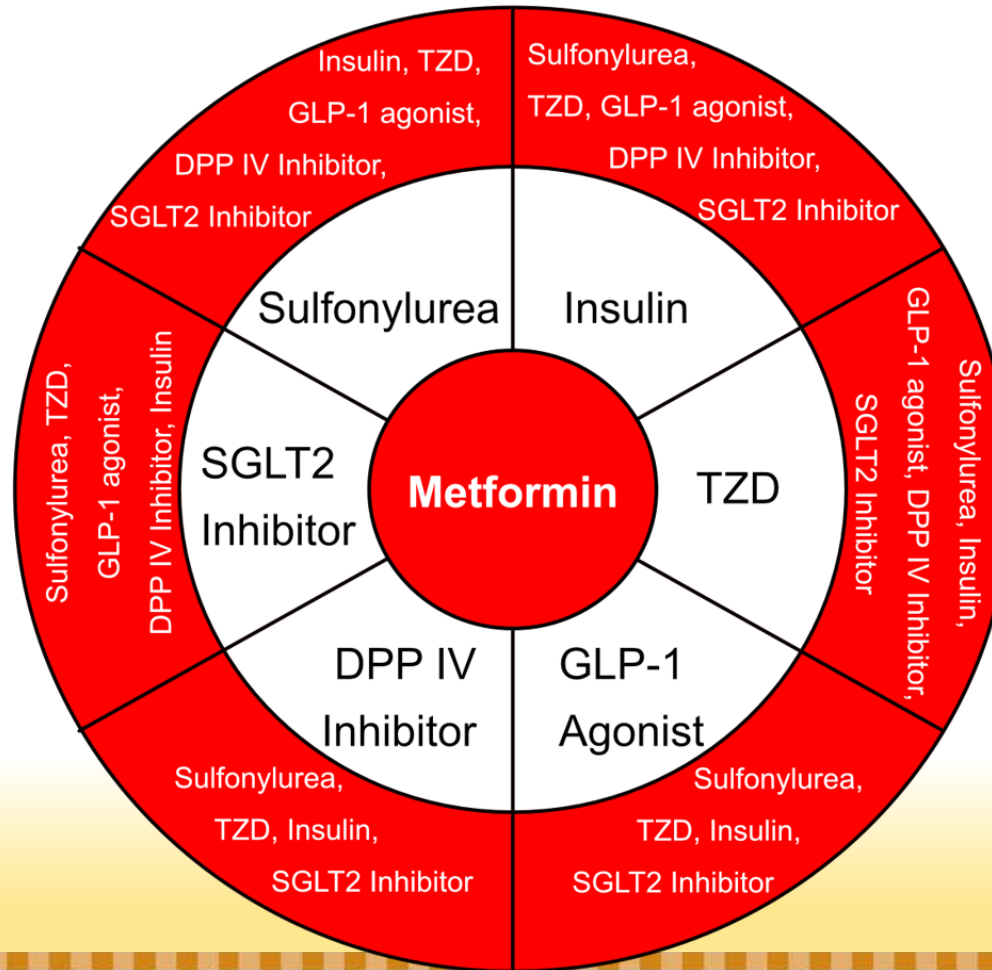


## Step 2: Add Another Agent



	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

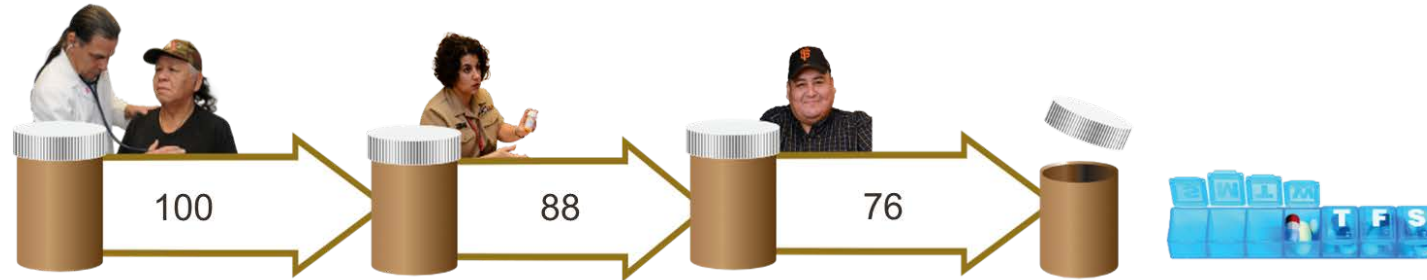


# Drugs don't work if....

## ....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.)

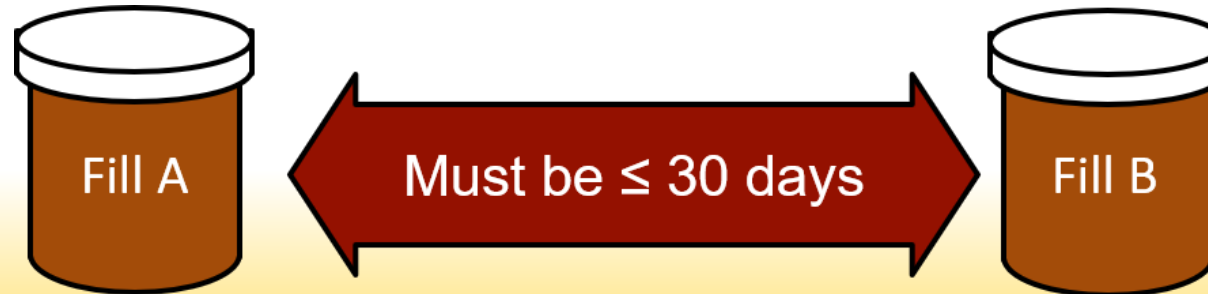


- Proportion of Days Covered (PDC)

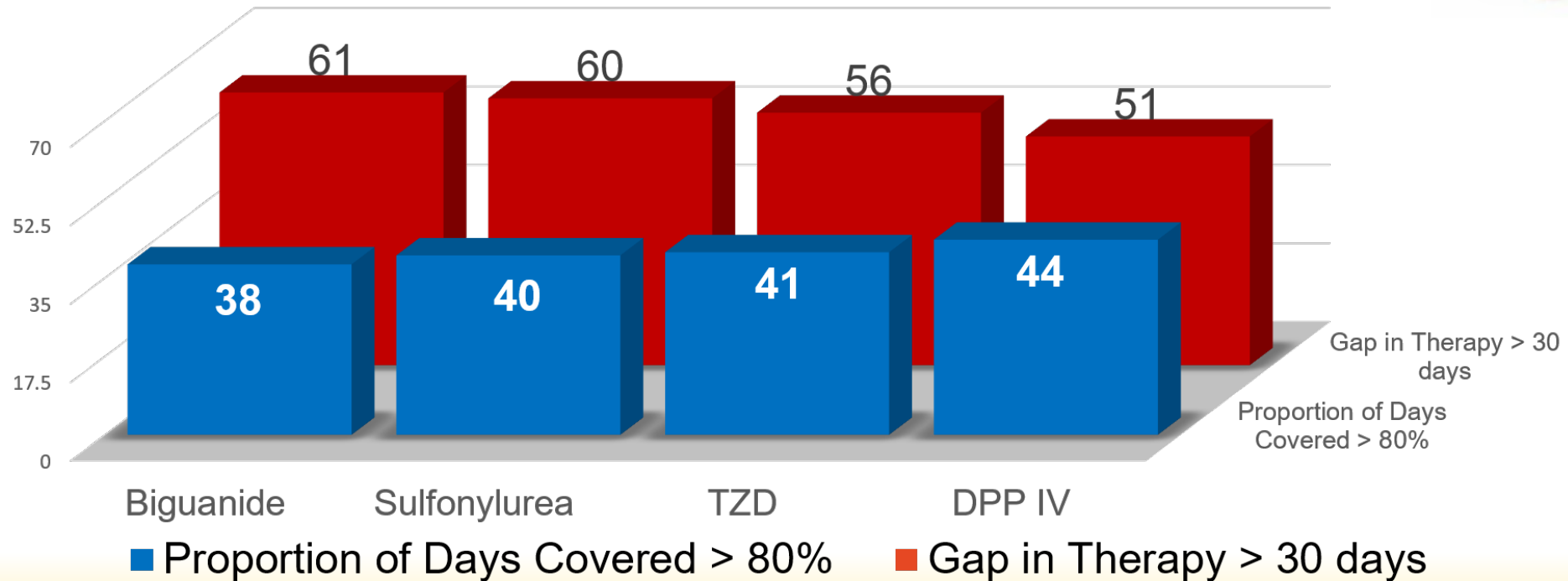


Total days must be  $\geq 80\%$  ( $> 292$  days supply)

- Gaps in Therapy

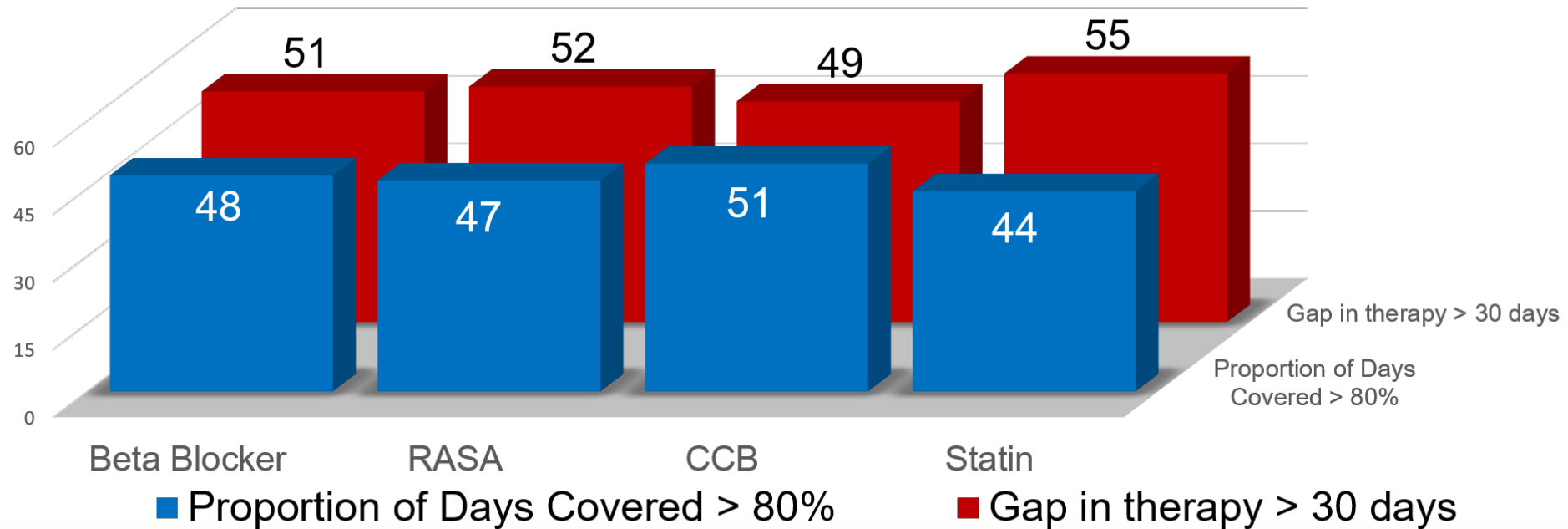


# Diabetes Medications

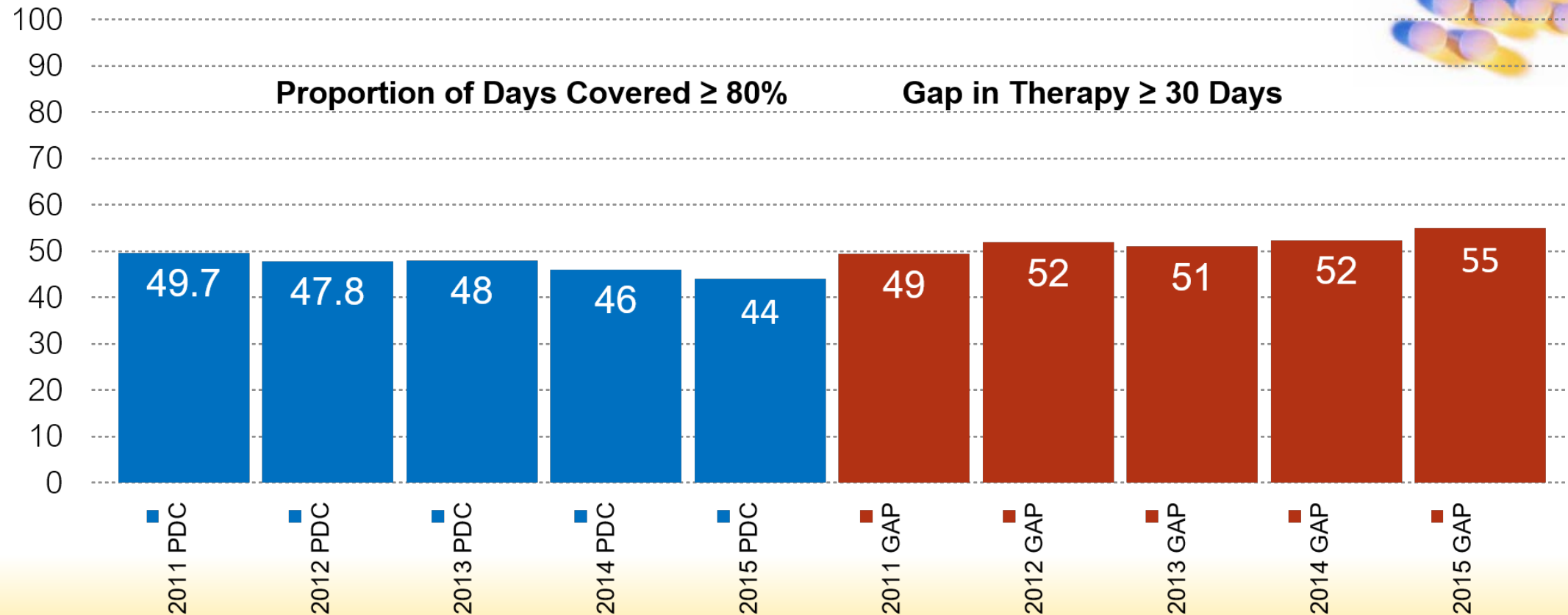




# Cardiovascular Medications

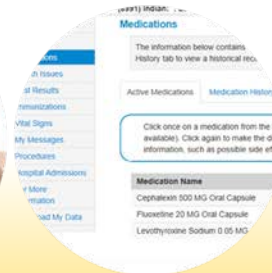


# Adherence to Statin Medications 2011-2015



# 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



**Indian Health Service**  
The Federal Health Program for American Indians and Alaska Natives

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Division of Diabetes Treatment and Prevention

**Diabetes Treatment Algorithms**

The Diabetes Treatment Algorithms were developed to provide clinicians with a quick reference to treatment algorithms based on national guidelines and the Standards of Care and Clinical Practice Recommendations, Type 2 Diabetes. The algorithms are a collaborative effort between Indian health system professionals and have been reviewed by the IHS Division of Diabetes.

The algorithms provide the clinician with basic information needed at the point of patient care and also provide:

- Step-by-step management of the associated condition.
- Dosing, common adverse reactions and contraindications for medications on the IHS National Core Formulary.
- Treatment targets and goals.
- Recommended monitoring parameters.

The Diabetes Treatment Algorithms are intended to serve as a tool to enhance the information required in treating patients with type 2 diabetes. It is not a substitute for the knowledge and information provided by complete national guidelines or the IHS Diabetes Standards of Care for Patients with Type 2 Diabetes. The algorithms will be updated periodically but changes in national practice may occur more quickly—users are advised to stay abreast of current clinical practice recommendations.

**Chronic Kidney Disease in Type 2 Diabetes**  
Download Algorithm (PDF – 229 KB)  
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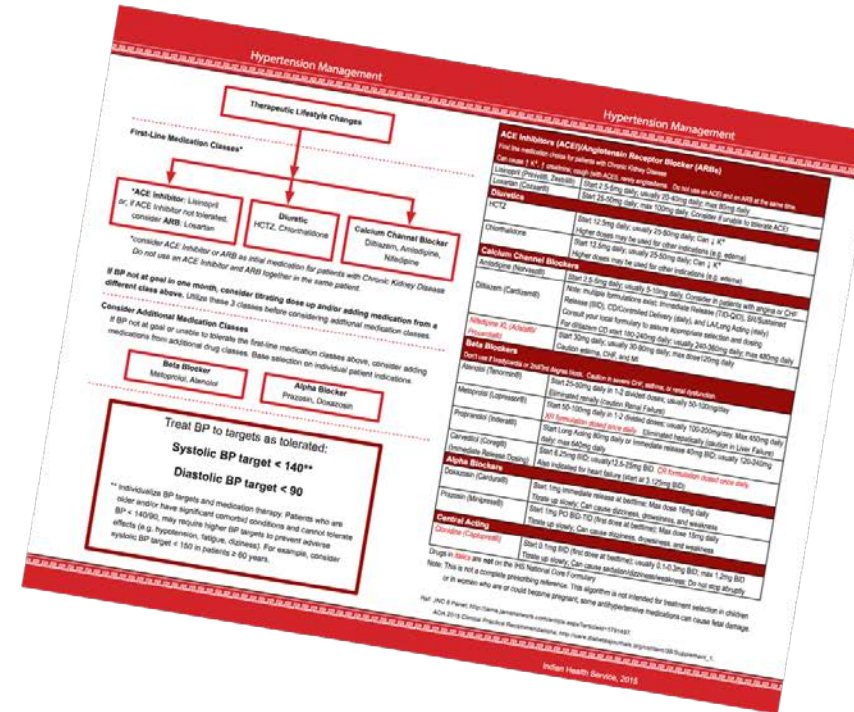
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<https://www.ihs.gov/diabetes/clinician-resources/dm-treatment-algorithms/>

# 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

Division of Diabetes Treatment and Prevention  
Leading the effort to treat and prevent diabetes in American Indians and Alaska Natives

Wednesday, July 05, 2017

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**Using Our Wit and Wisdom to Live Well with Diabetes**

Format: CD

Audience: Health Care Professionals, Patients/Clients, Program Staff

Topic: Behavioral Health, General Diabetes

Quantity:   
(Maximum: 200)

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**AUDIO CD SET**

Narrated by Author Barbara Mora  
Native Music by Bob Mora  
May 2008

**Using Our Wit & Wisdom to Live Well with Diabetes**

Produced by Indian Health Service  
Division of Diabetes Treatment & Prevention

Three audio CD set of the book written by Barbara Mora (Palute/Dine), recorded by the author, complete with audio effects and flute music played by Bob Mora, the author's husband. Barbara talks about her emotional journey with diabetes, and how she battled with denial and depression before learning how to take care of herself and live a joyful life. A valuable inspirational tool for those newly diagnosed with diabetes, those in denial or depressed because of diabetes, and health care providers wanting to better understand the emotional impact of a diabetes diagnosis.



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

# Thank you!

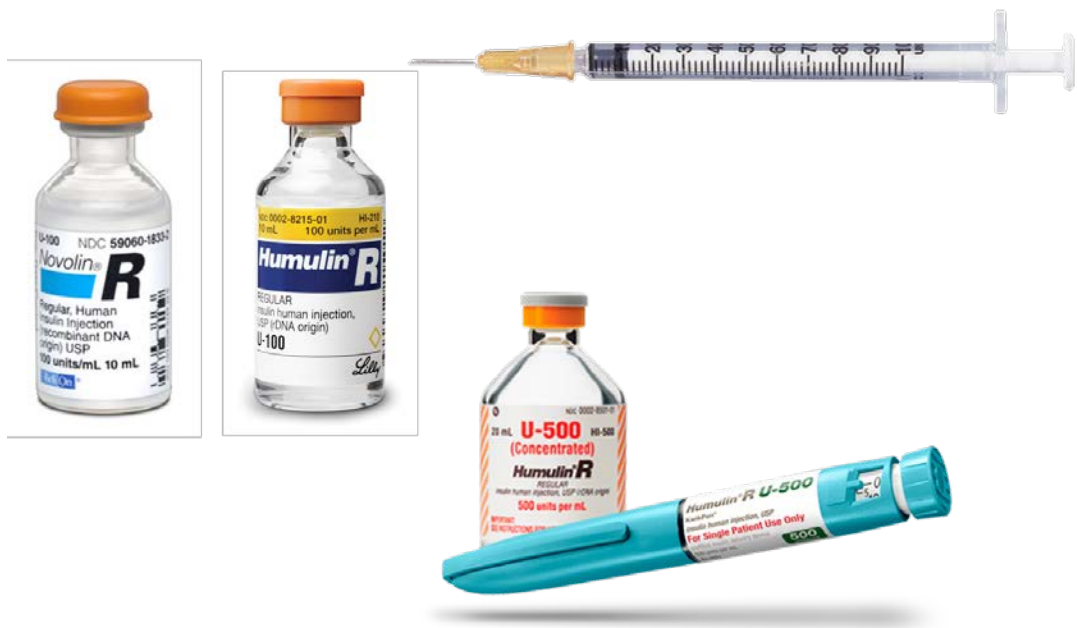


Chris.Lamer@ihs.gov





# 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