

# **הטיפול בסוכרת מסוג 2: הנחיות המועצה הלאומית לסוכרת**

**ד"ר עופרי מוסנזון  
מנהלת היחידה למחקר קליני בסוכרת,  
ביה"ח האוניברסיטאי הדסה עין כרם  
והמועצה הלאומית לסוכרת**

למה צריך הנחיות  
לטיפול בסוכרת??

למי צריך הנחיות  
לטיפול בסוכרת??

# The necessity of clinical guideline in the treatment of Type 2 diabetes (1)

## North America and Caribbean

2015 44.3 million  
2040 60.5 million

## Europe

2015 59.8 million  
2040 71.1 million

## Middle East and North Africa

2015 35.4 million  
2040 72.1 million

## Western Pacific

2015 153.2 million  
2040 214.8 million

## South East Asia

2015 78.3 million  
2040 140.2 million

## South and Central America

2015 29.6 million  
2040 48.8 million

## Africa

2015 14.2 million  
2040 34.2 million

2015 **415 million**  
2040 **642 million**

In 2015, **1 in 11** people have diabetes worldwide.  
In 2040, this will grow to **1 in 10**

# The necessity of clinical guideline in the treatment of Type 2 diabetes (1)

## North America and Caribbean

2015 44.3 million  
2040 60.5 million

## Europe

2015 59.8 million

2015 **415 million**  
2040 **642 million**

**Most patients with type 2 diabetes  
(and specifically most important patients)  
are treated by primary care physician/team**

## South and Central America

2015 29.6 million  
2040 48.8 million

## Africa

2015 14.2 million  
2040 34.2 million

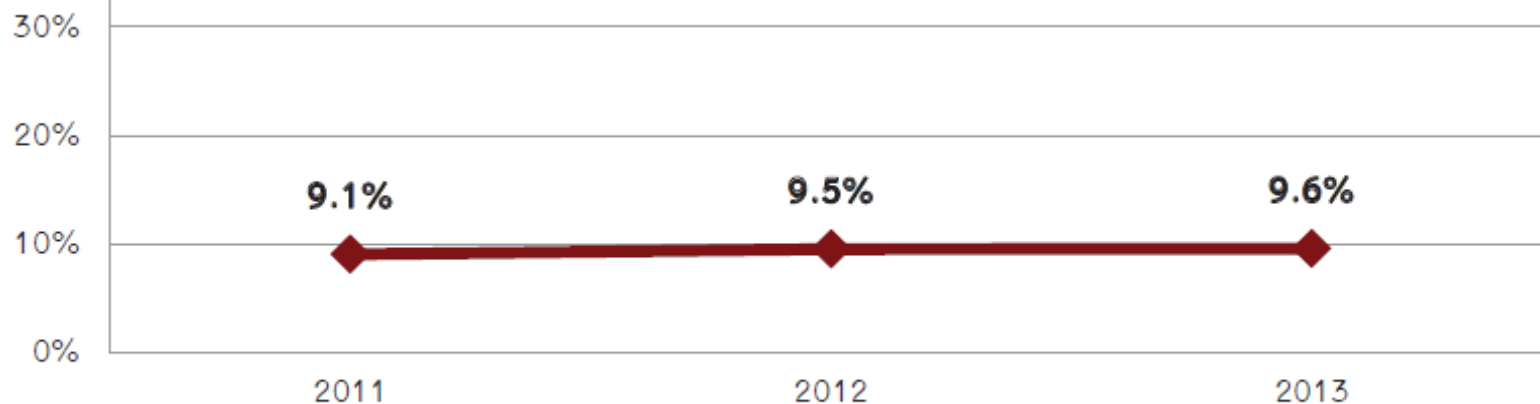
## South East Asia

2015 78.3 million  
2040 140.2 million

In 2015, **1 in 11** people have diabetes worldwide.  
In 2040, this will grow to **1 in 10**

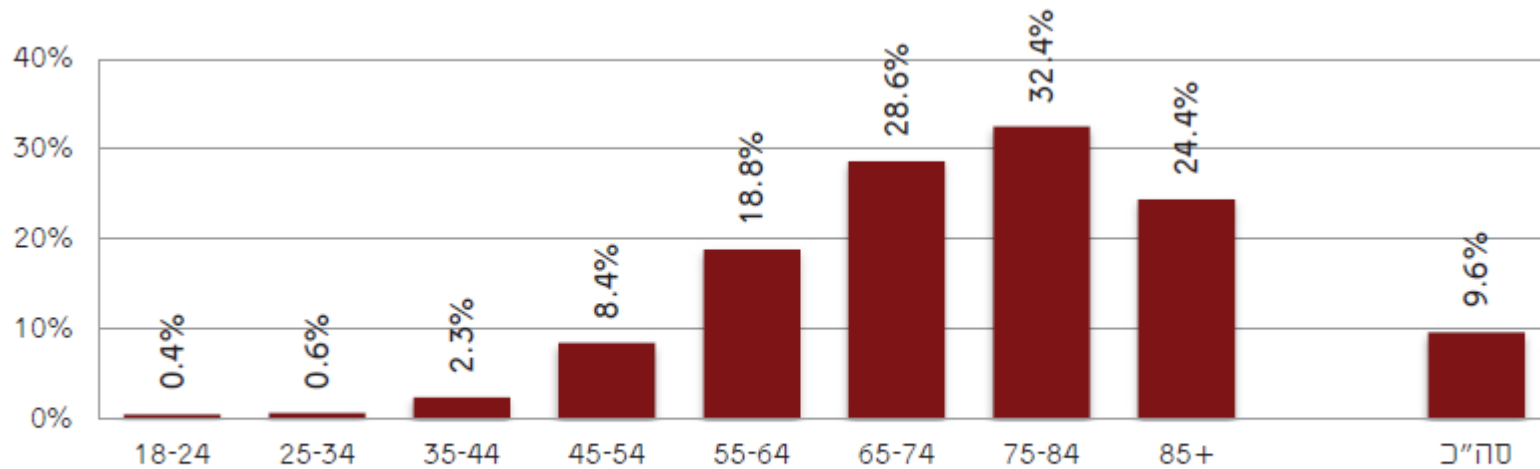
# הימצאות סוכרת בישראל

שיעור



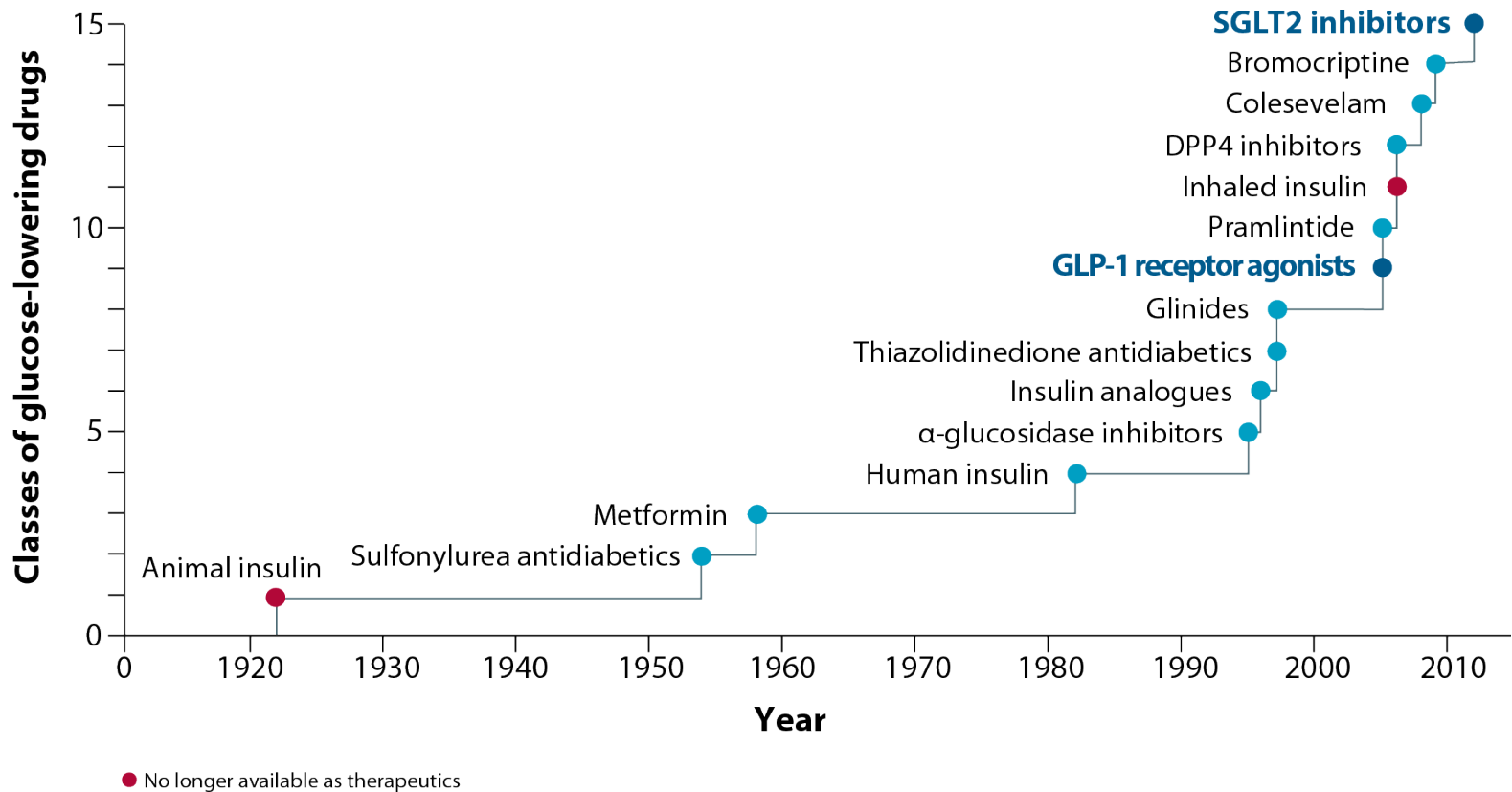
שנה

שיעור

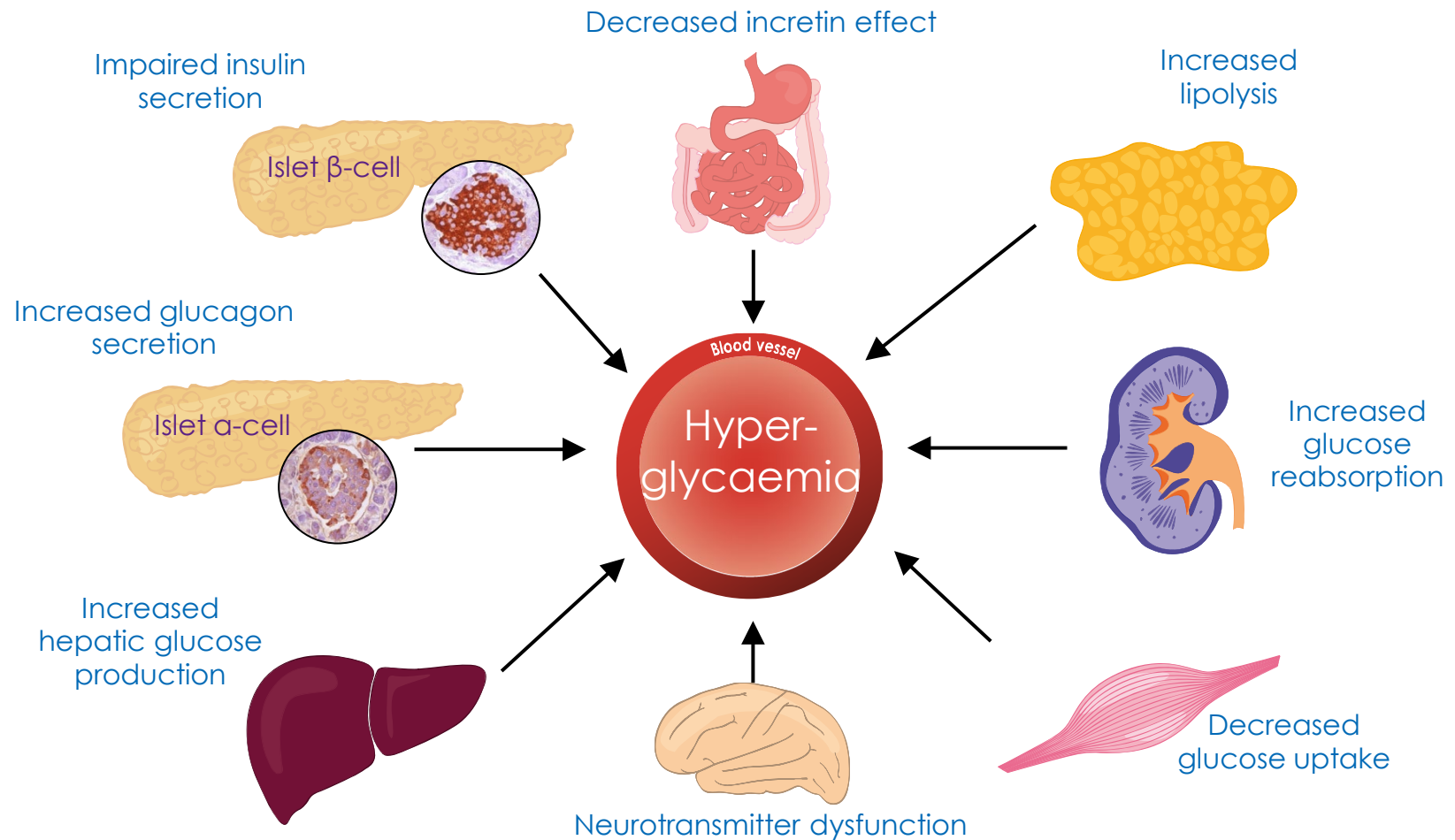


גיל

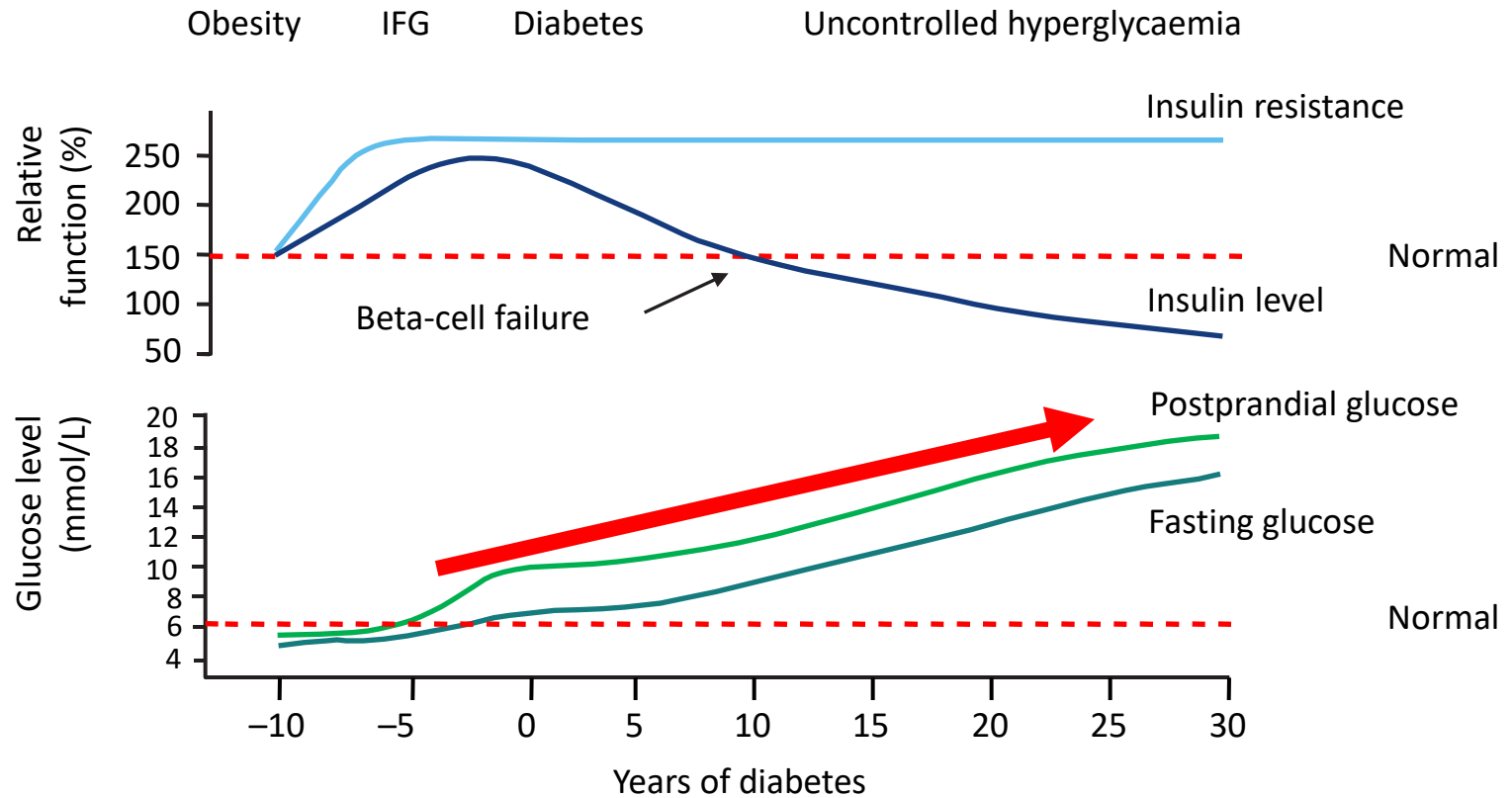
# The necessity of clinical guideline in the treatment of Type 2 diabetes (2)



# Multiple pathophysiological failures contribute to hyperglycaemia - The "Ominous Octet"



# Diabetes is a progressive Disease





# The necessity of clinical guideline in the treatment of Type 2 diabetes (3) “Patient Centered Approach”



## 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

<b>EFFICACY*</b>	high
<b>HYPO RISK</b>	low risk
<b>WEIGHT</b>	neutral/loss
<b>SIDE EFFECTS</b>	GI/lactic acidosis
<b>COSTS*</b>	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)
<b>EFFICACY*</b>	high	high	intermediate	intermediate	high	highest
<b>HYPO RISK</b>	moderate risk	low risk	low risk	low risk	low risk	high risk
<b>WEIGHT</b>	gain	gain	neutral	loss	loss	gain
<b>SIDE EFFECTS</b>	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
<b>COSTS*</b>	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 <sup>§</sup>	or GLP-1-RA	or Insulin <sup>§</sup>	or GLP-1-RA
or	Insulin <sup>§</sup>	or Insulin <sup>§</sup>		or Insulin <sup>§</sup>		

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).

### Combination Injectable Therapy

(See Figure 8.2)

**Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations.** The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. \*See ref. 21 for description of efficacy and cost categorization. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (21).

### Mono-therapy

Efficacy<sup>†</sup>  
 Hypo risk  
 Weight  
 Side effects  
 Costs<sup>‡</sup>

## Healthy eating, weight control, increased physical activity, and diabetes education

### Metformin

high  
 low risk  
 neutral / loss  
 GI / lactic acidosis  
 low

*If HbA<sub>1c</sub> target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

### Dual therapy<sup>†</sup>

Efficacy<sup>†</sup>  
 Hypo risk  
 Weight  
 Side effects  
 Costs<sup>‡</sup>

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high	high	intermediate	intermediate	high	highest
moderate risk	low risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	loss	gain
hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
low	low	high	high	high	variable

*If HbA<sub>1c</sub> target not achieved after ~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- and disease-specific factors):*

### Triple therapy

Efficacy<sup>†</sup>  
 Hypo risk  
 Weight  
 Side effects  
 Costs<sup>‡</sup>

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
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 Insulin <sup>§</sup>	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin <sup>§</sup>	or Insulin <sup>§</sup>		or GLP-1-RA
or Insulin <sup>§</sup>	or Insulin <sup>§</sup>				

*If HbA<sub>1c</sub> target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:*

### Combination injectable therapy<sup>†</sup>

Metformin +	Basal insulin +	Mealtime insulin	or	GLP-1-RA
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# **Treatment of Type 2 Diabetes: From “Guidelines” to “Position Statements” and Back Recommendations of the Israeli National Diabetes Council**

Ofri Mosenzon, Rena Pollack, and Itamar Raz

Diabetes Care 2016;39(Suppl. 2):S1–S8 | DOI:  
10.2337/dcS15-3003

**Mono-**

Efficacy*
Hypo risk
Weight
Side effects
Costs*

**Healthy eating, weight control, increased physical activity, and diabetes education**

**Metformin**

high
low risk
neutral / loss
GI / lactic acidosis
low

*If HbA<sub>1c</sub> target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):*

**Dual**

Efficacy*
Hypo risk
Weight
Side effects
Costs*

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high	high	intermediate	intermediate	high	highest
moderate risk	low risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	loss	gain
hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
low	low	high	high	high	variable

*If HbA<sub>1c</sub> target not achieved after ~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- and disease-specific factors):*

**Triple therapy**

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
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 Insulin <sup>§</sup>	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin <sup>§</sup>	or Insulin <sup>§</sup>		or GLP-1-RA
or Insulin <sup>§</sup>	or Insulin <sup>§</sup>				

*If HbA<sub>1c</sub> target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:*

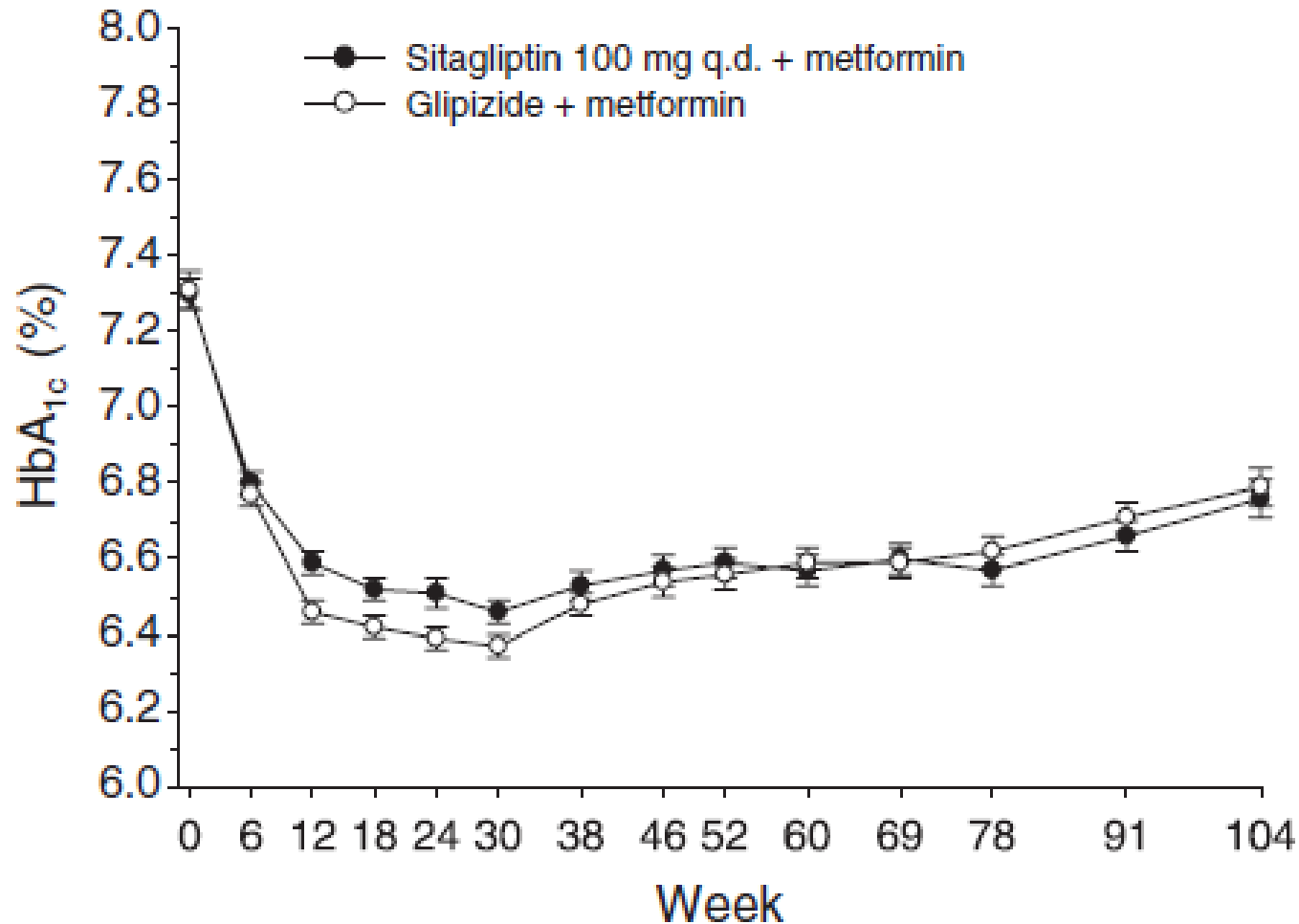
**Combination injectable therapy<sup>‡</sup>**

Metformin +	Basal insulin +	Mealtime insulin	or	GLP-1-RA
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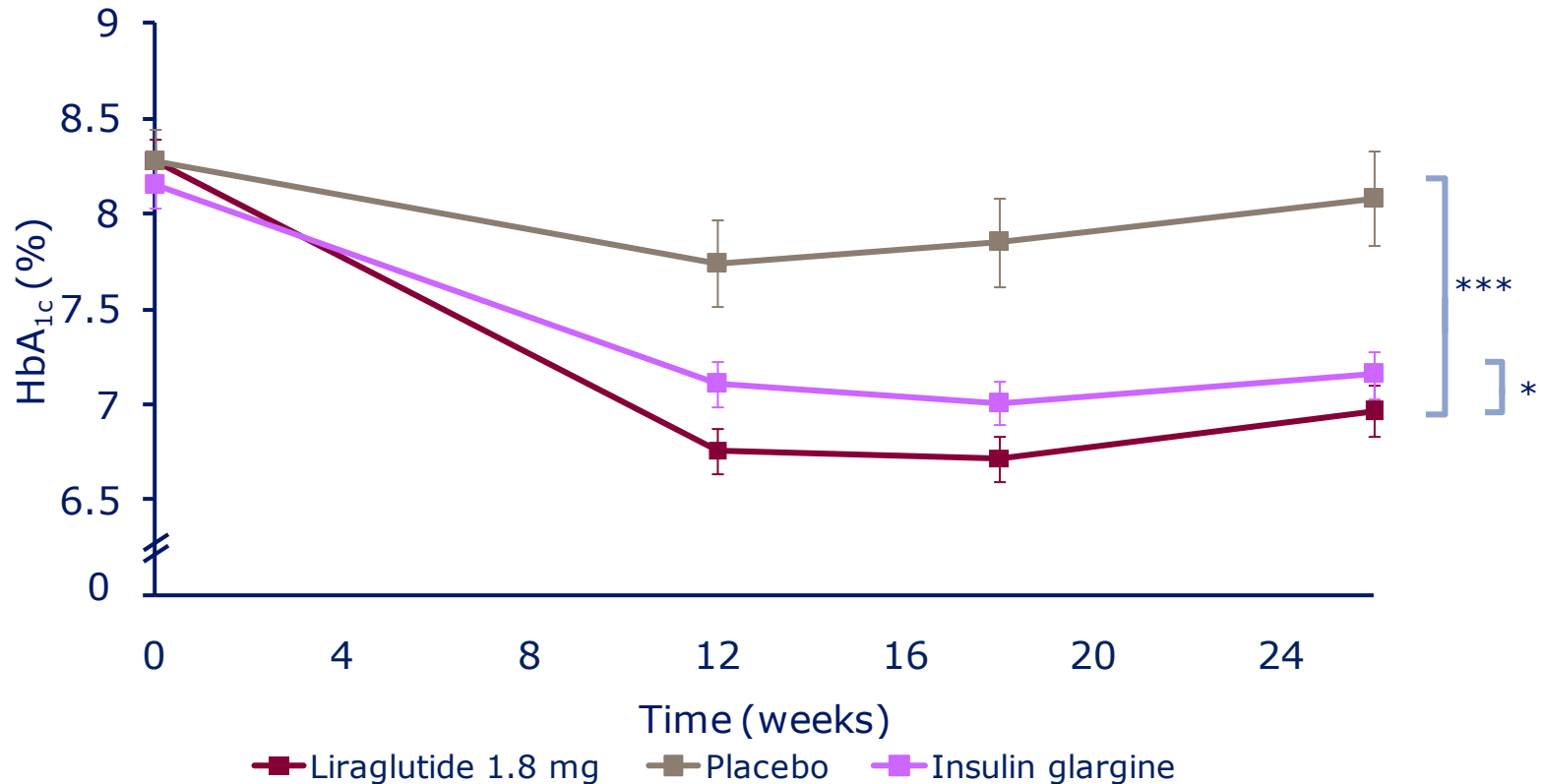
Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidine-dione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
Efficacy*	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo						
Weight						
Other Side Effects						
Cost						
CV Safety						
<b>Recommendation</b>						

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia

# HbA1c change with Januvia (DPP4 Inh.) vs. SU



# HbA<sub>1c</sub> change over 26 weeks with Glargine vs. Liraglutide



Mean±2SE; p values relate to estimated treatment difference for changes from baseline.

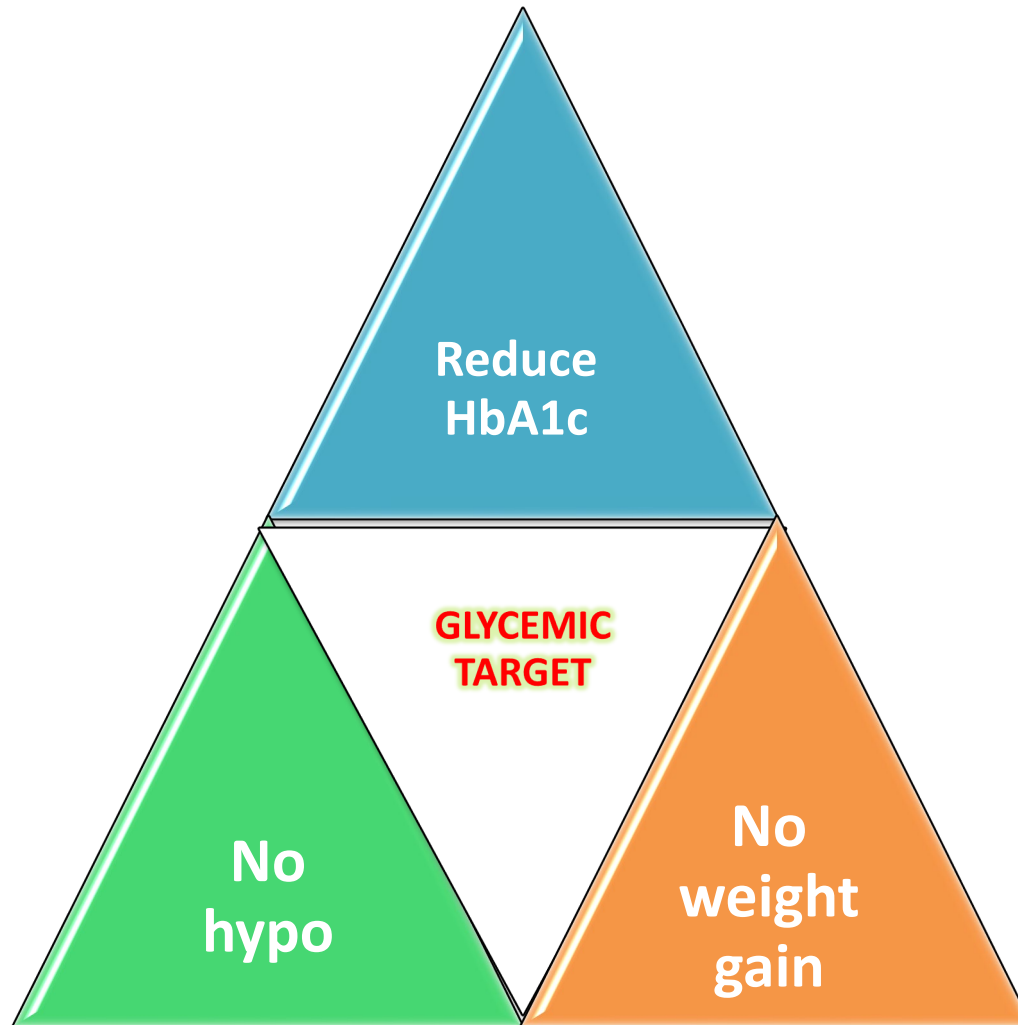
\* $p < 0.05$  \*\*\* $p < 0.0001$



Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidine-dione	DPP-4 Inhibitor	SGLT-2 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	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo						
Weight						
Other Side Effects						
Cost						
CV Safety						
<b>Recommendation</b>						

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia

# A clinically meaningful goal



Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidine-dione	DPP-4 Inhibitor	SGLT-2 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	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects						
Cost						
CV Safety						
<b>Recommendation</b>						

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia



# PROFILES OF ANTIDIABETIC MEDICATIONS



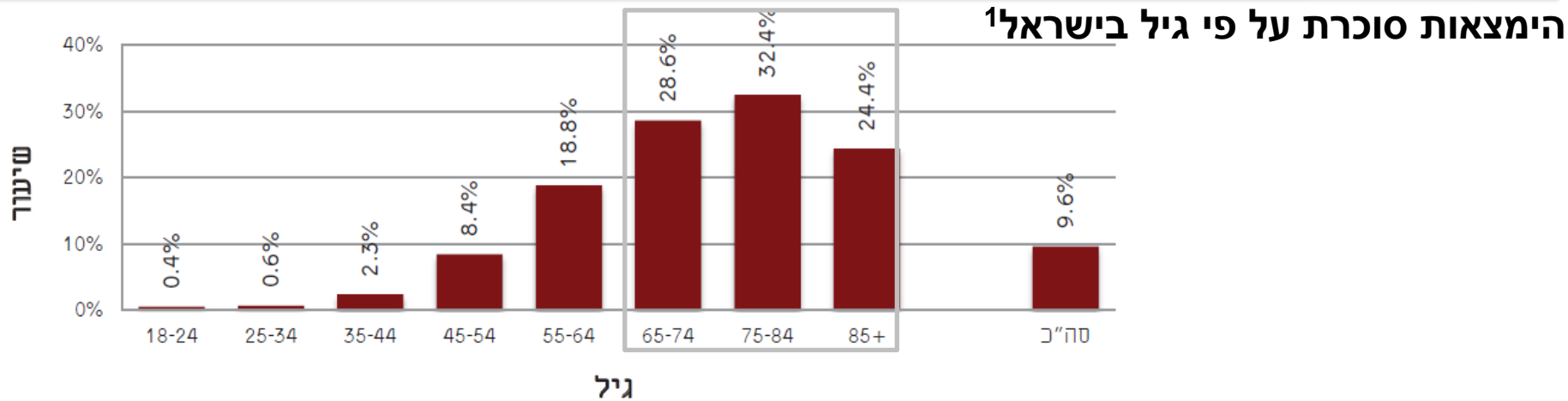
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra- indicated CKD Stage 3B,4,5	Exenatide Not Indicated CrCl < 30	Not Effective with eGFR < 45  Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	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 CARDIAC	Neutral	Neutral	Possible Benefit	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
ASCVD	Benefit					Neutral	?				
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

■ Few adverse events or possible benefits    
 ■ Use with caution    
 ■ Likelihood of adverse effects    
 ? Uncertain effect

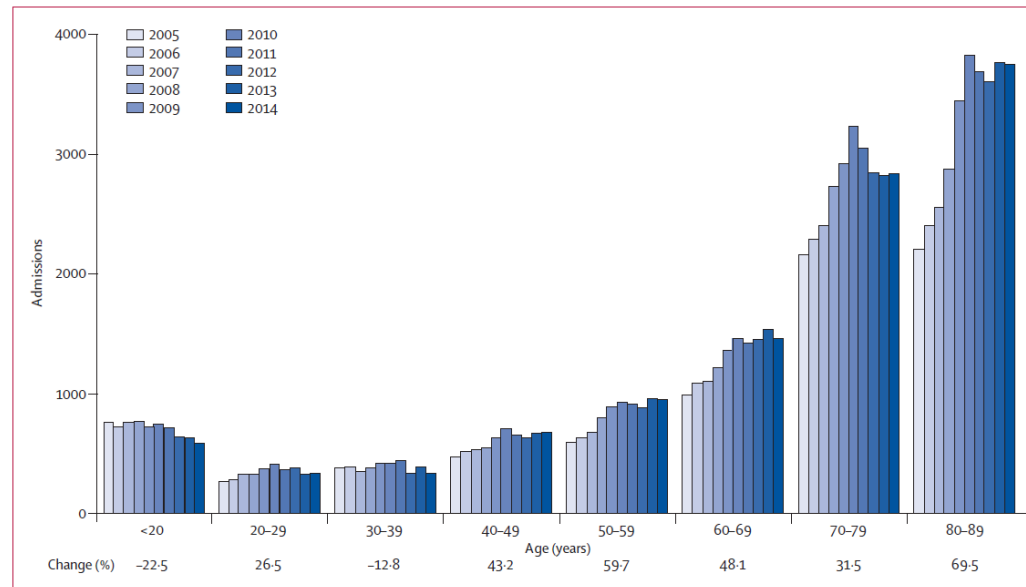
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Efficacy*	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side effects	↔	↑↑	↓	↑	↑	↔
Cost						
CV Safety						
<b>Recommendation</b>						

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia

# 49% מחולי הסוכרת בישראל הם בני 65 ומעלה<sup>1</sup>



## אישפוזים בגין היפוגליקמיה בחלוקה על פי גיל, 2005-2014<sup>2</sup>



מחקר רטרוספקטיבי, תצפיתי  
N=79,172

1. דו"ח ממדי איכות 2011-2013

2. Zaccardi et al., Lancet Diabetes Endocrinol. 2016 Aug;4(8):677-85.

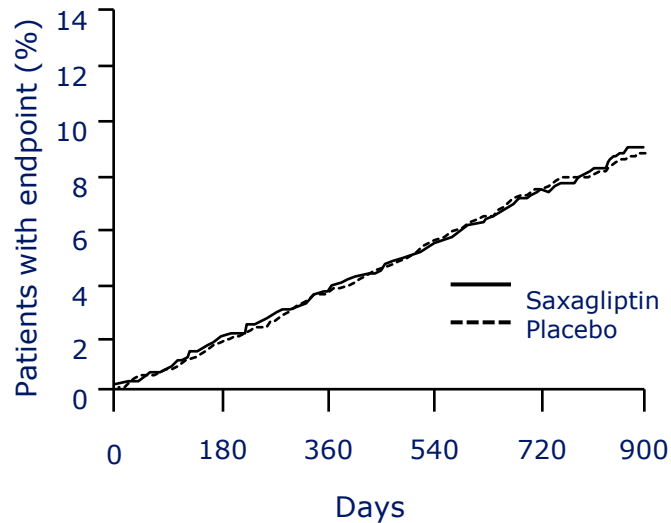
Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
Efficacy*	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety						
Recommendation						

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia

# CV safety of Dipeptidyl peptidase-4 inhibitors

## SAVOR-TIMI-53<sup>1</sup>

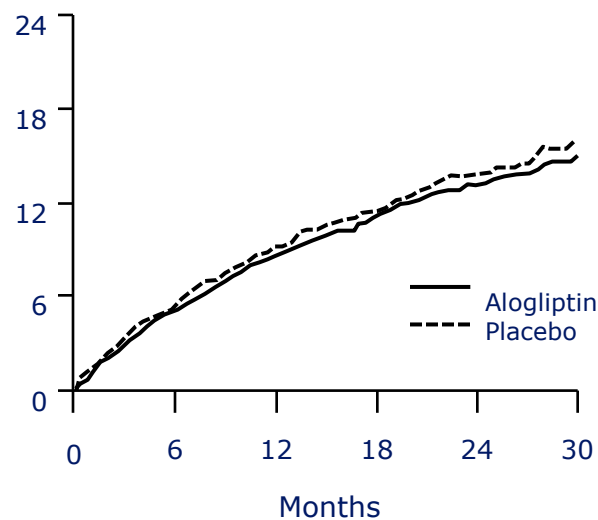
CV death, non-fatal MI or non-fatal ischaemic stroke



**HR: 1.00**  
95% CI (0.89;1.12)  
 $p < 0.001$  for non-inferiority  
 $p = 0.99$  for superiority

## EXAMINE<sup>2</sup>

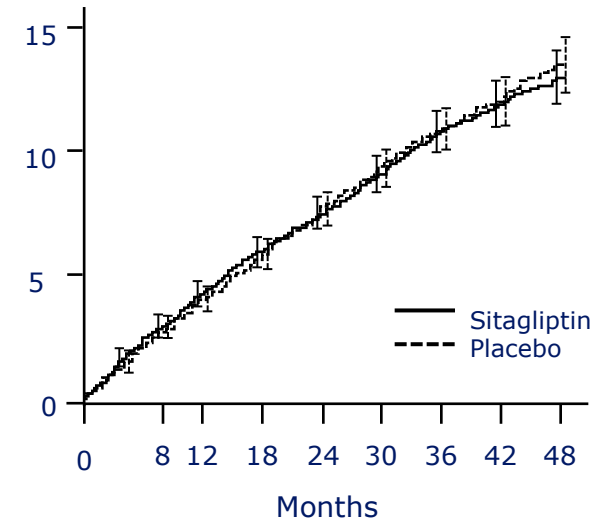
CV death, non-fatal MI or non-fatal stroke



**HR: 0.96**  
(upper boundary of the one-sided repeated CI, 1.16)  
 $p < 0.001$  for non-inferiority  
 $p = 0.32$  for superiority

## TECOS<sup>3</sup>

CV death, non-fatal MI, non-fatal stroke, or hospitalisation for UAP

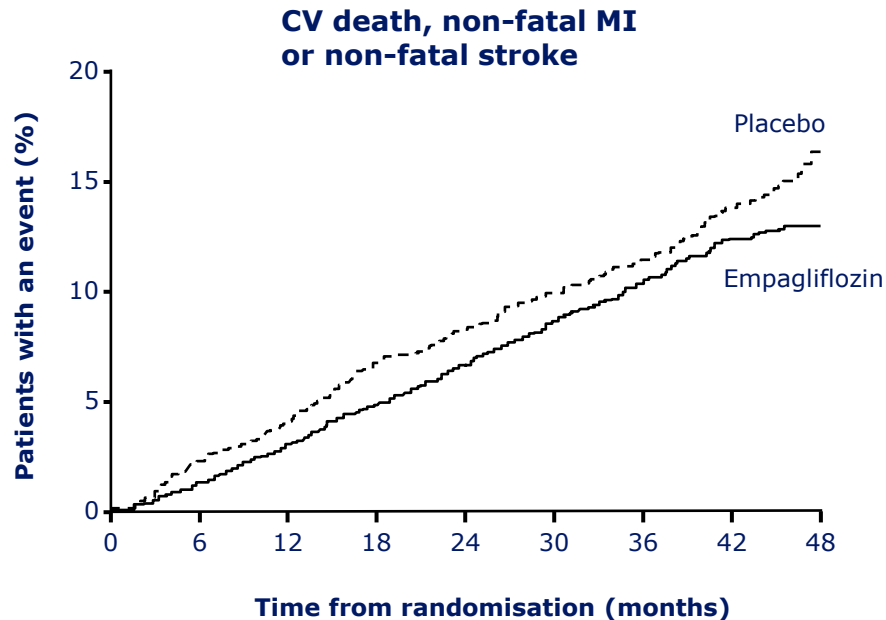


**HR: 0.98**  
95% CI (0.88;1.09)  
 $p < 0.001$  for non-inferiority  
 $p = 0.65$  for superiority



# CV efficacy of Sodium-glucose cotransporter-2 inhibitor

## EMPA-REG OUTCOME



HR: 0.86  
95.02% CI (0.74;0.99)  
 $p < 0.001$  for non-inferiority  
 $p = 0.04$  for superiority

# EMPA REG CVOT: CV and renal results:

## בחולים עם מחלה קרדיוואסקולארית קודמת:

- Jardiance הפחית את התוצא הראשוני: 3-point MACE: MI, Stroke, CV death ב-14%
- Jardiance הפחית את התמותה הקרדיו-וסקולארית ב-38%
- Jardiance הפחית את התמותה הכוללת ב-32%
- Jardiance הפחית אשפוזים עקב כשל לבבי ב-35%
- Jardiance הפחית נפרופתיה או החמרה של נפרופתיה ב-39%
- Jardiance הפחית הגעה ל-ESRD ב-55%

התרופה קבלה אינדיקציית FDA ומשרד הבריאות למניעה שניונית של מחלה קרדיוואסקולארית!

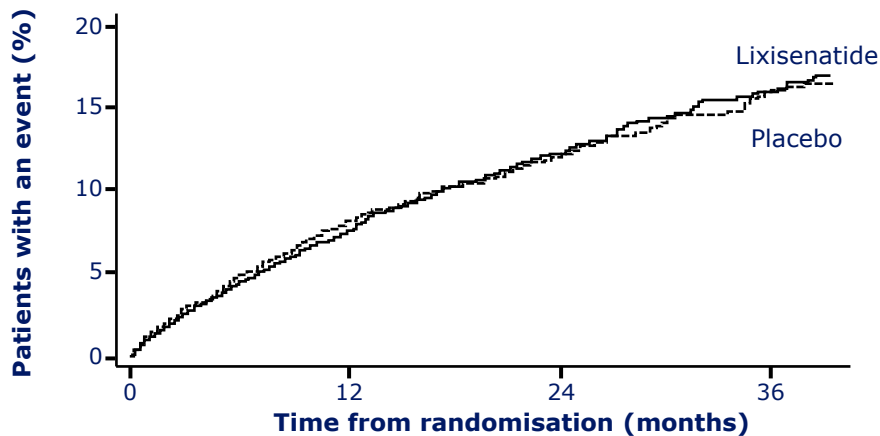
**SGLT2 Inhibitors בסל הבריאות לחולים עם מחלה לבבית איסכמית!**

# CV safety and efficacy of Glucagon-like peptide-1 receptor agonists

Post-approval studies

## ELIXA<sup>1</sup>

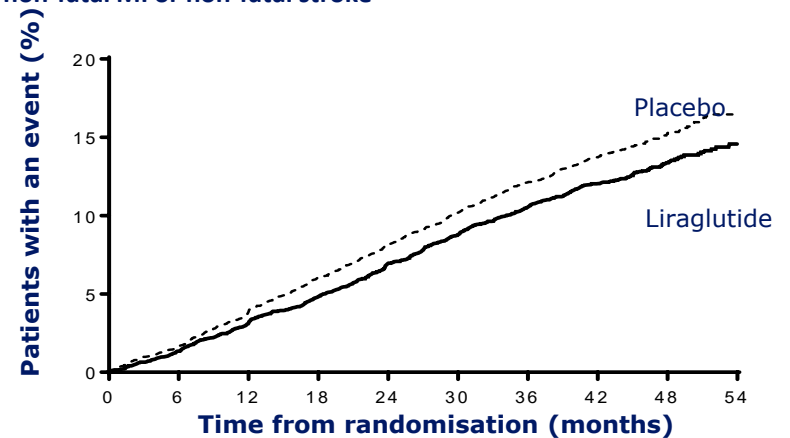
Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for UAP



HR: 1.02  
95% CI (0.89;1.17)  
 $p < 0.001$  for non-inferiority  
 $p = 0.81$  for superiority

## LEADER<sup>2</sup>

Time to first occurrence of CV death, non-fatal MI or non-fatal stroke



HR: 0.87  
95% CI (0.78;0.97)  
 $p < 0.001$  for non-inferiority  
 $p = 0.01$  for superiority

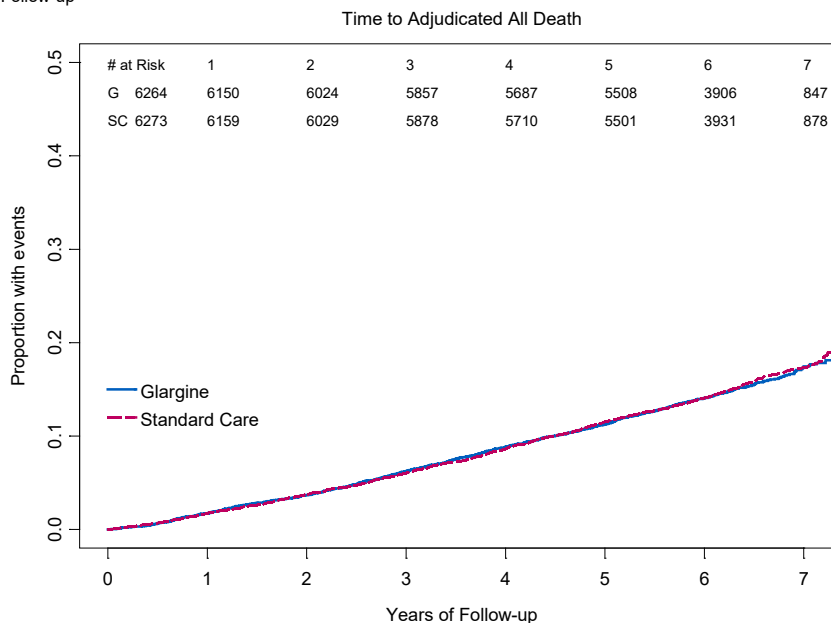
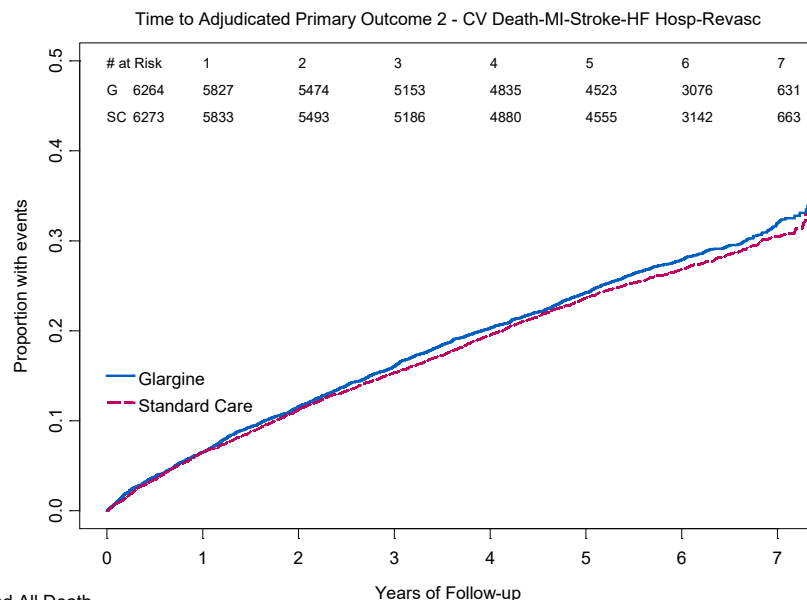
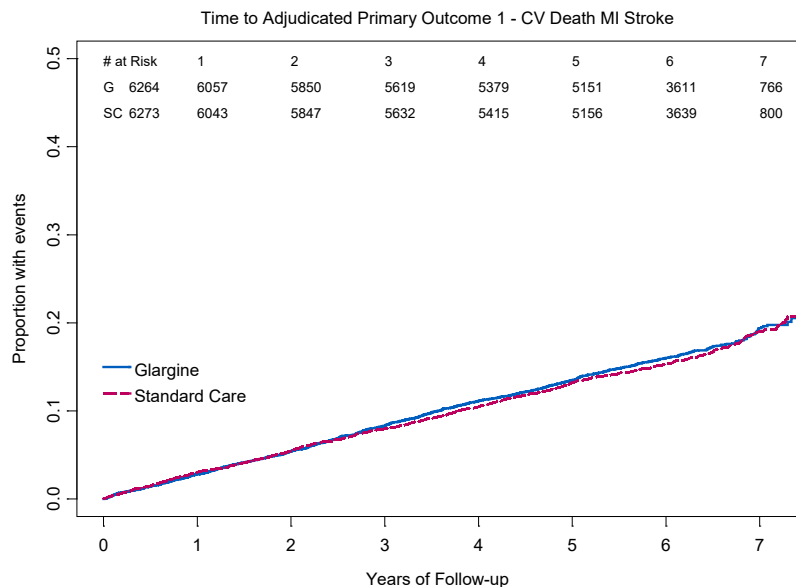
## LEADER: CV and renal results:

### בחולים עם מחלה קרדיוואסקולארית קודמת או גורמי סיכון למחלה שכזו:

- Victoza הפחיתה את התוצא הראשוני: 3-point MACE: MI, Stroke, CV death ב-13%
- Victoza הפחיתה את התמותה הקרדיו-וסקולארית ב-22%
- Victoza הפחיתה את התמותה הכוללת ב-15%
- Victoza לא הפחיתה או הגבירה אשפוזים עקב כשל לבבי
- Victoza הפחיתה נפרופתיה או החמרה של נפרופתיה ב-26%

# ORIGIN: Lantus-Primary Endpoints and Mortality

Targeting fasting normoglycemia has a neutral effect on cardiovascular outcomes with neither an increase nor a decrease in CV events



**DEVOTE trial:** randomised, double-blinded trial conducted to confirm the cardiovascular safety of Tresiba<sup>®</sup> (insulin degludec=Tregludec) compared to insulin glargine U100. In the trial, more than 7,500 people with type 2 diabetes at high risk of major adverse cardiovascular events were treated for a period of approximately two years.

**“The trial achieved its primary endpoint by demonstrating non-inferiority of major adverse cardiovascular events (MACE) with Tresiba<sup>®</sup> compared to insulin glargine U100.”**

## **Tregludec:**

**27% fewer episode of severe hypoglycaemia.**

**40% overall reduction of total episodes of adjudicated severe hypoglycaemia.**

**54% relative reduction in the rate of nocturnal severe hypoglycaemia**

**These differences were all statistically significant.**

Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 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	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑
<b>Recommendation</b>						

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia



Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
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Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑
Recommendation	3 <sup>rd</sup> line	3 <sup>rd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	1 <sup>st</sup> or 3 <sup>rd</sup> line

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Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑
<b>Recommendation</b>	<b>3<sup>rd</sup> line</b>	<b>3<sup>rd</sup> line</b>	<b>2<sup>nd</sup> line</b>	<b>2<sup>nd</sup> line</b>	<b>2<sup>nd</sup> line</b>	<b>1<sup>st</sup> or 3<sup>rd</sup> line</b>

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# **הטיפול בסוכרת מסוג 2: הנחיות המועצה הלאומית לסוכרת**

**ד"ר עופרי מוסנזון  
מנהלת היחידה למחקר קליני בסוכרת,  
ביה"ח האוניברסיטאי הדסה עין כרם  
והמועצה הלאומית לסוכרת**

Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
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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	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑
Recommendation	3 <sup>rd</sup> line	3 <sup>rd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	1 <sup>st</sup> or 3 <sup>rd</sup> line

\* Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures etc. \*\* Some preparation are cheap and some expensive. High cost for treatment of side effects including hypoglycemia

# Lifestyle Modification, Teamwork and Patient Empowerment

Target HbA1c

SET HbA1c TARGET according to patient characteristics and glucose-lowering agents

A1c < 6.5%

Lifestyle intervention + metformin \*eGFR > 30 ml/min/BSA

A1c > 7.5%

Consider combination therapy

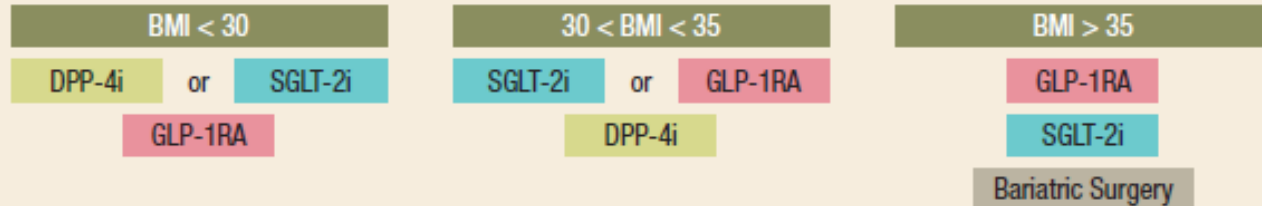
A1c > 9%

and/or symptomatic consider (short term) insulin

If HbA1c not at target after 3-6 months add:



A1c < 7%



When cost is a major limiting factor less preferable GLAs to consider: TZD, AGI, insulin, glinide, sulfonylurea

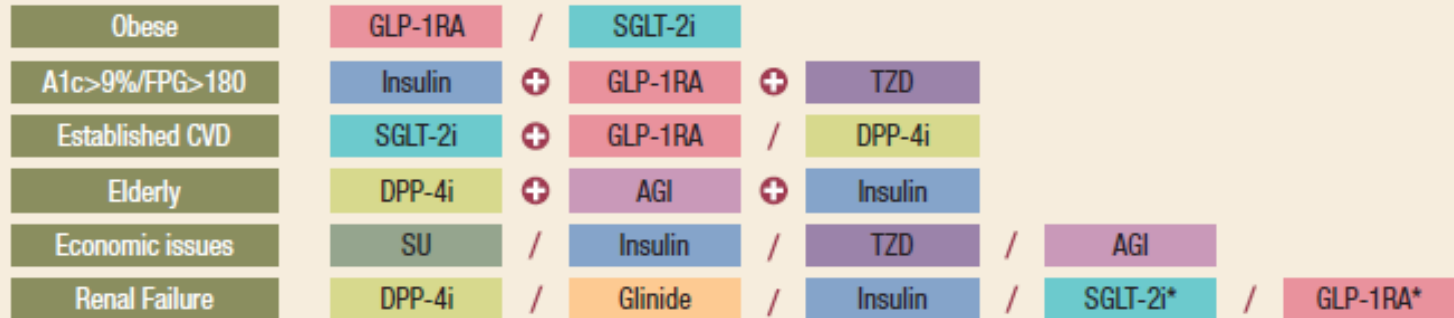
If HbA1c not at target after 3-6 months add/replace:



A1c < 7% (LR<sup>1</sup>)

A1c < 8% (HR<sup>2</sup>)

Combination therapy according to patient characteristics



If HbA1c not at target after 6-12 months add/replace:



\*eGFR > 45 ml/min/BSA

\*eGFR > 30 ml/min/BSA

A1c < 7% (LR<sup>1</sup>)

A1c < 8% (HR<sup>2</sup>)

MDI vs. Insulin Pump/Metabolic surgery +/- MET, SGLT-2i, GLP-1RA

<sup>1</sup> LR - Low Risk from Hypoglycemia. <sup>2</sup> HR - High Risk from Hypoglycemia.

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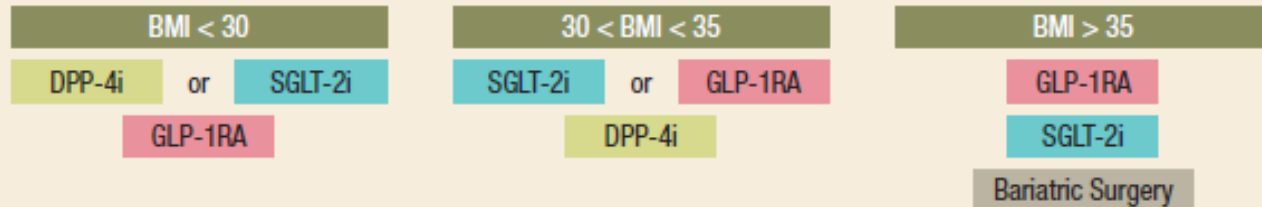
Consider combination therapy

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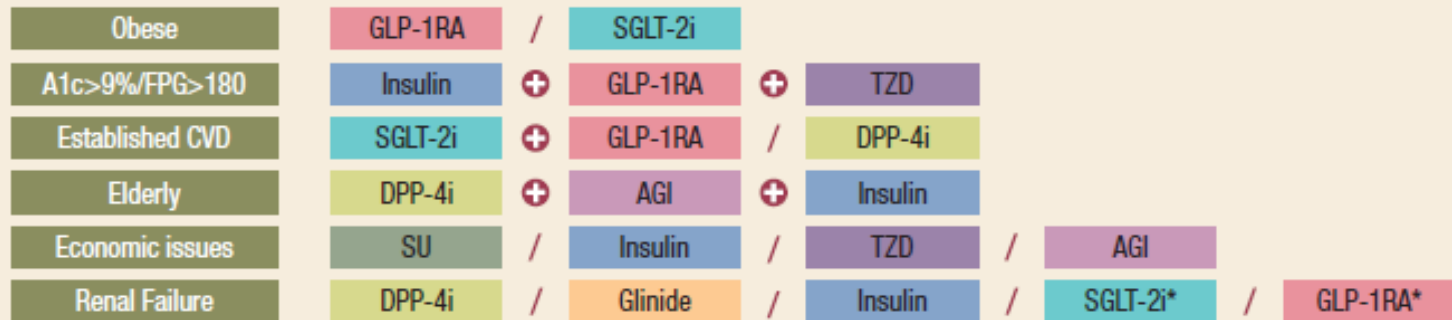
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If HbA1c not at target after 3-6 months add/replace:

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**A1c < 8% (HR<sup>2</sup>)**

Combination therapy according to patient characteristics



If HbA1c not at target after 6-12 months add/replace:

\*eGFR > 45 ml/min/BSA

\*eGFR > 30 ml/min/BSA

**A1c < 7% (LR<sup>1</sup>)**

**A1c < 8% (HR<sup>2</sup>)**

MDI vs. Insulin Pump/Metabolic surgery +/- MET, SGLT-2i, GLP-1RA

<sup>1</sup> LR - Low Risk from Hypoglycemia. <sup>2</sup> HR - High Risk from Hypoglycemia.

# Lifestyle Modification, Teamwork and Patient Empowerment

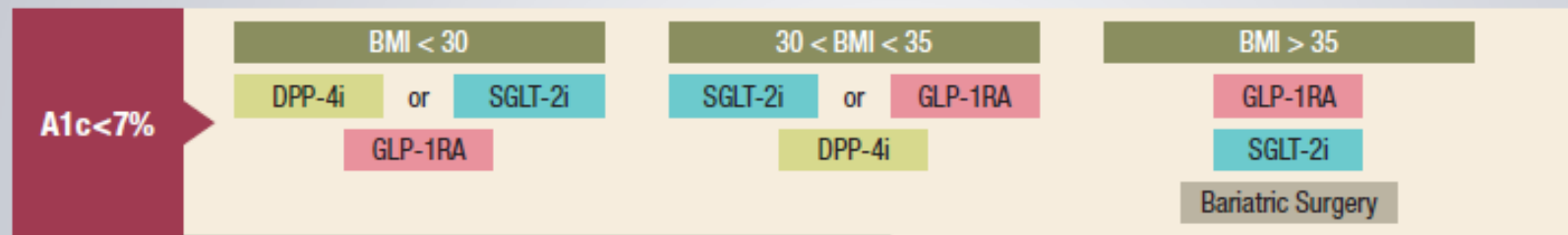
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**A1c > 7.5%** → Consider combination therapy

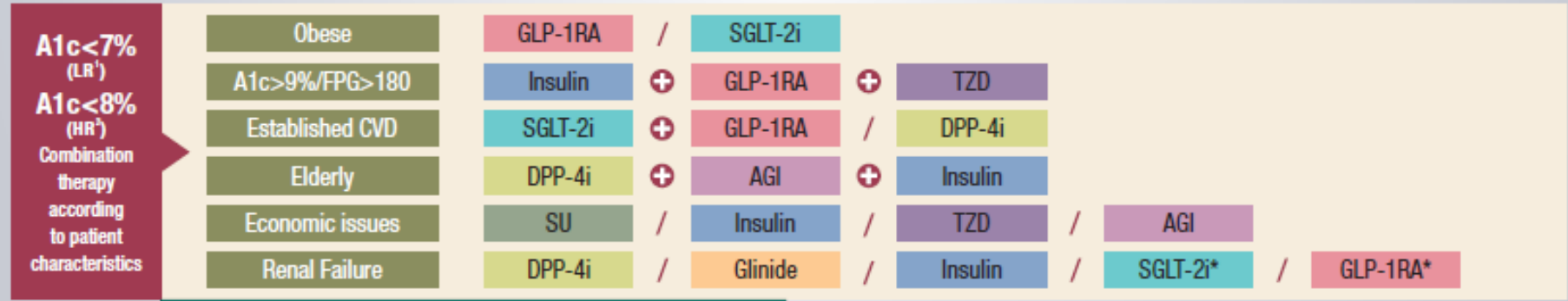
**A1c > 9%** → and/or symptomatic consider (short term) insulin

If HbA1c not at target after 3-6 months add: +



When cost is a major limiting factor less preferable GLAs to consider: TZD, AGI, insulin, glinide, sulfonylurea

If HbA1c not at target after 3-6 months add/replace: +



If HbA1c not at target after 6-12 months add/replace: +

\*eGFR > 45 ml/min/BSA      \*eGFR > 30 ml/min/BSA

**A1c < 7% (LR<sup>1</sup>)**  
**A1c < 8% (HR<sup>2</sup>)** → MDI vs. Insulin Pump/Metabolic surgery +/- MET, SGLT-2i, GLP-1RA

<sup>1</sup> LR - Low Risk from Hypoglycemia. <sup>2</sup> HR - High Risk from Hypoglycemia.

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**A1c > 7.5%**

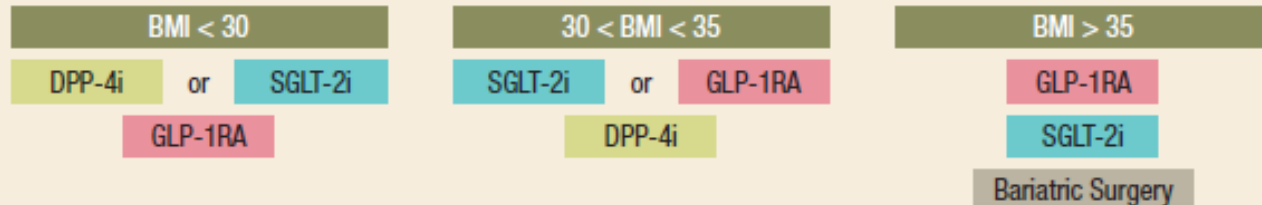
Consider combination therapy

**A1c > 9%**

and/or symptomatic consider (short term) insulin

If HbA1c not at target after 3-6 months add:

**A1c < 7%**



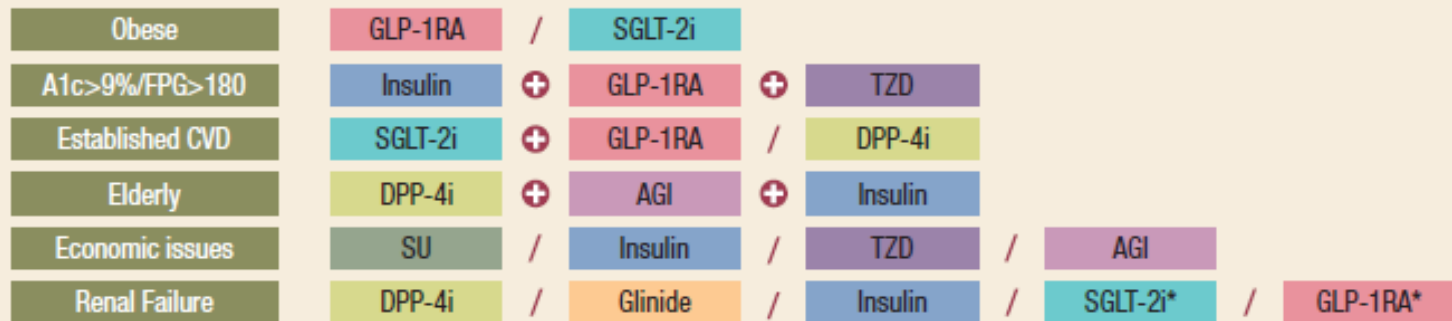
When cost is a major limiting factor less preferable GLAs to consider:  
TZD, AGI, insulin, glinide, sulfonylurea

If HbA1c not at target after 3-6 months add/replace:

**A1c < 7% (LR<sup>1</sup>)**

**A1c < 8% (HR<sup>2</sup>)**

Combination therapy according to patient characteristics



If HbA1c not at target after 6-12 months add/replace:

\*eGFR > 45 ml/min/BSA

\*eGFR > 30 ml/min/BSA

**A1c < 7% (LR<sup>1</sup>)**

**A1c < 8% (HR<sup>2</sup>)**

MDI vs. Insulin Pump/Metabolic surgery +/- MET, SGLT-2i, GLP-1RA

<sup>1</sup> LR - Low Risk from Hypoglycemia. <sup>2</sup> HR - High Risk from Hypoglycemia.



# קומבינציות של שתי תרופות פומיות בכדור :אחד:

Januet  
Eucreas  
Trajenta Due  
Combo-Glyza

מטפורמין

DPP-4  
Inhibitors

Jardiance  
Due  
Xigduo XR

מטפורמין

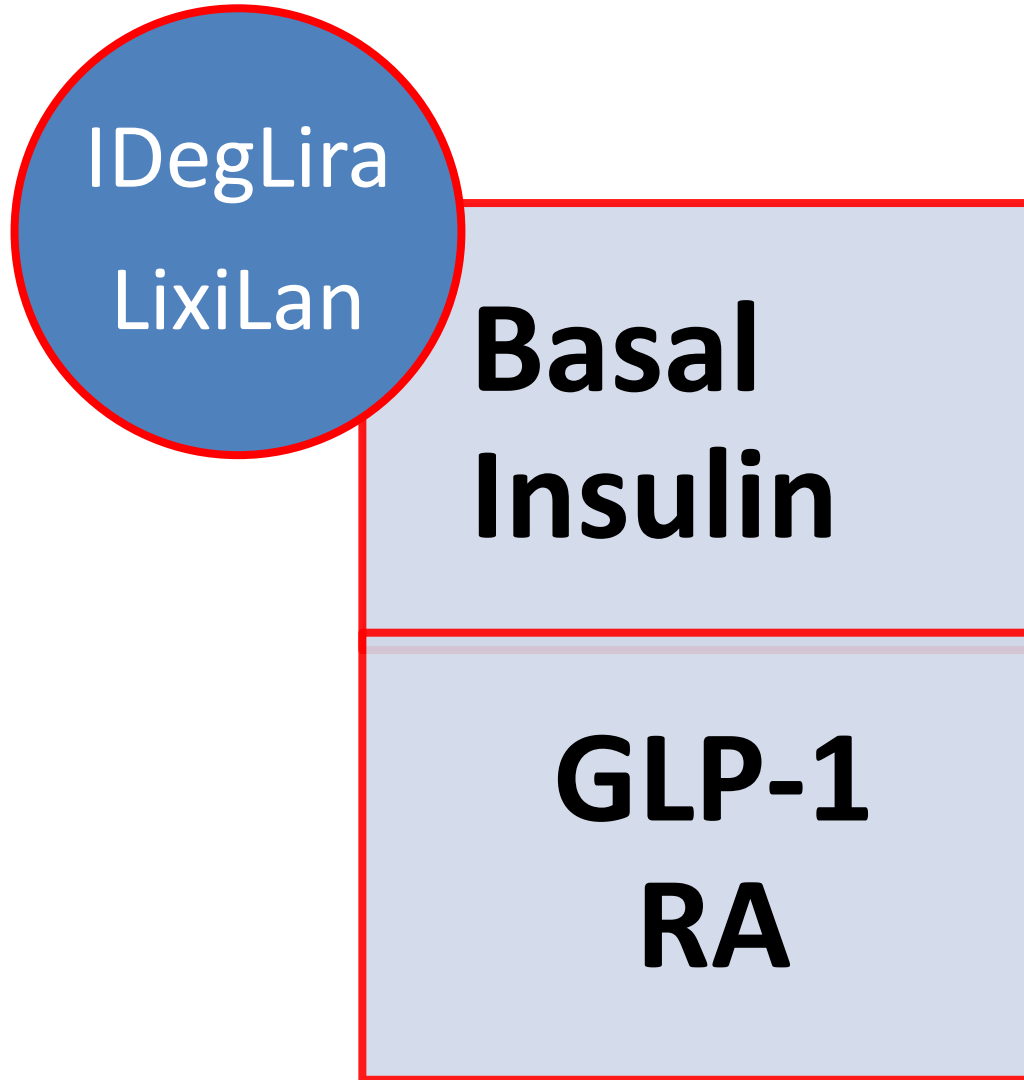
SGLT2  
Inhibitors

Glyxambi

SGLT2  
Inhibitors

DPP-4  
Inhibitors

# קומבינציה של שתי תרופות בהזרקה:



# One-Pen Combination

1.8 mg Victoza+ 50 U Tregludec



+



= Xultophy®

**Soliqua:**

20 mcg Lyxumia + 40 U Lantus

20 mcg Lyxumia + 60 U Lantus



# Lifestyle Modification, Teamwork and Patient Empowerment

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Lifestyle intervention + metformin \*eGFR > 30 ml/min/BSA

**A1c > 7.5%**

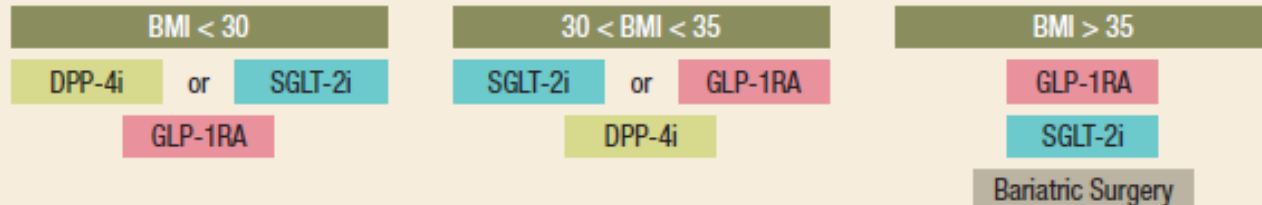
Consider combination therapy

If HbA1c not at target after 3-6 months add:

**A1c > 9%**

and/or symptomatic consider (short term) insulin

**A1c < 7%**



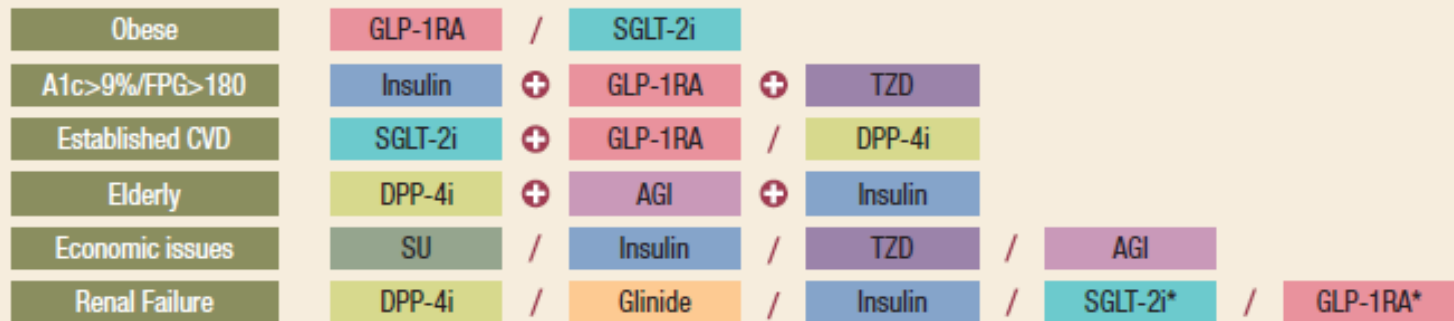
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**A1c < 8% (HR<sup>2</sup>)**

Combination therapy according to patient characteristics



If HbA1c not at target after 6-12 months add/replace:

\*eGFR > 45 ml/min/BSA

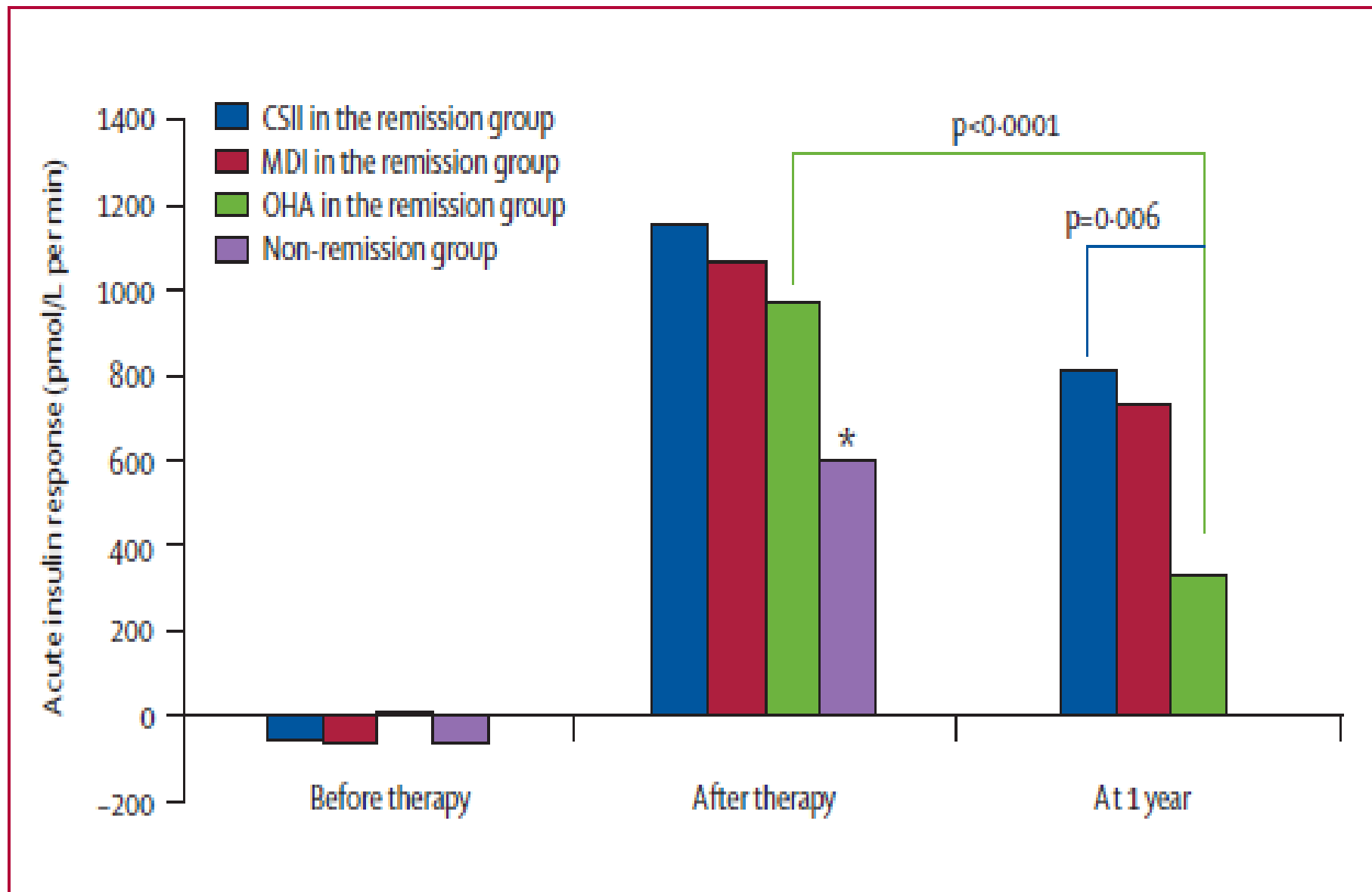
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**A1c < 7% (LR<sup>1</sup>)**

**A1c < 8% (HR<sup>2</sup>)**

MDI vs. Insulin Pump/Metabolic surgery +/- MET, SGLT-2i, GLP-1RA

<sup>1</sup> LR - Low Risk from Hypoglycemia. <sup>2</sup> HR - High Risk from Hypoglycemia.



**Figure 3: Acute insulin response (shown as median) before and after different interventions and at 1 year**  
 \* $p < 0.05$  in the non-remission group compared with that in each intervention in the remission group (after treatment).

# Lifestyle Modification, Teamwork and Patient Empowerment

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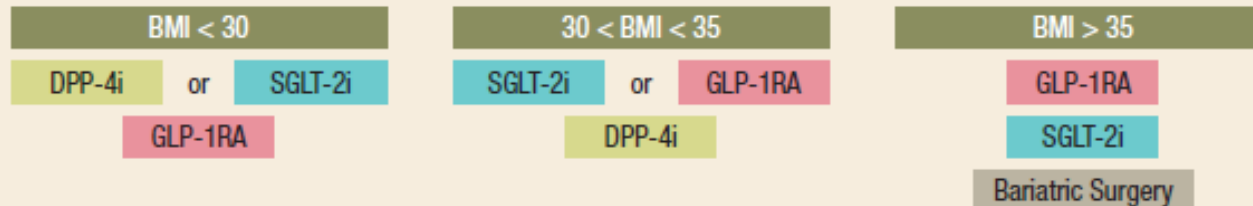
**A1c > 7.5%**

Consider combination therapy

**A1c > 9%**

and/or symptomatic consider (short term) insulin

**A1c < 7%**



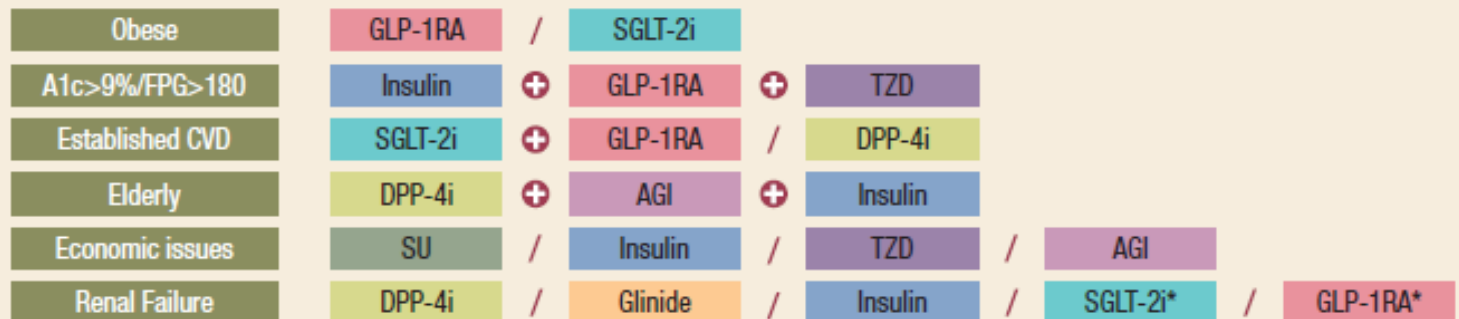
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Combination therapy according to patient characteristics



If HbA1c not at target after 6-12 months add/replace:

\* eGFR > 45 ml/min/BSA

\* eGFR > 30 ml/min/BSA

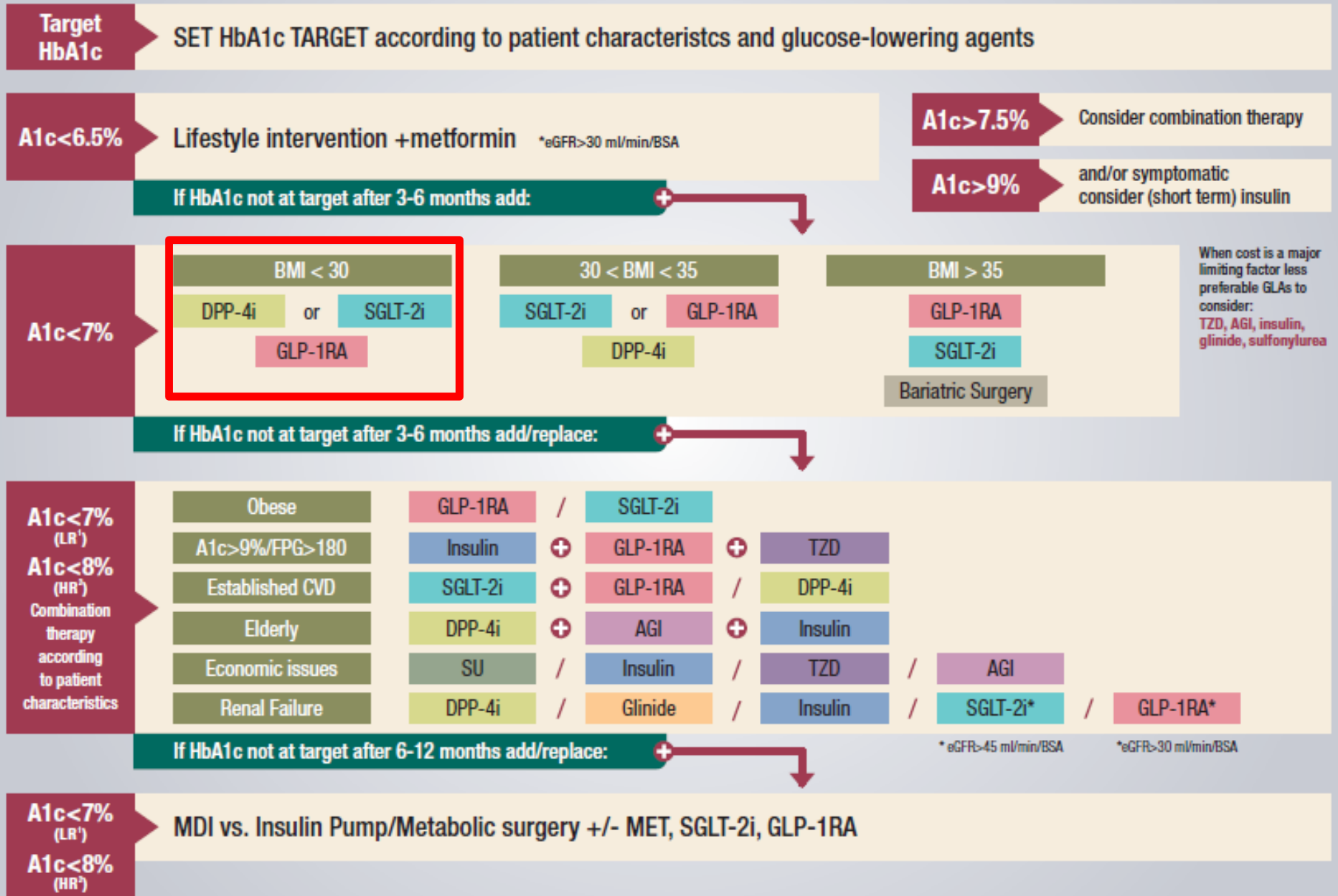
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<sup>1</sup> LR - Low Risk from Hypoglycemia. <sup>2</sup> HR - High Risk from Hypoglycemia.

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Lifestyle intervention + metformin \*eGFR > 30 ml/min/BSA

**A1c > 7.5%**

Consider combination therapy

**A1c > 9%**

and/or symptomatic consider (short term) insulin

If HbA1c not at target after 3-6 months add:

**A1c < 7%**

BMI < 30  
DPP-4i or SGLT-2i  
GLP-1RA

30 < BMI < 35  
SGLT-2i or GLP-1RA  
DPP-4i

BMI > 35  
GLP-1RA  
SGLT-2i  
Bariatric Surgery

When cost is a major limiting factor less preferable GLAs to consider: TZD, AGI, insulin, glinide, sulfonylurea

If HbA1c not at target after 3-6 months add/replace:

**A1c < 7% (LR<sup>1</sup>)**

**A1c < 8% (HR<sup>2</sup>)**

Combination therapy according to patient characteristics

Obese	GLP-1RA	/	SGLT-2i			
A1c > 9%/FPG > 180	Insulin	+	GLP-1RA	+	TZD	
Established CVD	SGLT-2i	+	GLP-1RA	/	DPP-4i	
Elderly	DPP-4i	+	AGI	+	Insulin	
Economic issues	SU	/	Insulin	/	TZD	AGI
Renal Failure	DPP-4i	/	Glinide	/	Insulin	SGLT-2i* / GLP-1RA*

If HbA1c not at target after 6-12 months add/replace:

\*eGFR > 45 ml/min/BSA

\*eGFR > 30 ml/min/BSA

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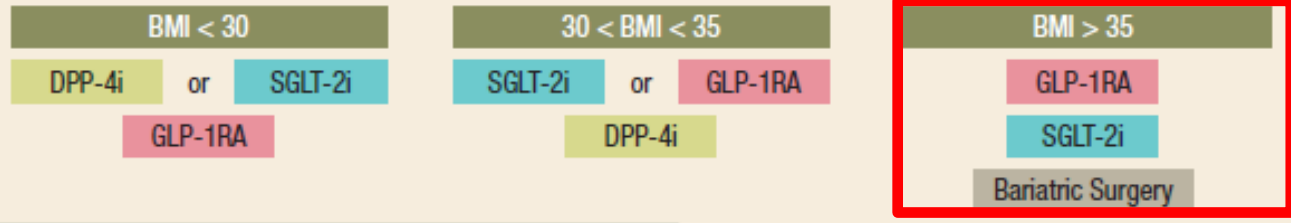
**A1c > 7.5%**

Consider combination therapy

**A1c > 9%**

and/or symptomatic consider (short term) insulin

**A1c < 7%**



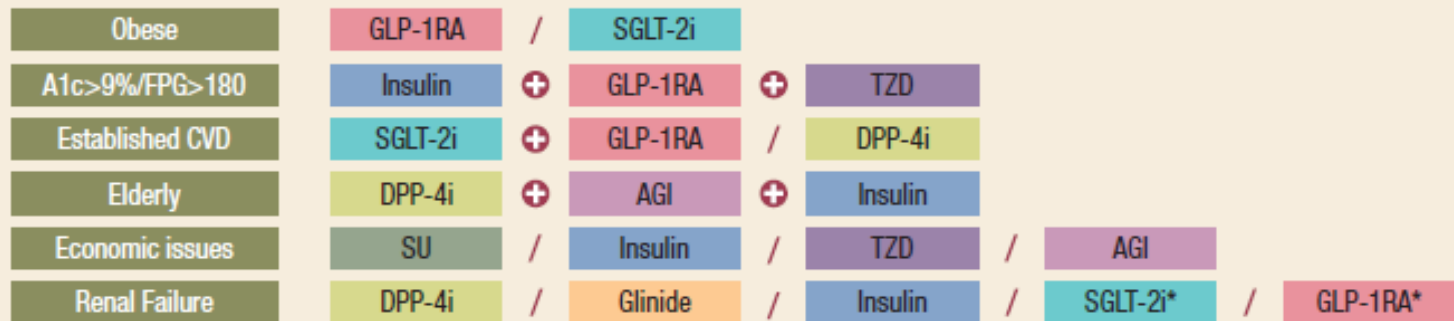
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**A1c < 8% (HR<sup>2</sup>)**

Combination therapy according to patient characteristics



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\*eGFR > 45 ml/min/BSA

\*eGFR > 30 ml/min/BSA

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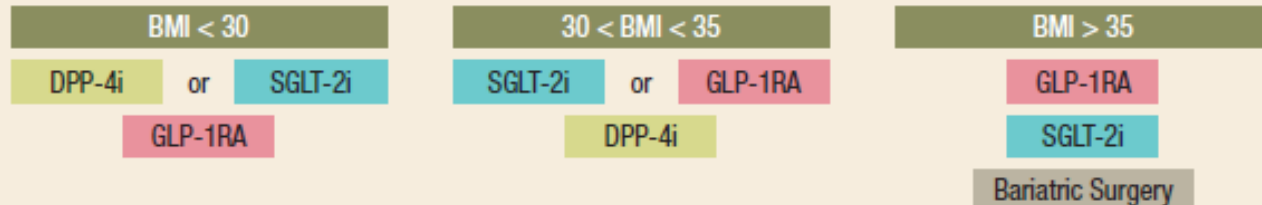
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and/or symptomatic consider (short term) insulin

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**A1c < 7%**



When cost is a major limiting factor less preferable GLAs to consider:  
TZD, AGI, insulin, glinide, sulfonylurea

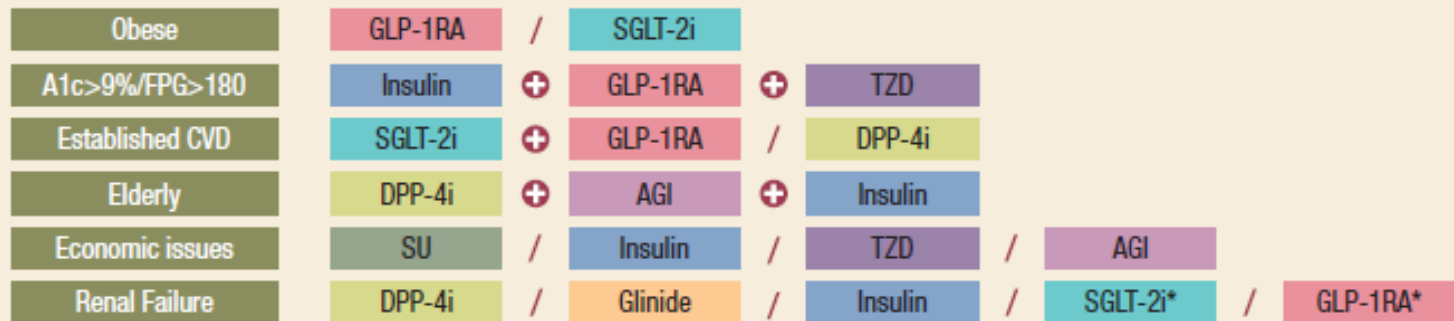
If HbA1c not at target after 3-6 months add/replace:



**A1c < 7% (LR<sup>1</sup>)**

**A1c < 8% (HR<sup>2</sup>)**

Combination therapy according to patient characteristics



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\*eGFR > 45 ml/min/BSA

\*eGFR > 30 ml/min/BSA

**A1c < 7% (LR<sup>1</sup>)**

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# Lifestyle Modification, Teamwork and Patient Empowerment

**Target HbA1c**

SET HbA1c TARGET according to patient characteristics and glucose-lowering agents

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Lifestyle intervention + metformin \*eGFR > 30 ml/min/BSA

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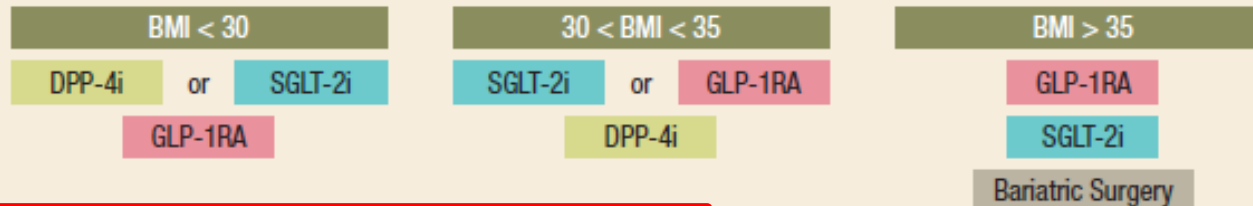
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**A1c > 9%**

and/or symptomatic consider (short term) insulin

If HbA1c not at target after 3-6 months add:

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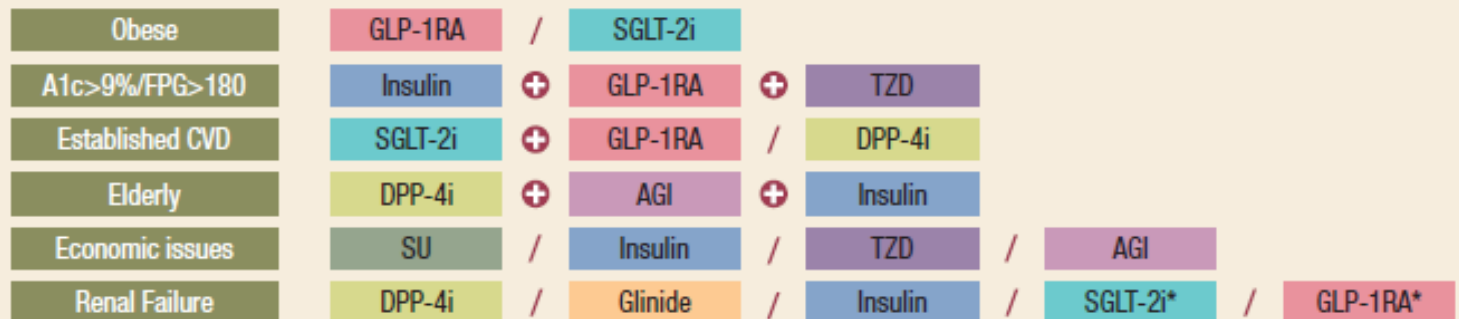
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Combination therapy according to patient characteristics



If HbA1c not at target after 6-12 months add/replace:

\* eGFR > 45 ml/min/BSA

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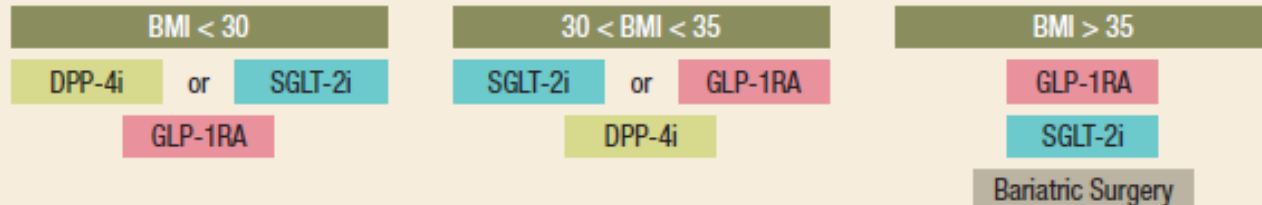
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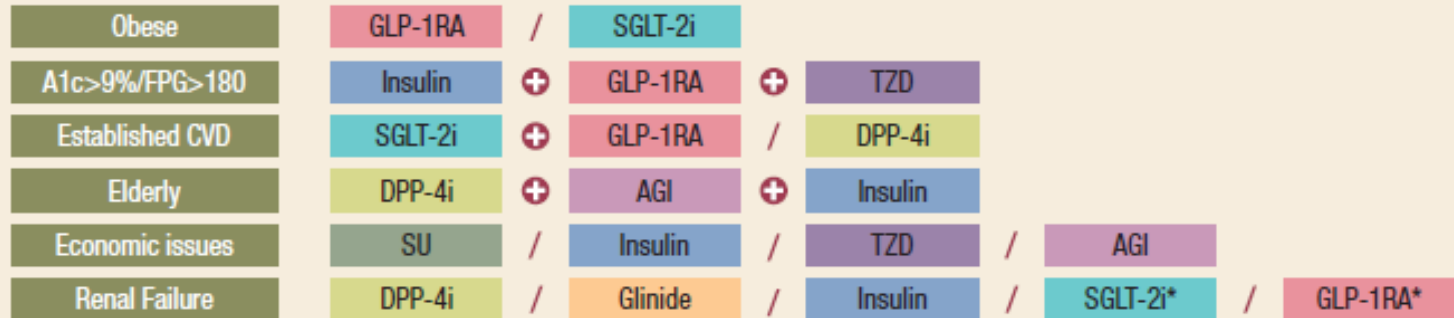
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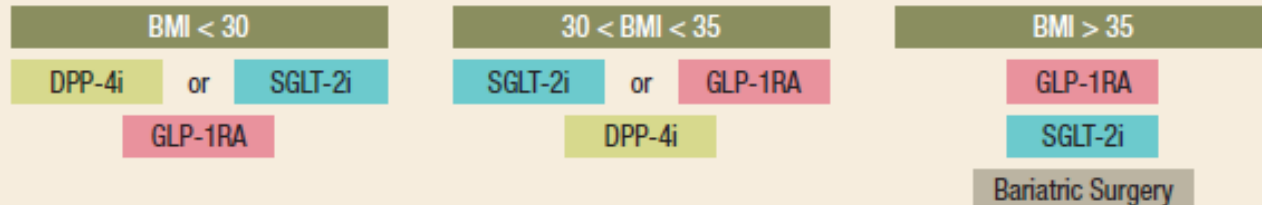
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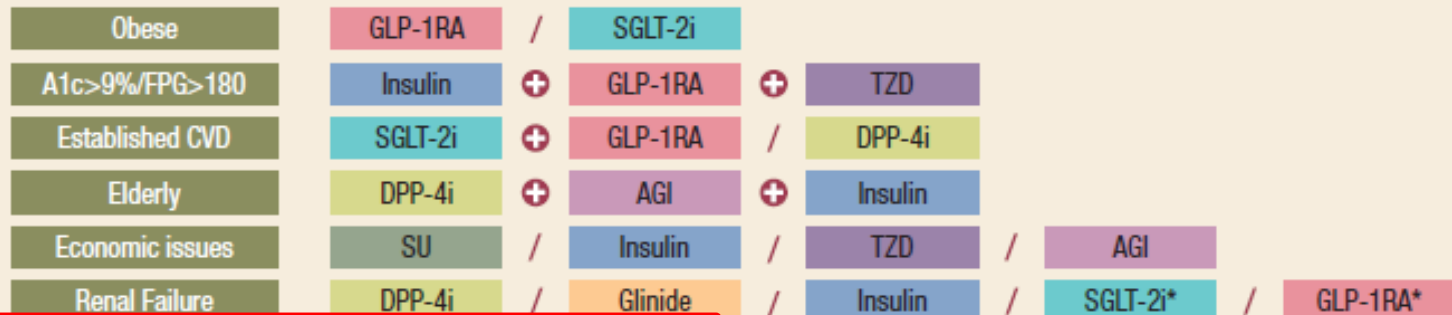
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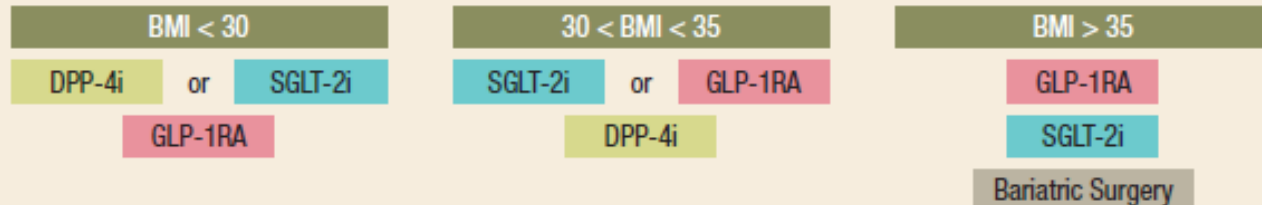
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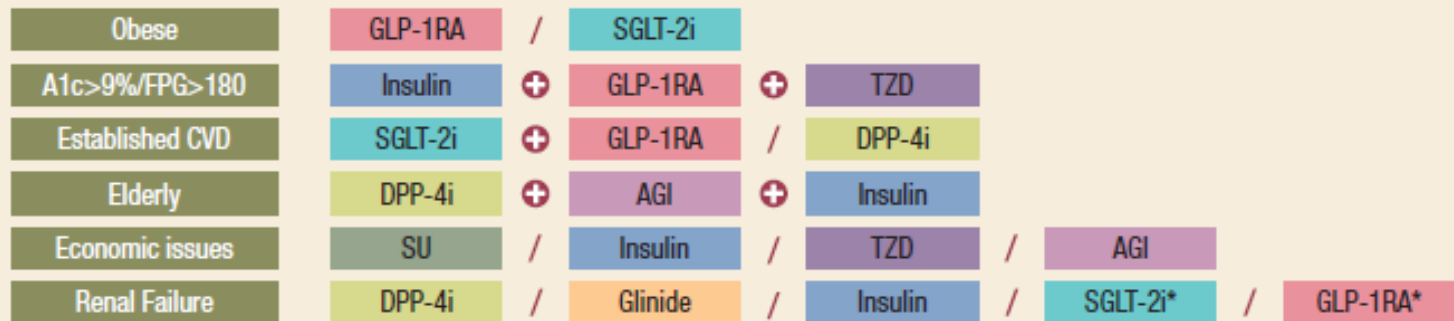
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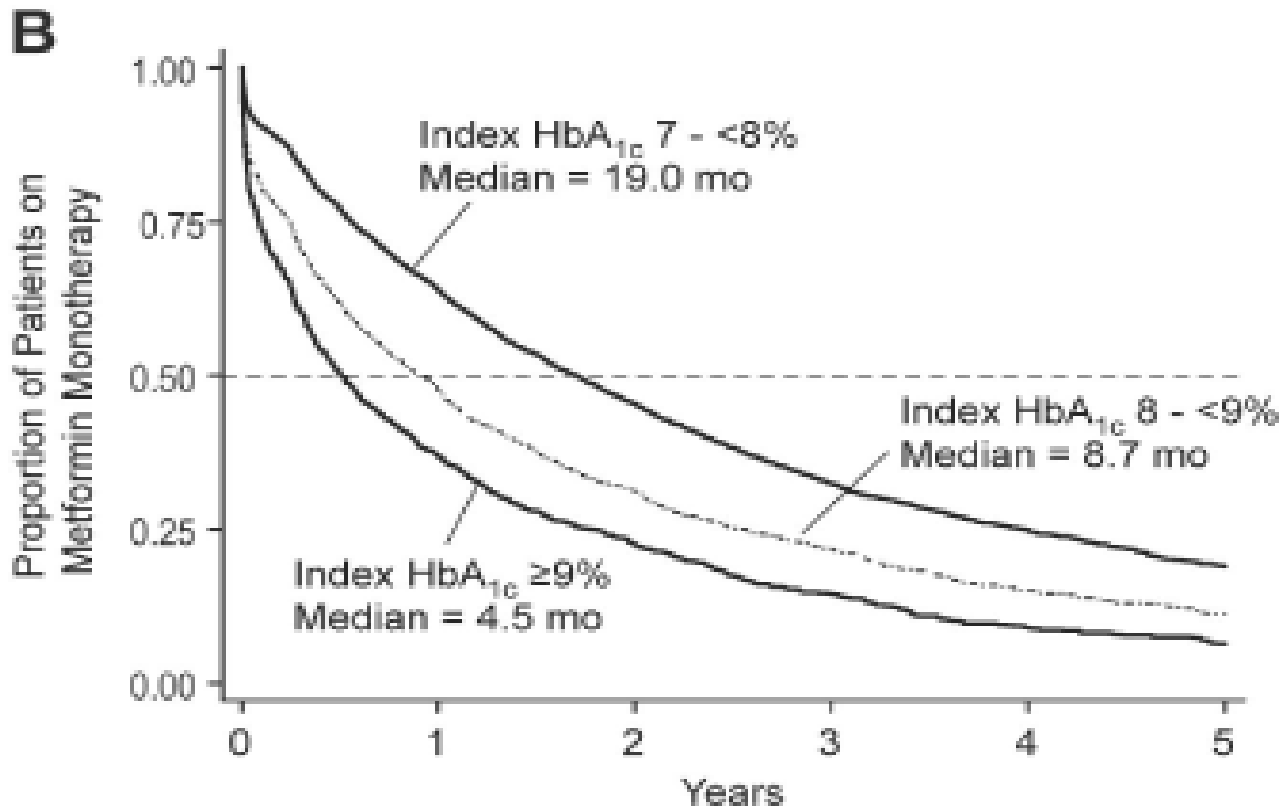
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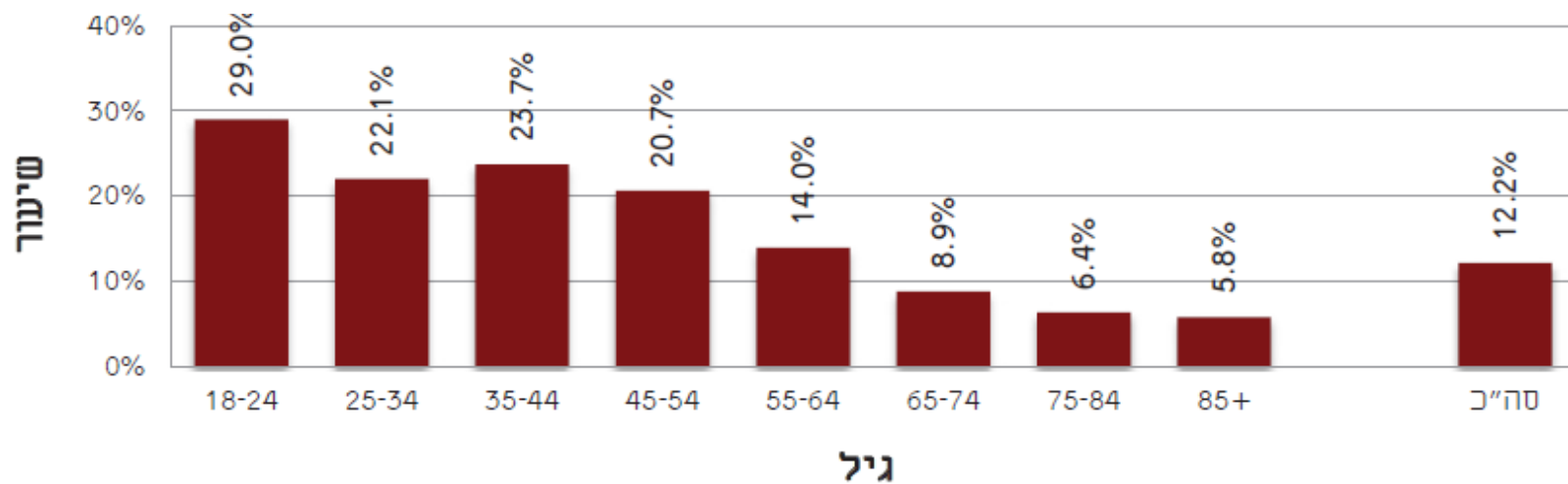
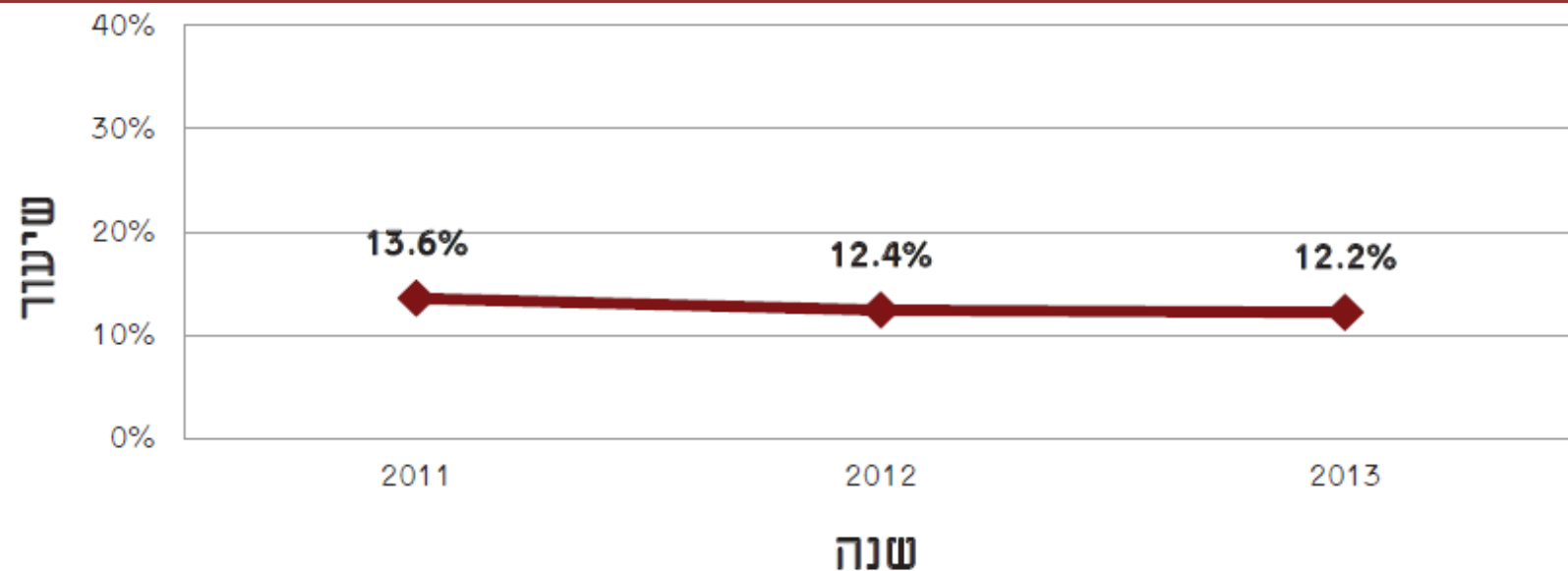
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# Treatment intensification in patients with T2DM who failed metformin monotherapy (A1C >7%)

Overall median = 14 months



# שיעור בעלי רמת $HbA1c > 9\%$ בחולי סוכרת





תודה על ההאזנה!

[ofrim@hadassah.org.il](mailto:ofrim@hadassah.org.il)

Dual Therapy <sup>†</sup> <small>According to ADA/EASD position statement</small>	Sulfonylurea	Thiazolidine-dione	DPP-4 Inhibitor	SGLT-2 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	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
<b>Efficacy/ Durability</b>						
<b>Hypo</b>						
<b>Weight</b>						
<b>Other Side Effects</b>						
<b>Cost</b>						
<b>CV Safety</b>						
<b>Recommendation</b>						

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Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑
Recommendation	3 <sup>rd</sup> line	3 <sup>rd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	1 <sup>st</sup> or 3 <sup>rd</sup> line

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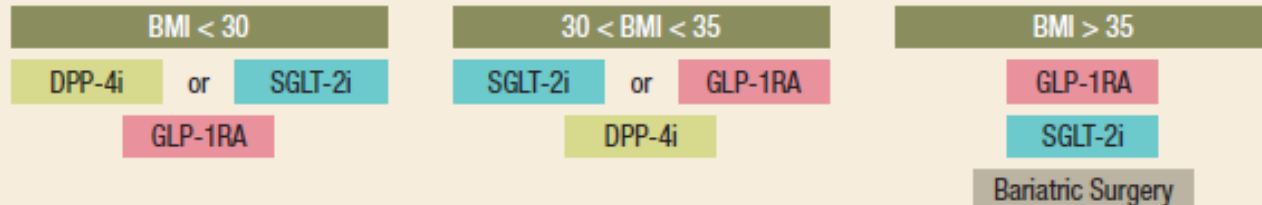
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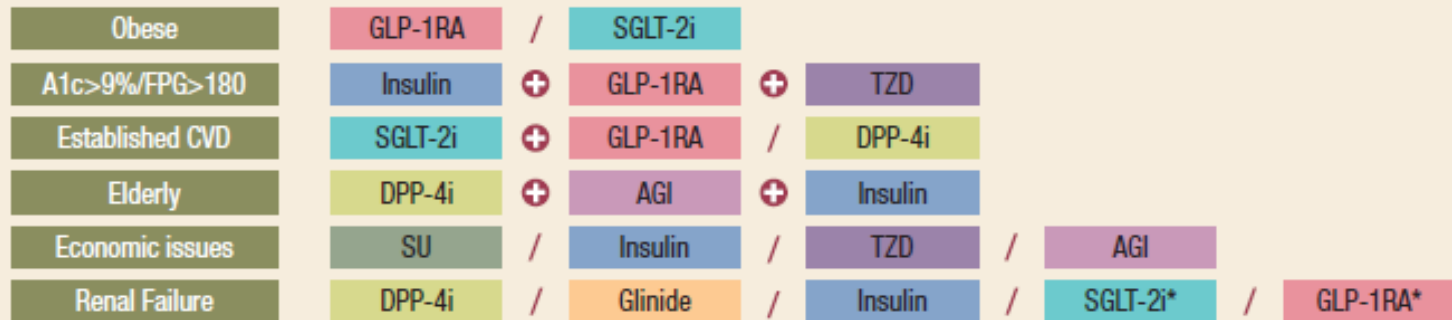
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