OAD ve İnsülinomimetik Tedavi Yaklaşımında Değişenler

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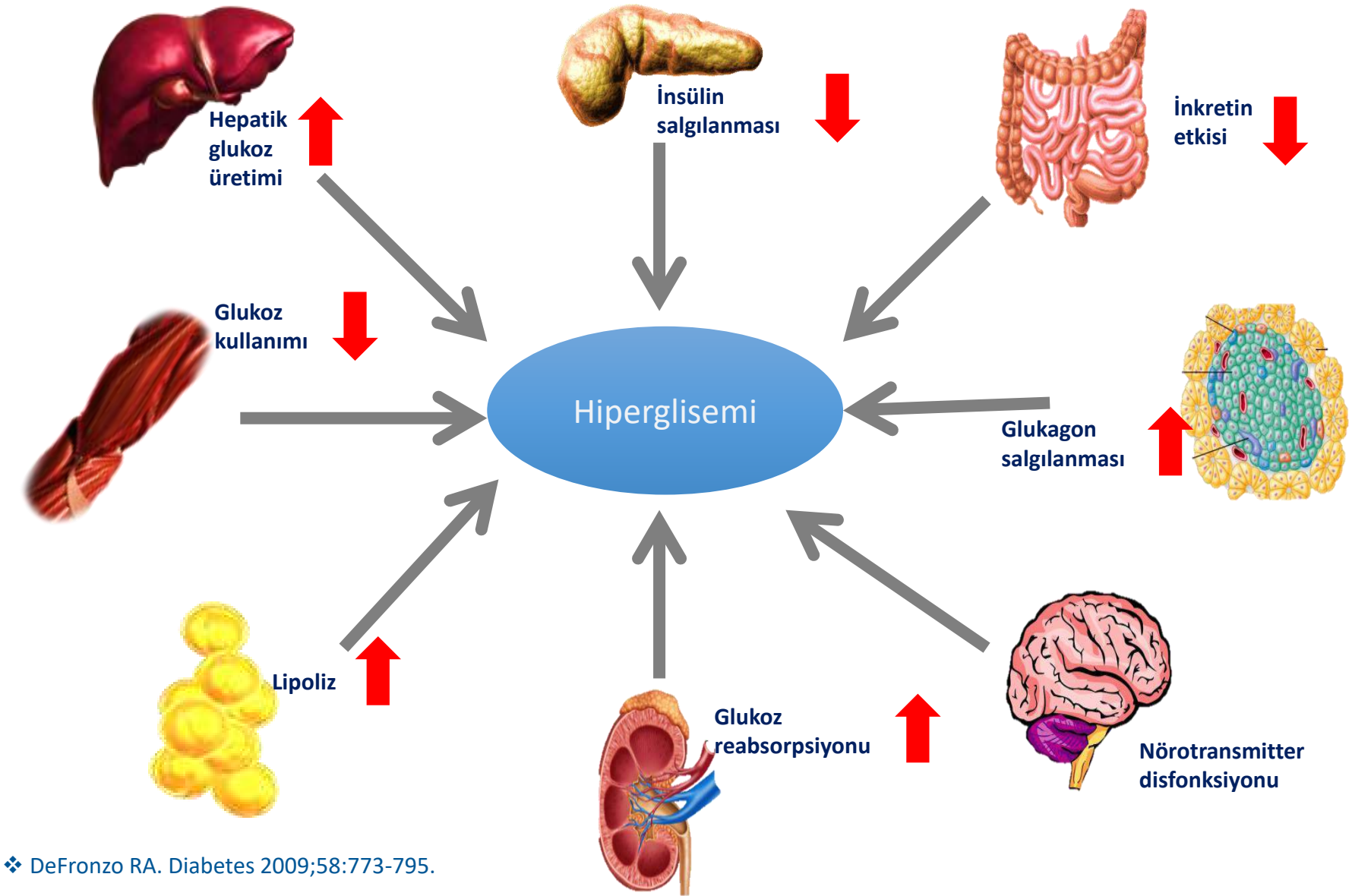
Endokrinoloji ve Metabolizma Bilim dalı

TİP 2 DIYABET Patogenezi



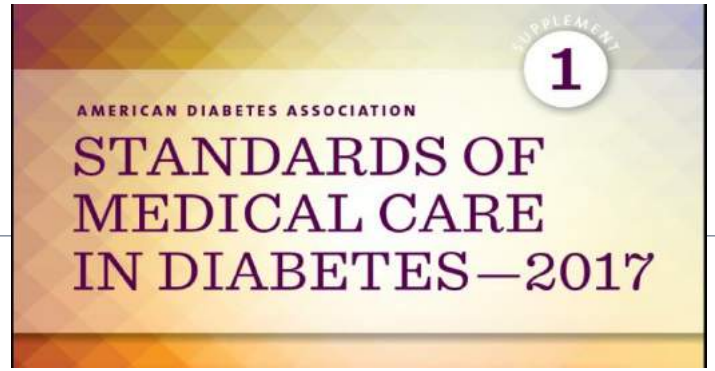
❖ DeFronzo RA. Diabetes 2009;58:773-795.

Diyabet tedavisinde tarihsel gelişim

Konvansiyonel Tedaviler

İlaç	Klinik pratiğe giriş (yıl)
İnsulin	1921
İnhale insulin	2006
Sülfonilüreler	1946
Biguanidler	1957
Glukozidaz inhibitörleri	1995
Meglitinidler	1998
Tiazolidinedionlar	1999
İnkretin bazlı tedaviler	
GLP-1 reseptör agonistleri	2007
DPP-4 inhibitörleri	2007
Glukozürik tedaviler	
SGLT-2 inhibitörleri	2015

- Tip 2 diyabet tedavisinde 2009 ve 2012 yıllarında yayınlanan ADA-EASD ortak bildirgelerindeki değişim göze çarpmaktadır
- Bir önceki bildirgede her diyabet hastası için ortak hedefler koyulmuşken, 3 yıl sonra tedavinin bireyselleştirilmesi ve buna göre her hasta için farklı glisemik kontrol düzeylerinin seçilmesi önerilmektedir.
- Aslında bu yıllardır tıp fakültelerinde öğretilen, "Hastalık yoktur, hasta vardır,'' sözünün bilimsel olarak açıklanması olarak da algılanabilir.



Start with Monotherapy unless:

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

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

Monotherapy — Metformin — Lifestyle Management

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

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

Dual Therapy — Metformin + — Lifestyle Management

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

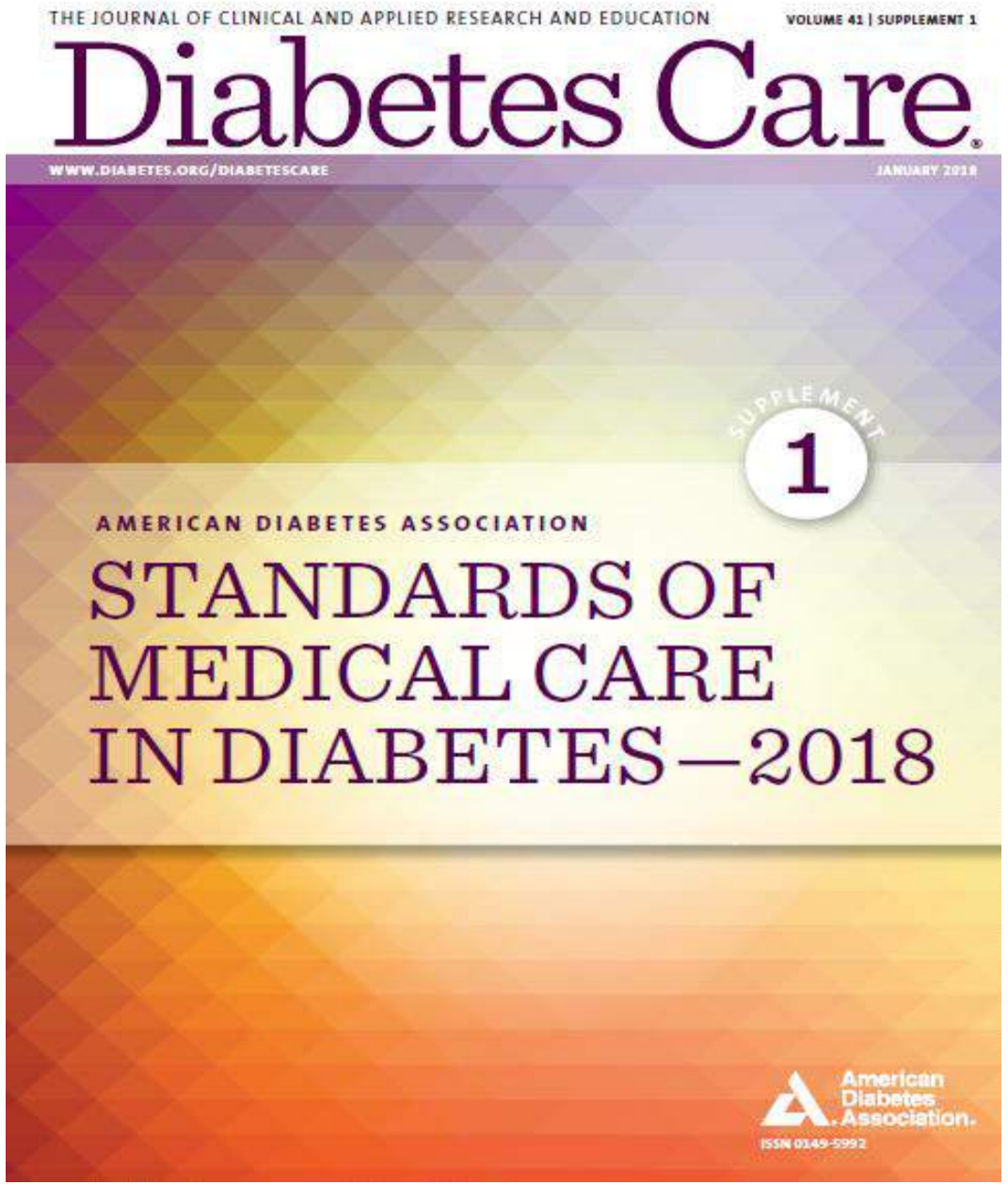
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

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

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)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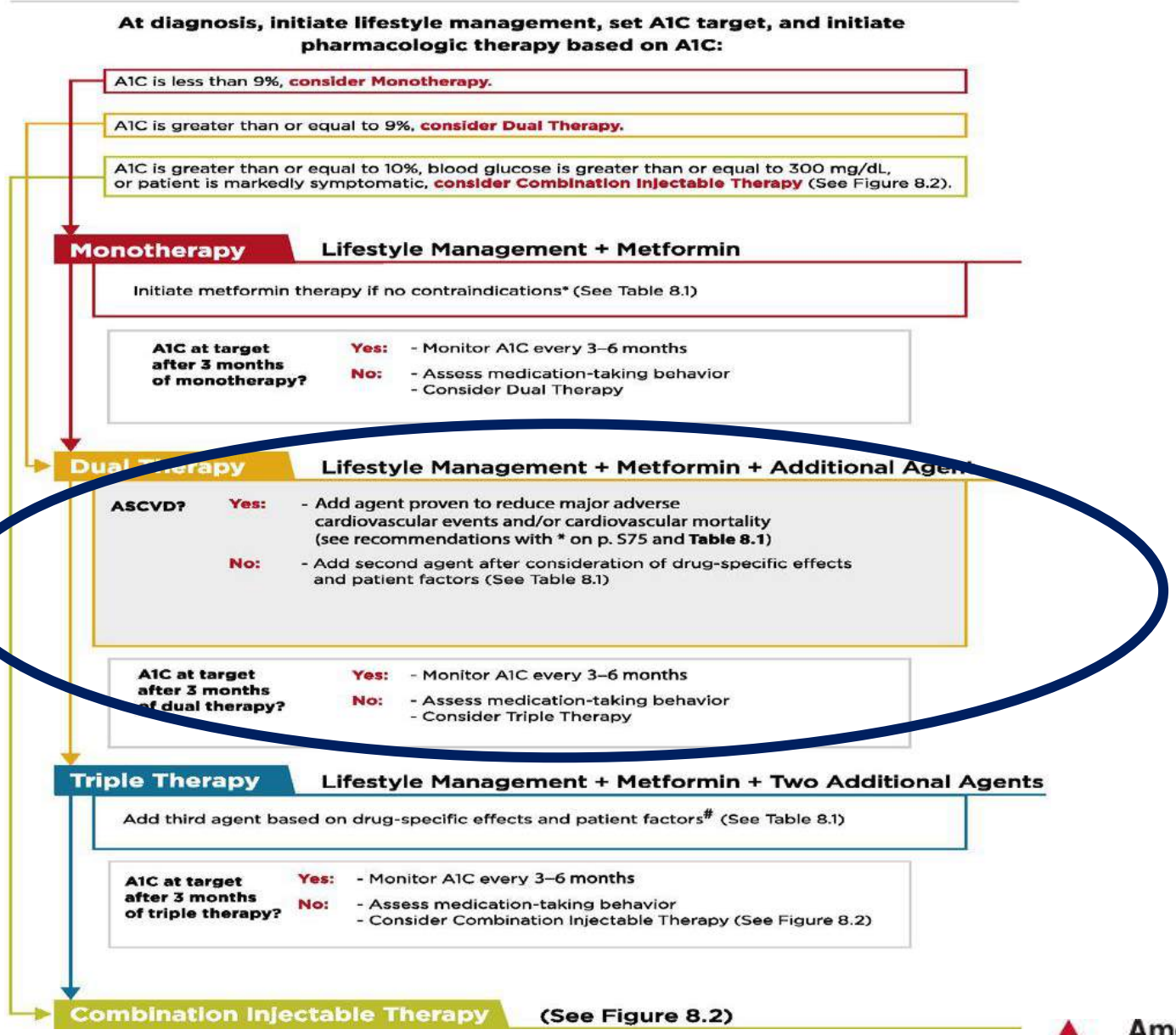
Antihyperglycemic Therapy in Adults with Type 2 Diabetes



American Diabetes Association.

T2D Tedavi Yönetimi Önerileri

Öneriler	LOE
Kontrendike değilse ve hasta tarafından tolere edilebiliyorsa, metformin, tip 2 diyabet hastalığının tedavisinde tercih edilen ilk farmakolojik ajandır.	A
Aterosklerotik kardiyovasküler hastalığı da bulunmayan hastalarda, monoterapi veya ikili tedaviyle 3 ay içerisinde A1C hedefine ulaşılamaması ya da bu hedef düzeyin sürdürülememesi halinde, ilaca özgü ve hastaya ilişkin faktörlere göre tedaviye bir ilave antihiperglisemik ajanın daha ilave edilmesi gerekir.	A
Farmakolojik ajanların seçimine kılavuzluk etmek üzere hasta merkezli bir yaklaşımın benimsenmesi ve kullanılması gerekir. Dikkate alınması gereken mülahazalar arasında ilacın etkinliği, hipoglisemi riski, hastanın aterosklerotik kardiyovasküler hastalık geçmişi, ilacın vücut ağırlığı üzerindeki etkisi, potansiyel yan etkileri, renal etkileri, uygulama yöntemi (subkütanöz uygulamaya karşı oral uygulama), maliyeti ve hasta tercihleri de sayılabilir.	E
Tip 2 diyabeti ve tanı konulmuş aterosklerotik kardiyovasküler hastalığı bulunan hastalarda, antihiperglisemik tedaviye yaşam tarzı yönetimi ve metformin ile başlanmalı ve ardından, ilaca özgü ve hastaya ilişkin faktörler dikkate alındıktan sonra, tedavi rejimine, **major advers kardiyovasküler olayları ve kardiyovasküler mortaliteyi azalttığı kanıtlanmış bulunan bir ajan** ***(şu anda empagliflozin ve liraglutide)*** ilave edilmelidir.	**A**
Tip 2 diyabeti ve tanı konulmuş aterosklerotik kardiyovasküler hastalığı bulunan hastalarda, yaşam tarzı yönetimi ve metformin ile tedaviden sonra, ilaca özgü ve hastaya ilişkin faktörler dikkate alındıktan sonra, tedavi rejimine, **major advers kardiyovasküler olayları azaltmak amacıyla antihiperglisemik ajan *canagliflozin*'in ilave edilmesi düşünülebilir.**	C
Kontrendike değilse ve hasta tarafından tolere edilebiliyorsa, diğer ajanlarla birlikte ve kombinasyon halinde kullanıldığı takdirde, metformin tedavisine devam edilmelidir.	A

PROFILES OF ANTIDIABETIC MEDICATIONS

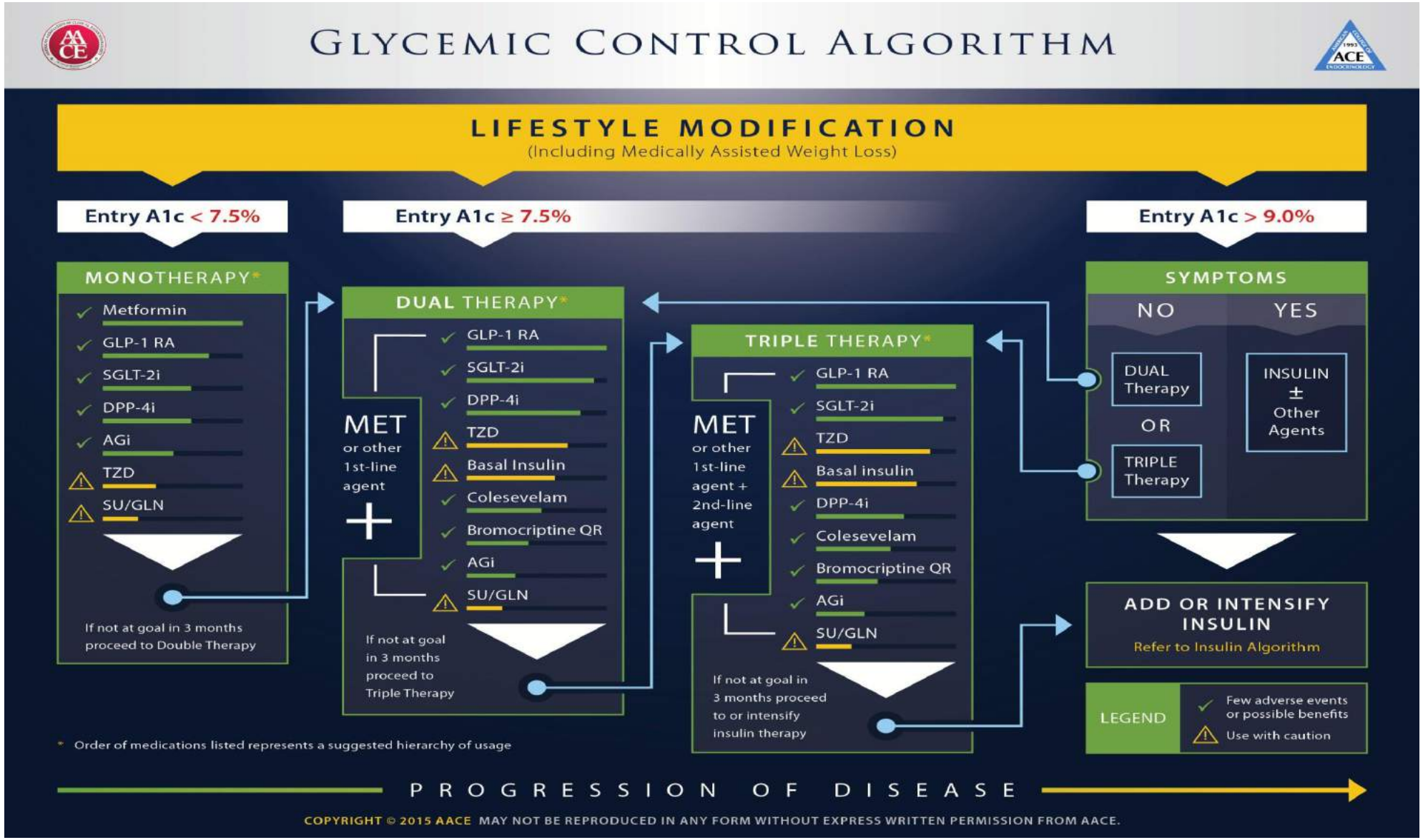
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated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

Few adverse events or possible benefits

Use with caution

Likelihood of adverse effects

Glycemic Control Algorithm



AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

2018

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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 if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30	Not Indicated for eGFR < 45 mL/min/1.73 m²	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
			Genital Mycotic Infections								
			Possible Benefit of Empagliflozin								
GI Sx	Moderate		Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF / CARDIAC / ASCVD	Ne		e #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Ne	Neutra	Fracture isk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

FDA Liraglutid MACE azalttığı için kabul etti

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

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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 if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible B… of Empa…	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	N…	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1			Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
ASCVD											
BONE	Neutral	Neutral	…ure …sk	…	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutra…	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

FDA EMPA'yı KV mortaliteyi azalttığı için kabul etti CANA MACE'yi azaltır

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

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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 if eGFR < 30 mL/min/ 1.73 m²	Exenatide Not Indicated CrCl < 30 / Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/ min/1.73 m² / Genital Mycotic Infections / Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagli[illegible]n) Effect[illegible] Red[illegible] Albu[illegible]	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	[illegible]	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF / CARDIAC / ASCVD	Neutral	See #1	See #2	[illegible]	[illegible]	[illegible]derate / May Reduce Stroke Risk	Neutral / Possible ASCVD Risk	Neutral / Benefit	Neutral / Safe	CHF Risk / Neutral	Neutral
BONE	Neutral	Neutral	Mild Fractur[illegible] Risk	[illegible]utral	[illegible]	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can C[illegible] in Vari[illegible]s Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Saxa ve Alogliptin ile muhtemelen KKY hosp artmakta

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

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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 if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
ASCVD											
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits

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3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

 DOI 10.4158/CS-2017-0153

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

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

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

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

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

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

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

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

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND

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

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

PROGRESSION OF DISEASE

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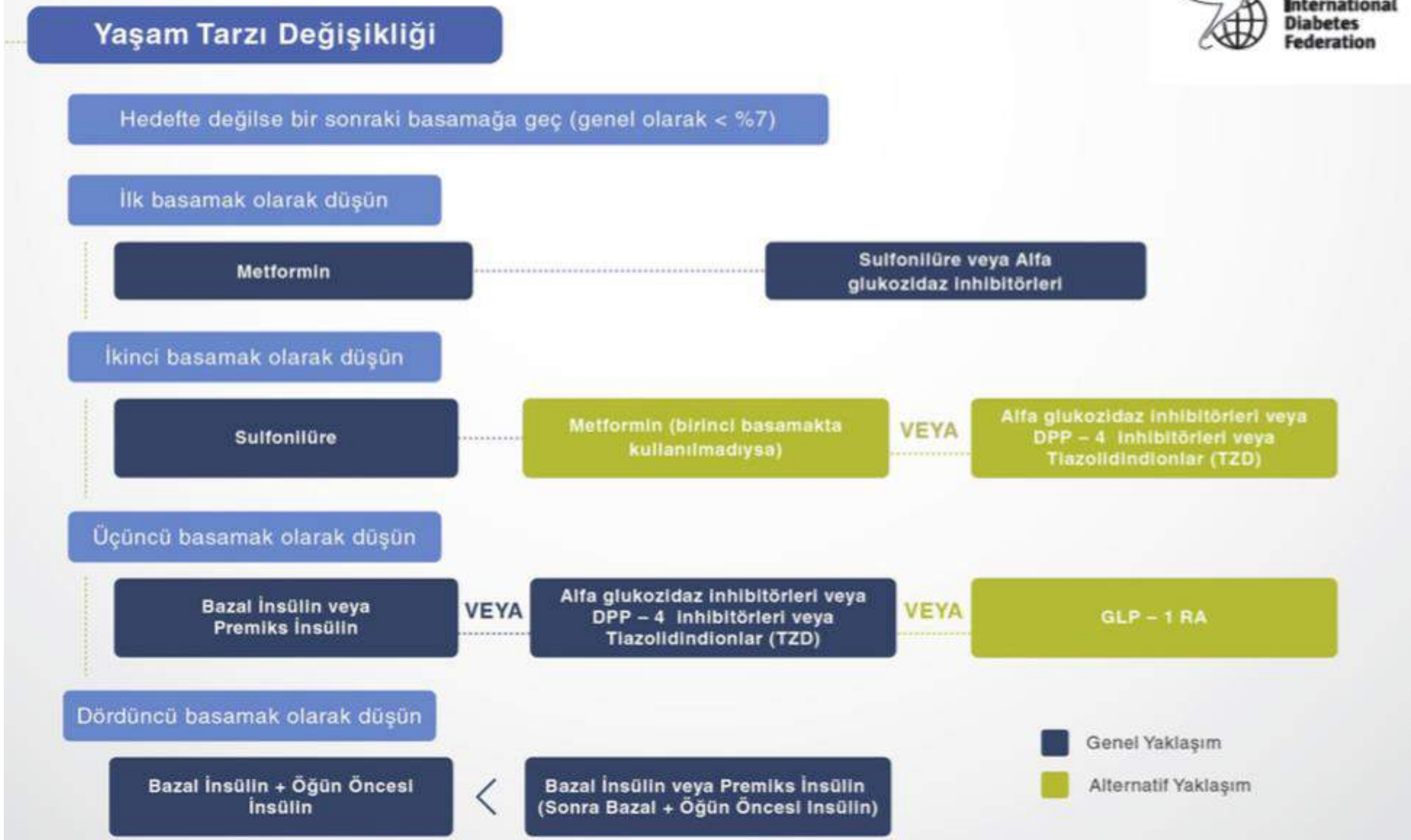
International Diabetes Federation
Yaşam Tarzı Değişikliği
Hedefte değilse bir sonraki basamağa geç (genel olarak < %7)
İlk basamak olarak düşün
Metformin
Sulfonilüre veya Alfa glukozidaz inhibitörleri
İkinci basamak olarak düşün
Sulfonilüre
Metformin (birinci basamakta kullanılmadıysa)
VEYA
Alfa glukozidaz inhibitörleri veya DPP – 4 inhibitörleri veya Tiazolidindionlar (TZD)
Üçüncü basamak olarak düşün
Bazal İnsülin veya Premiks İnsülin
VEYA
Alfa glukozidaz inhibitörleri veya DPP – 4 inhibitörleri veya Tiazolidindionlar (TZD)
VEYA
GLP – 1 RA
Dördüncü basamak olarak düşün
Bazal İnsülin + Öğün Öncesi İnsülin
Bazal İnsülin veya Premiks İnsülin (Sonra Bazal + Öğün Öncesi İnsülin)
Genel Yaklaşım
Alternatif Yaklaşım


IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care
International Diabetes Federation - 2017

Table 3. Risks and Benefits of Common GLDs (Excluding Insulin)

	Metformin	Sulfonylurea	Glinides	Pioglitazone	Alpha-Glucosidase Inhibitors	DPP4 Inhibitors	GLP1 Receptor Agonists	SGLT2 Inhibitors
Hypo	Neutral	Moderate/severe	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
Weight	Slight loss	Gain	Gain	Gain	Neutral	Neutral	Loss	Loss
CKD stages 3A, 3B	Reduce dose in stage 3A Contraindicated in stage 3B	Caution higher risk hypo	Caution higher risk hypo	Neutral	Neutral	Neutral but must reduce dose except linagliptin	Caution with exenatide ER	Contraindicated in stage 3B
CKD stages 4, 5	Contraindicated	Contraindicated except glipizide and gliclazide	Contraindicated		Contraindicated		Contraindicated	Contra indicated
GI SE	Moderate	Neutral	Neutral	Neutral	Moderate	Neutral	Moderate	Neutral
Other SE				Edema and bone fracture		Pancreatitis Heart failure (not a class effect)		Mycotic genital infections, fractures, amputations Bone Fractures and Amputations (may not be a class effect)
Major CV events	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit (2RCT*)	Benefit (2 RCT*)
CHF	Neutral	Neutral	Neutral	Increased risk	Neutral	Neutral	Neutral	Benefit (2 RCT**)

CKD, chronic kidney disease; CH, chronic heart failure; CV, cardiovascular; hypo, hypoglycemia; GI, gastrointestinal; SE, side effects; RCT, randomized controlled trial.

* Reduced risk in RCTs designed for non-inferiority with liraglutide, semaglutide, empagliflozin and canagliflozin

** Reduced risk in RCT designed for non-inferiority with empagliflozin and canagliflozin

Recommendations: Initial combination therapy

- The PCP should consider starting with a combination of metformin and another GLD when the baseline HbA1c is 1% to 2% points above target.
- The preferred combinations may be metformin plus SU (except glibenclamide/glyburide), DPP4 inhibitor or SGLT2 inhibitor.

Recommendations: Dual therapy

- A second GLD should be added if monotherapy with metformin (or its replacement) is not sufficiently effective to reach the HbA1c target or fails afterwards.
- The best choice of add-on is an SU (except glibenclamide/glyburide), a DPP4 inhibitor or a SGLT2 inhibitor. An AGI can be used as well. GLP1 receptor agonist can be used if weight loss is a priority and the drug is affordable.
- The PCP may consider patient's profile (age, body weight, complications and duration of disease) when choosing the best GLD to add.

Recommendations: Triple therapy

- A third GLD should be added if a combination of a GLD with metformin is not sufficiently effective to reach or maintain the HbA1c target.
- The most common choice to add to two oral GLDs is basal insulin. GLP1 receptor agonist can be added instead, if weight loss has been insufficient.

The profile of the patient (ABCD) may guide the selection of the second GLD and help to define the HbA1c target:

A **Age**: younger people may benefit from lower targets.

B **Body weight**: people with excess weight may benefit from drugs that enhance weight loss.

C **Complications**: people with CKD or severe CVD or who are more susceptible to hypoglycemia, may benefit from a GLD with proven benefit and safety under those circumstances.

D **Duration**: people with longer duration may harbor complications requiring treatment adjustments including the need for insulin.

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2018 Clinical Practice Guidelines

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

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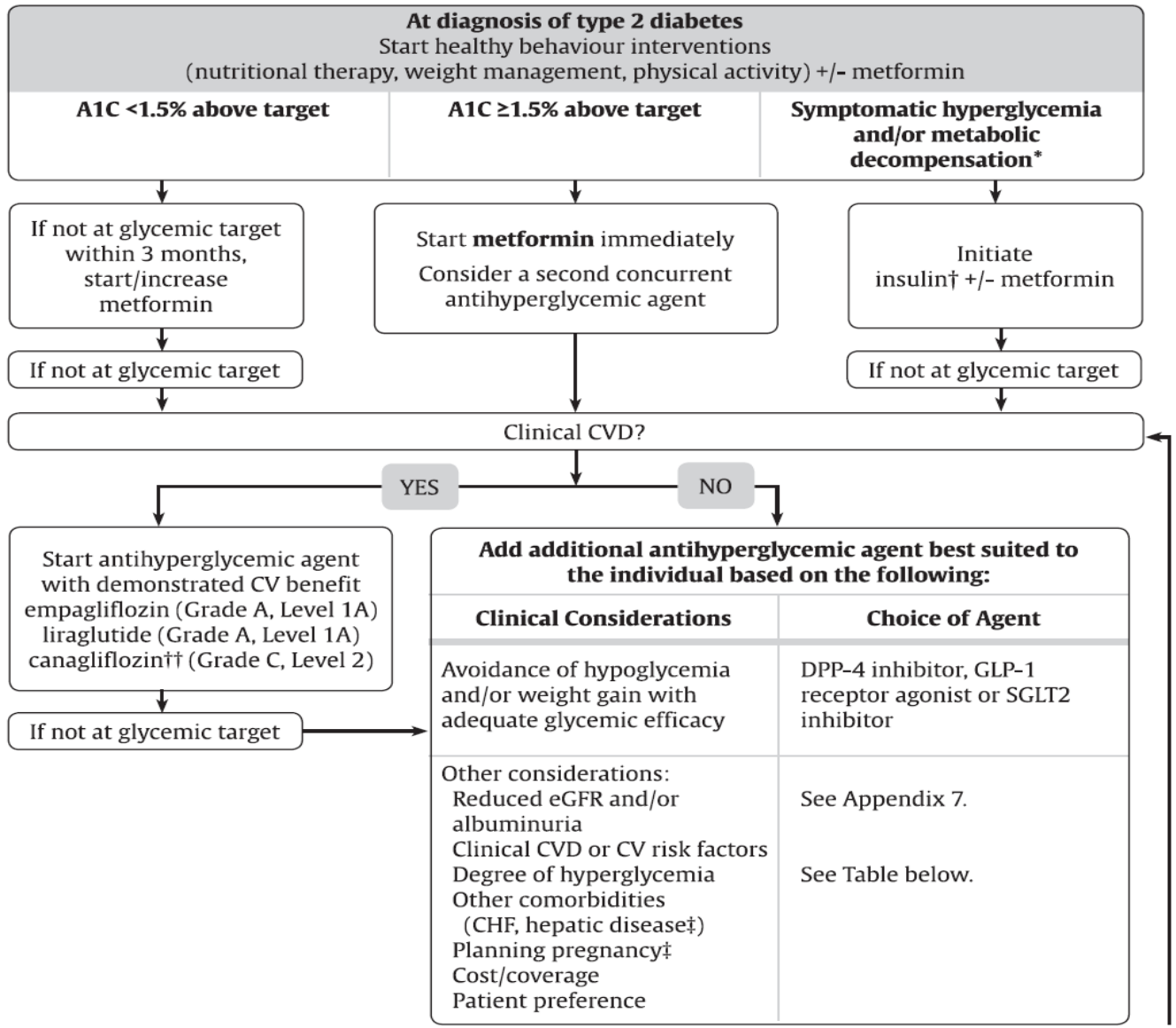
HEALTHY BEHAVIOUR INTERVENTIONS



* May include dehydration, DKA, HHS
† Insulin may be required at any point for symptomatic hyperglycemia/metabolic decompensation or if unable to achieve glycemic targets with other antihyperglycemic agents
†† Avoid in people with prior lower extremity amputation
‡ See product monographs

Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (Classes listed in alphabetical order)

Class*	Effect on CVD outcomes	Hypo-glycemia	Weight	Relative A1C lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1 receptor agonists	lira: Su-periority in people with type 2 diabetes with clini-cal CVD exenatide LAR & lixi: Neutral	Rare	↓ ↓	↓ ↓ to ↓ ↓ ↓	GI side-effects Gallstone disease Contraindicated with personal/family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	cana & empa: Superiority in people with type 2 diabetes with clini-cal CVD	Rare	↓ ↓	↓ ↓ to ↓ ↓ ↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin Reduced progression of nephropathy and CHF hos-pitalizations with empagliflozin and canagliflozin in persons with clinical CVD	$$$
DPP-4 Inhibitors	Neutral (alo, saxa, sita)	Rare	Neutral	↓ ↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑ ↑	↓ ↓ to ↓ ↓ ↓ ↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$-$$$$
Thiazolidine-diones	Neutral	Rare	↑ ↑	↓ ↓	CHF, edema, fractures, rare bladder cancer (piogl-itazone), cardiovascular controversy (rosiglita-zone), 6–12 weeks required for maximal effect	$$
Alpha-glucosi-dase inhibitors (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretatogue: Meglitinide		Yes	↑	↓ ↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing	$$
Sulfonylurea		Yes	↑	↓ ↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

alo, alogliptin; *cana*, canagliflozin; *empa*, empagliflozin; *glar*, glargine; *lira*, liraglutide; *exe LAR*, exenatide long-acting release; *lixi*, lixisenatide; *saxa*, saxagliptin; *sita*, sitagliptin.

↓

If not at glycemic targets

↓

Add another antihyperglycemic agent from a different class and/or add/intensify insulin regimen
Make timely adjustments to attain target A1C within 3–6 months

* Listed by CV outcome data

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin, pioglitazone[a] and an SU
  - *metformin, pioglitazone[a] or an SU, and an SGLT-2i[b]*
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 [illegible] insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
  - an SGLT-2i[b] instead of a DPP-4i if an SU or pioglitazone[a] is not appropriate
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or** would otherwise need twice daily NPH insulin [illegible] support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option[b].*

b. See NICE technology appraisal guidance 288 & 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

Abbreviations: DPP-4 Dipeptidyl peptidase-4 inhibitor, GLP-1 Glucagon-like peptide-1, SGLT-2 Sodium–glucose cotransporter 2 inhibitors, SU Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. See NICE technology appraisal guidance 288 & 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and** a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

'Type 2 diabetes in adults: management', NICE guideline NG28. Published December 2015, last updated April 2017.

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; Linda L. Humphrey, MD, MPH; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on oral pharmacologic treatment of type 2 diabetes in adults. This guideline serves as an update to the 2012 ACP guideline on the same topic. This guideline is endorsed by the American Academy of Family Physicians.

CLINICAL GUIDELINE

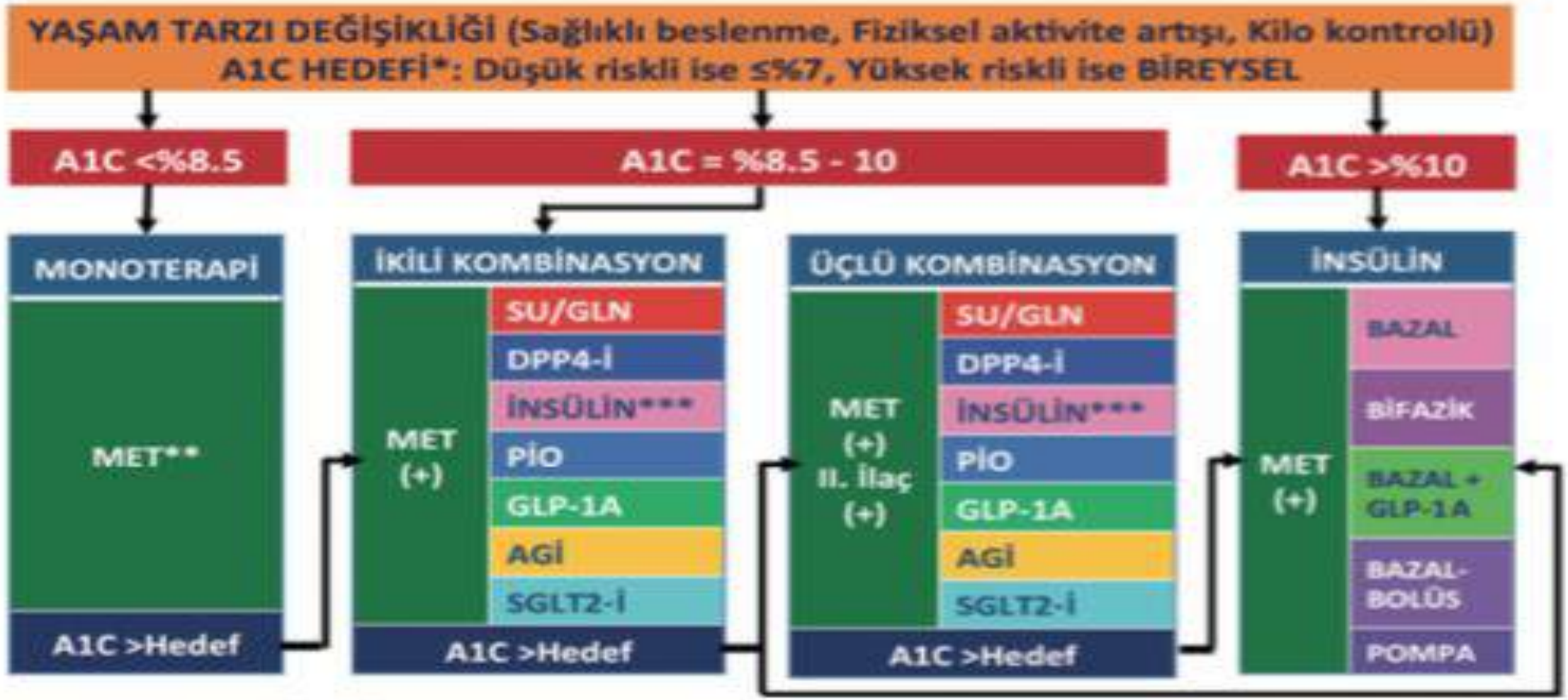
tions by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with type 2 diabetes.

Table 2. Comparative Efficacy, Adverse Effects, and Costs for Add-on Oral Therapies to Metformin

Comparative Efficacy vs. Other Combinations With Metformin (Quality of Evidence)	Comparative Harms vs. Other Combinations With Metformin/Class Adverse Effects and FDA Warnings	Agents	Fair Price for a 60-d Supply, $*	Adverse Effects
SUs				
SU + metformin favored for weight vs. TZD + metformin (moderate)	Higher risk for hypoglycemia than with metformin combinations with TZD, DPP-4 inhibitor, or SGLT-2 inhibitor	Glipizide, 5 mg	9	Diarrhea, gas, jitteriness, dizziness, uncontrollable shaking, red or itchy skin, rash, hives, and blisters
		Glimepiride, 4 mg	14	Dizziness and nausea
		Glyburide (DiaBeta, Sanofi-Aventis), 5 mg	111	Nausea and upper abdominal fullness
		Glyburide (Glynase, Pfizer), 6 mg	226	Nausea and upper abdominal fullness
TZDs				
TZD + metformin favored for short-term CVD mortality (rosiglitazone only) (low) and HbA_{1c} vs. DPP-4 inhibitor + metformin (moderate)	TZDs increase risk for congestive heart failure May also be associated with increased risk for fracture or bladder cancer	Pioglitazone, 30 mg	24	Headache; muscle, arm, or leg pain; sore throat; and gas
		Rosiglitazone (Avandia, GlaxoSmithKline), 2 mg	178	Headache, runny nose and other cold symptoms, sore throat, and back pain
DPP-4 inhibitors				
DPP-4 inhibitor + metformin favored for long-term all-cause mortality, long-term CVD mortality, and CVD morbidity vs. SU + metformin (low) DPP-4 inhibitor + metformin favored for short-term CVD morbidity vs. pioglitazone + metformin (low) DPP-4 inhibitor + metformin favored for weight vs. SU + metformin (high) or TZD + metformin (moderate)	FDA warns that sitagliptin, saxagliptin, linagliptin, and alogliptin may be associated with potentially severe and disabling joint pain	Alogliptin, 25 mg	335	Headache, stuffy or runny nose, sore throat, and joint pain
		Linagliptin (Tradjenta, Boehringer Ingelheim), 5 mg	734	Headache and joint pain
		Saxagliptin (Onglyza, AstraZeneca), 5 mg	752	Sore throat, headache, and joint pain
		Sitagliptin (Januvia, Merck), 100 mg	746	Stuffed or runny nose, sore throat, headache, diarrhea, nausea, and joint pain
SGLT-2 inhibitors				
SGLT-2 inhibitor + metformin favored for CVD mortality (low), HbA_{1c} (moderate), weight (high), systolic blood pressure (high), and heart rate (moderate) vs. SU + metformin SGLT-2 inhibitor + metformin favored for weight and systolic blood pressure (moderate) vs. DPP-4 inhibitor + metformin	Higher risk for genital mycotic infection than metformin alone or metformin combinations with SU or DPP-4 inhibitor FDA warns that canagliflozin may be associated with increased risk for bone fracture and risk for decreased bone mineral density	Canagliflozin (Invokana, Janssen), 300 mg	808	Excessive urination, including at night; increased thirst; constipation; and dry mouth
		Dapagliflozin (Farxiga, AstraZeneca), 10 mg	812	Excessive urination, including at night, and increased thirst
		Empagliflozin (Jardiance, Boehringer Ingelheim), 25 mg	812	Excessive urination, including at night, and increased thirst

ŞEKİL 9.1: TEMD TİP 2 DİYABETTE TEDAVİ ALGORİTMASI - 2017



*Tedavi değişikliği için A1C >%7 veya bireysel hedefin üstünde olmalı. **Monoterapide MET tercih edilir, MET kontrendike/ intolerans varsa diğer bir OAD başlanabilir. ***Bazal insülin tercih edilmeli, SU/GLN ile verilmemek koşulu ile, bifazik insüline de başlanabilir. (MET: Metformin, OAD: Oral antidiyabetik, DPP4-İ: Dipeptidil peptidaz 4 inhibitörü, SU: Sulfonilüre, GLN: Glinid, PİO: Pioglitazon, GLP-1A: Glukagon benzeri peptid 1 analoğu, AGİ: Alfa glukozidaz inhibitörü, SGLT2-İ: Sodyum glukoz kotransportu 2 inhibitörü).

TABLO 9.1: **Diyabet ilaçlarının metabolik ve eşlik eden sorunlar üzerine etkileri**

	MET	DPP4-İ	GLP-1A	SU	GLN	PİO	AGİ	SGLT2-İ	İNS
PPG	-	- -	- - / - - -	- -	- -	-	- -	-	- - / - - -
APG	- -	-	-	- -	-	- -	N	- -	- - / - - -
KB	N / -	N	-	N	N	-	N	-	N
HL/DL	- / - -	N	N	- / N	- / N	N / -	N / -	LDL ++	- / - -
NAYKH	-	N	-	N	N	- -	N	N	N
HİPOG	N	N	N	+ +	+	N	N	N	+ + / + + +
GİS YE	+ +	N	++	N	N	N	++	N	N
KBY/GUI	Orta ise !	Doz düşür	Orta ise !	Orta ise !	N	Hafif ise !	N	Genital mikotik inf.	Doz ayarı
KCY/LA	Ağır ise KE	N	N	Orta ise !	Orta ise !	Orta ise !	N	N	N
KKY/KVH	Ağır ise KE	N	N	Orta ise !	N	Ağır ise KE	N	N	N (PİO ile !)
KİLO	N / -	N	- -	+ / + +	+	+ +	N	- -	+ / + +
KIRIK	N	N	N	N	N	+ +	N	KMK kaybı	N
İLAÇ ETK	N	N	N	+ +	+ +	N	N	N	N
MALİYET	- - -	+ +	+ + +	- - -	+	++	+	++	-

Diabetes Mellitus Ve Komplikasyonlarının Tanı, Tedavi Ve İzlem Kılavuzu - 2017 TEMD

TEMD GÖRÜŞÜ

- *TEMD, ileri derecede böbrek yetersizliği (eGFR <30 ml/dk , linagliptin için <15 mldk) olan ve/veya diyalize giren vakalarda insülin dışında, herhangi bir anti-hiperglisemik ilaç kullanımını önermemektedir.*
- *Metformin, orta derecede böbrek yetersizliğinde (eGFR <45 ml/dk/1.73 m^2) kontrendikedir. İleri derecede böbrek yetersizliğinde (eGFR 60-45 ml/dk/1.73 m^2), metformin dozu %50 azaltılmalıdır.*
- *Ayrıca iyotlu kontrast madde kullanılarak anjiyografik inceleme yapılacaksa metformin, işlemden 24 saat önce kesilmeli, hasta hidrate edilmeli ve 24 saat sonra tekrar başlanmalıdır.*
- *Metformin kullanan hastalarda B-12 vitamin düzeyi periyodik olarak ölçülmeli ve gerekiyorsa replasman yapılmalıdır.*
- *KV olay öyküsü olan veya KV riski yüksek olan hastalarda empagliflozin ve/veya liraglutid kullanılması, KV nedenli ölümleri azaltır.*

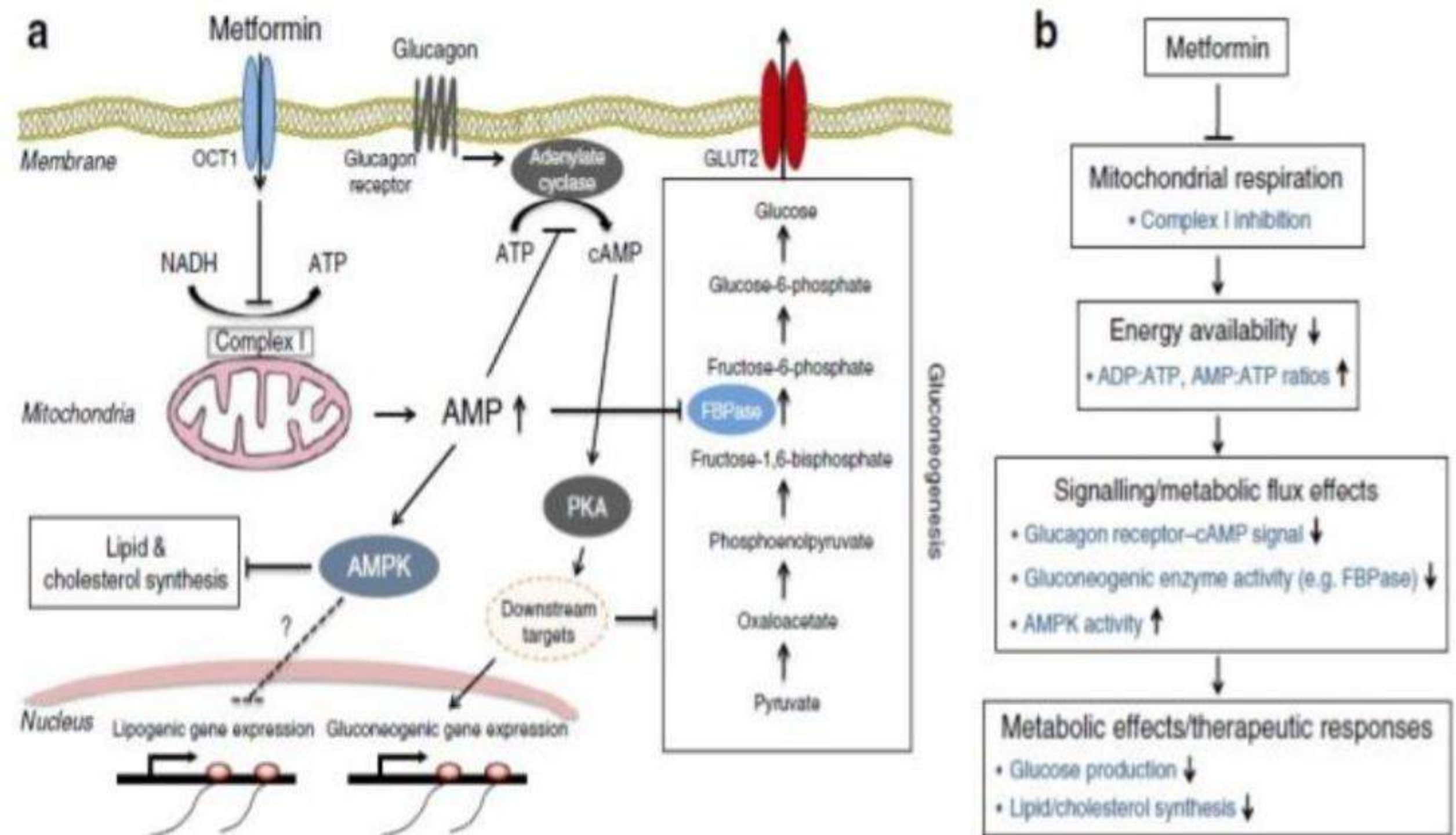

ULUSAL DİYABET KONSENSUS GRUBU
Diyabet
Tanı ve Tedavi
Rehberi
2017
TÜRKİYE DİYABET VAKFI

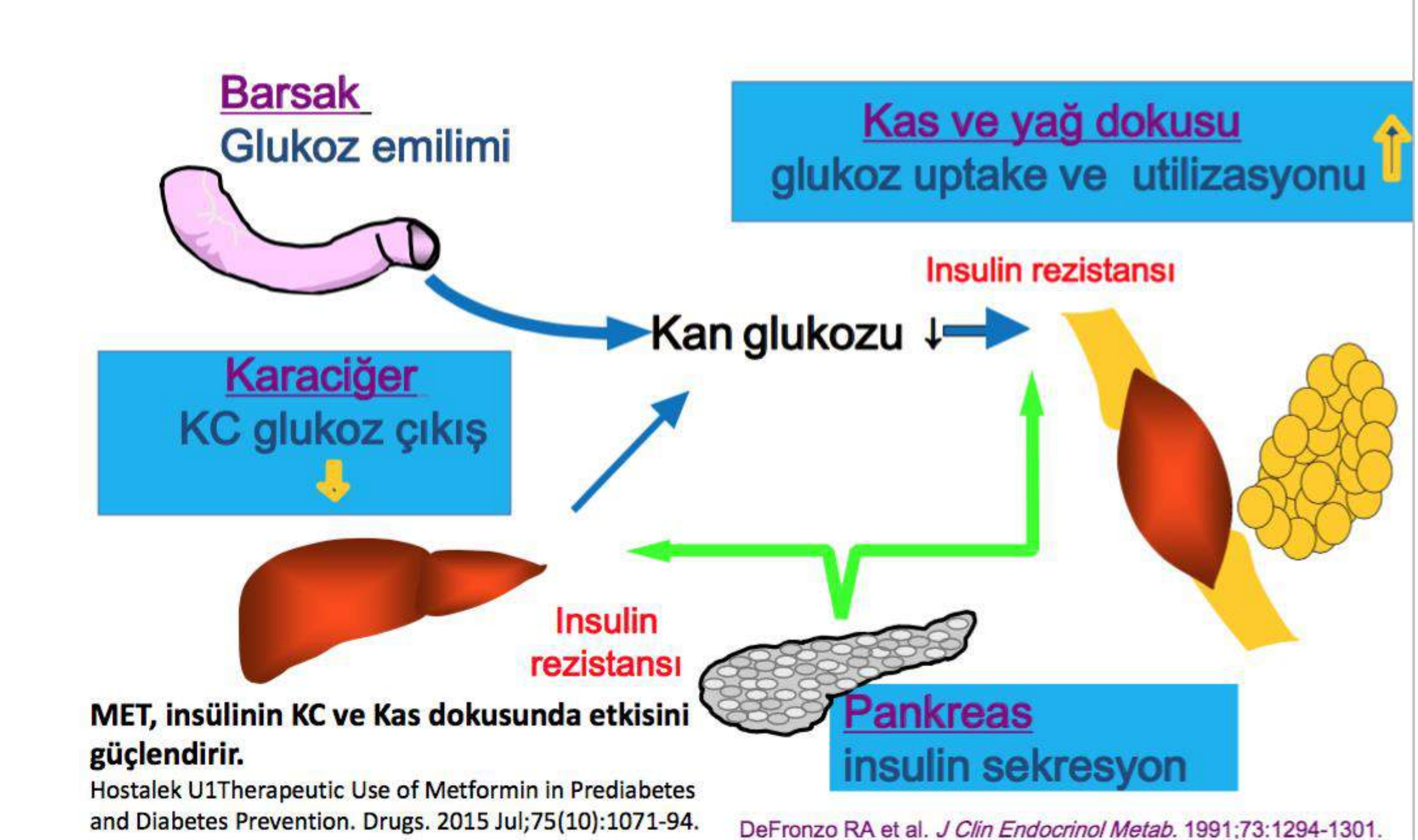
YENİ TANI ALAN TİP 2 DİYABETTE TEDAVİ YAKLAŞIMI

HbA1c	BETA HÜCRE REZERVİ (C peptid: ng/ml)	TEDAVİ PLANI	TEDAVİ SEÇENEKLERİ
<7.5	YETERLİ (C peptid: > 2 ng/ml)	MONOTERAPİ	Yaşam Tarzı Değişikliği; Metformin
7.5 - 9	YETERLİ (C peptid: > 2 ng/ml)	İKİLİ KOMBİNASYON	Metformin Sülfonilüre; Metformin Pioglitazon; Metformin İnkretin Bazlı Tedaviler; Metformin SGLT-2 İnhibitörü; Kombinasyon Tedavisi 1
>9	YETERLİ (C peptid: > 2 ng/ml)	ÜÇLÜ KOMBİNASYON	Metformin Sülfonilüre - İnkretin Bazlı Tedaviler; Metformin Sülfonilüre Pioglitazon; Metformin İnkretin Bazlı Tedaviler Pioglitazon; Metformin İnkretin Bazlı Tedaviler SGLT-2 inhibitörü; Kombinasyon Tedavisi 2
	SINIRDA (C peptid: <0.5 - 2 ng/ml)	BAZAL İNSÜLİN KOMBİNASYONLARI	Metformin Bazal İnsülin; Metformin Bazal İnsülin Glinid; Metformin Bazal İnsülin İnkretin Bazlı Tedaviler; Metformin - Bazal insülin Pioglitazon / SGLT-2 inhibitörü
	YETERSİZ (C peptid: <0.5 ng/ml)	ÇOKLU DOZ İNSÜLİN KOMBİNASYONLARI	Metformin Bazal +Bolus İnsülin Tedavisi; Metformin Bazal-Bolus İnsülin Tedavisi (Pioglitazon/SGLT-2 İnhibitörü); Metformin Hazır Karışım İnsülinler (25/30/50) İnkretin Bazlı Tedaviler /Pioglitazon/SGLT2 inhibitörleri

Metformin

- Hepatik glukoz üretimini baskılar,
- periferik dokulardaki insulin direncini azaltarak esas olarak iskelet kasında glukoz kullanımını arttırır.
- Etkisini esas olarak AMP- aktive protein kinaz (AMPK) aktivasyonu ile sağlar. Bunu da karaciğer kinaz B1 (LKB1) üzerinden gerçekleştirir
- AMPK adenosin monofosfat/trifosfat oranını algılayan hücresel düzeyde santral bir enerji düzenleyicisidir
- Gıda yokluğunda AMPK aktive olur ve enerji harcayan mekanizmaları inhibe ederken enerji üreten mekanizmaları da aktive eder.
- AMPK ile kontrol edilen ana büyüme yolaklarından biri memeli rapamisin hedefidir (mTOR)
- mTOR hücre büyüme faktörlerini regüle ederek hücre büyümesi ve anjiogenezi kontrol eder.

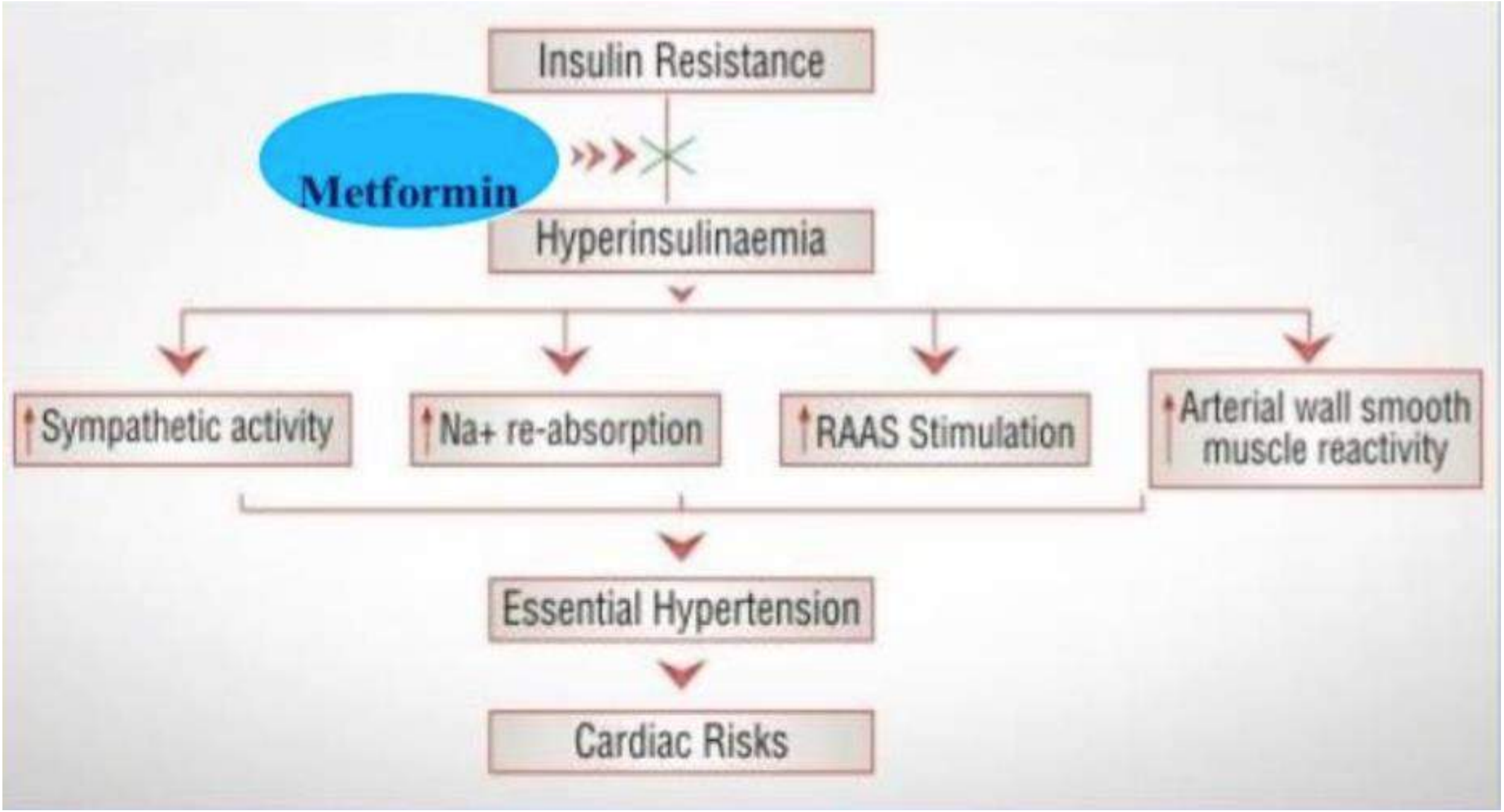

a
Metformin
Glucagon
Membrane
OCT1
Glucagon receptor
Adenylate cyclase
GLUT2
NADH
ATP
ATP
cAMP
Complex I
Mitochondria
AMP ↑
Glucose
Glucose-6-phosphate
Fructose-6-phosphate
FBPase
Fructose-1,6-bisphosphate
Phosphoenolpyruvate
Oxaloacetate
Pyruvate
Gluconeogenesis
PKA
Lipid & cholesterol synthesis
AMPK
Downstream targets
?
Nucleus
Lipogenic gene expression
Gluconeogenic gene expression
b
Metformin
Mitochondrial respiration
• Complex I inhibition
Energy availability ↓
• ADP:ATP, AMP:ATP ratios ↑
Signalling/metabolic flux effects
• Glucagon receptor–cAMP signal ↓
• Gluconeogenic enzyme activity (e.g. FBPase) ↓
• AMPK activity ↑
Metabolic effects/therapeutic responses
• Glucose production ↓
• Lipid/cholesterol synthesis ↓



MET, insülinin KC ve Kas dokusunda etkisini güçlendirir.

Hostalek U1Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs. 2015 Jul;75(10):1071-94.

DeFronzo RA et al. *J Clin Endocrinol Metab.* 1991;73:1294-1301.


Insulin Resistance
Metformin
Hyperinsulinaemia
↑Sympathetic activity
↑Na+ re-absorption
↑RAAS Stimulation
↑Arterial wall smooth muscle reactivity
Essential Hypertension
Cardiac Risks

Metformin

UKPDS - Substudy

Aggregate Endpoint	ARR	RRR	p
Any diabetes related endpoint	13.5 %	32%	0.0023
Microvascular disease	2.5%	29%	0.19
Myocardial infarction	7.0%	**39%**	**0.010**
All-cause mortality	7.1%	**36%**	**0.011**

342 overweight patients
Median followup of 10.7 years (6-20)
Mean HbA1c only 0.6% lower

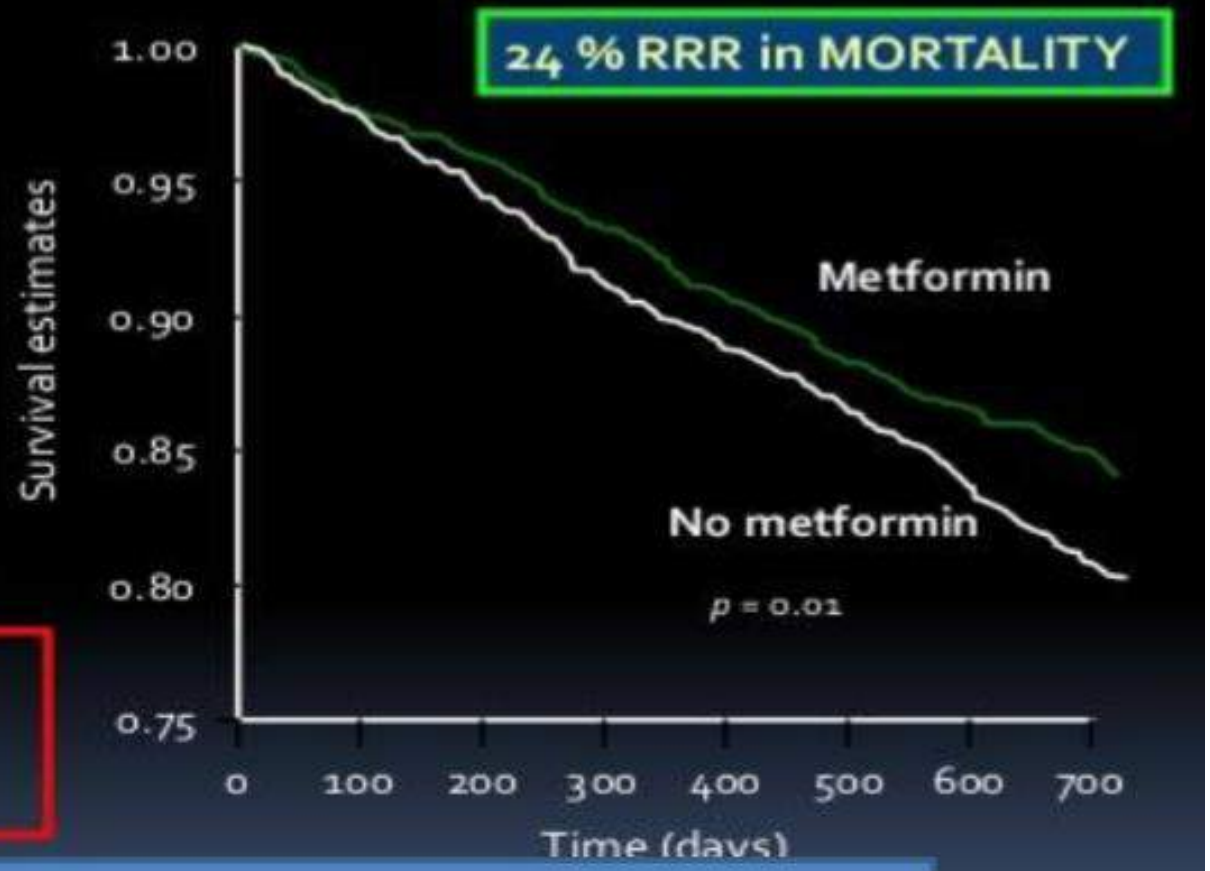
UKPDS 34. Lancet 1998;352:837-853

Metformin Use in Heart Failure Patients

Veterans Affairs

- 6,185 with CHF & DM
- Oral antihyperglycemic:
  - With metformin (n=1,561)
  - Without metformin
- Statistically adjusted for co-variables

Death:	0.76 (0.63-0.92) $p < 0.01$
CHF hospitalization:	0.93 (0.74-1.18) $p = 0.56$
Total hospitalization:	0.94 (0.83-1.07) $p = 0.35$



Mortalite de %24 azalma saptanmış

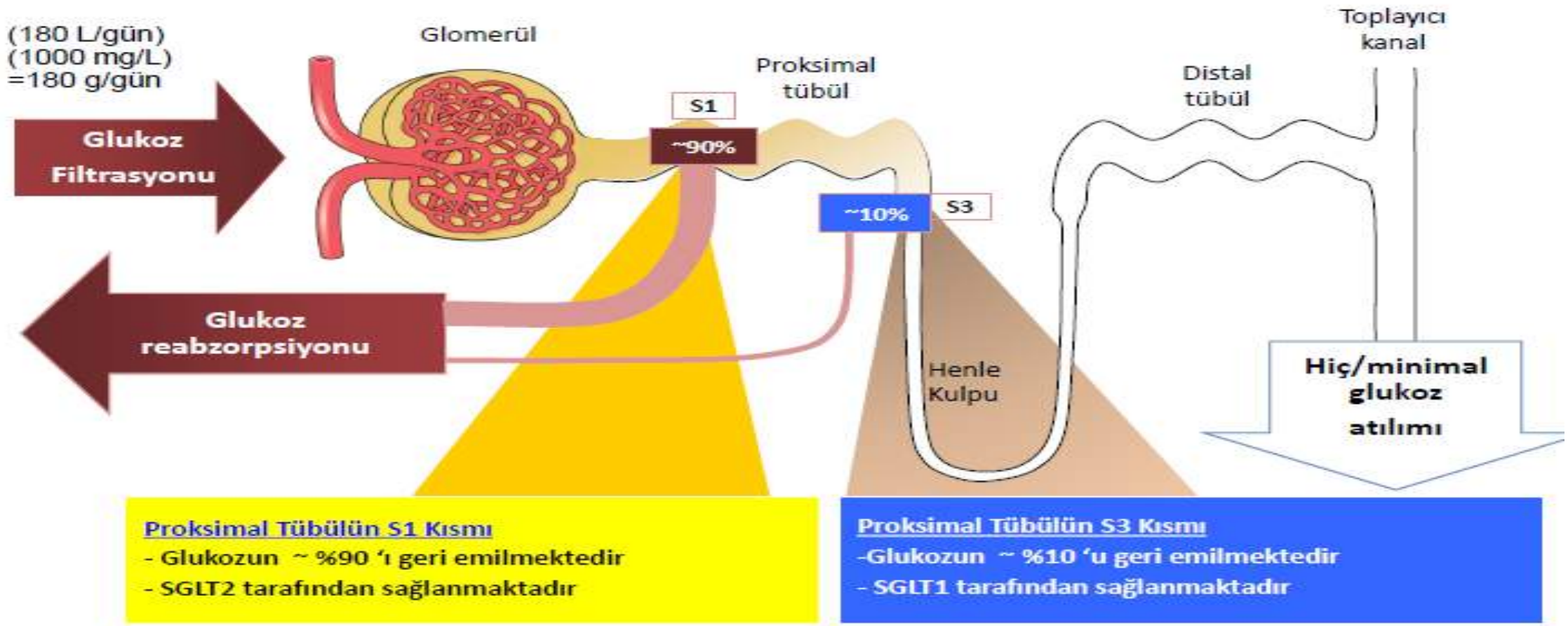
Aguilar D, et al. Circ Heart Fail 2011;4:53-8.

2017 ADA

Compound(s)	Cellular mechanism(s)	action(s)	Advantages	Disadvantages	Cost*
• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR < 30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low

2018 ADA

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency



SGLT = Sodium-bağımlı glukoz taşıyıcısı

1. Bailey CJ. Trends in Pharmacol Sci 2011;32:63-71., 2. Chao EC. Core Evidence 2012;7:21-28.

EMPA-REG OUTCOME®

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

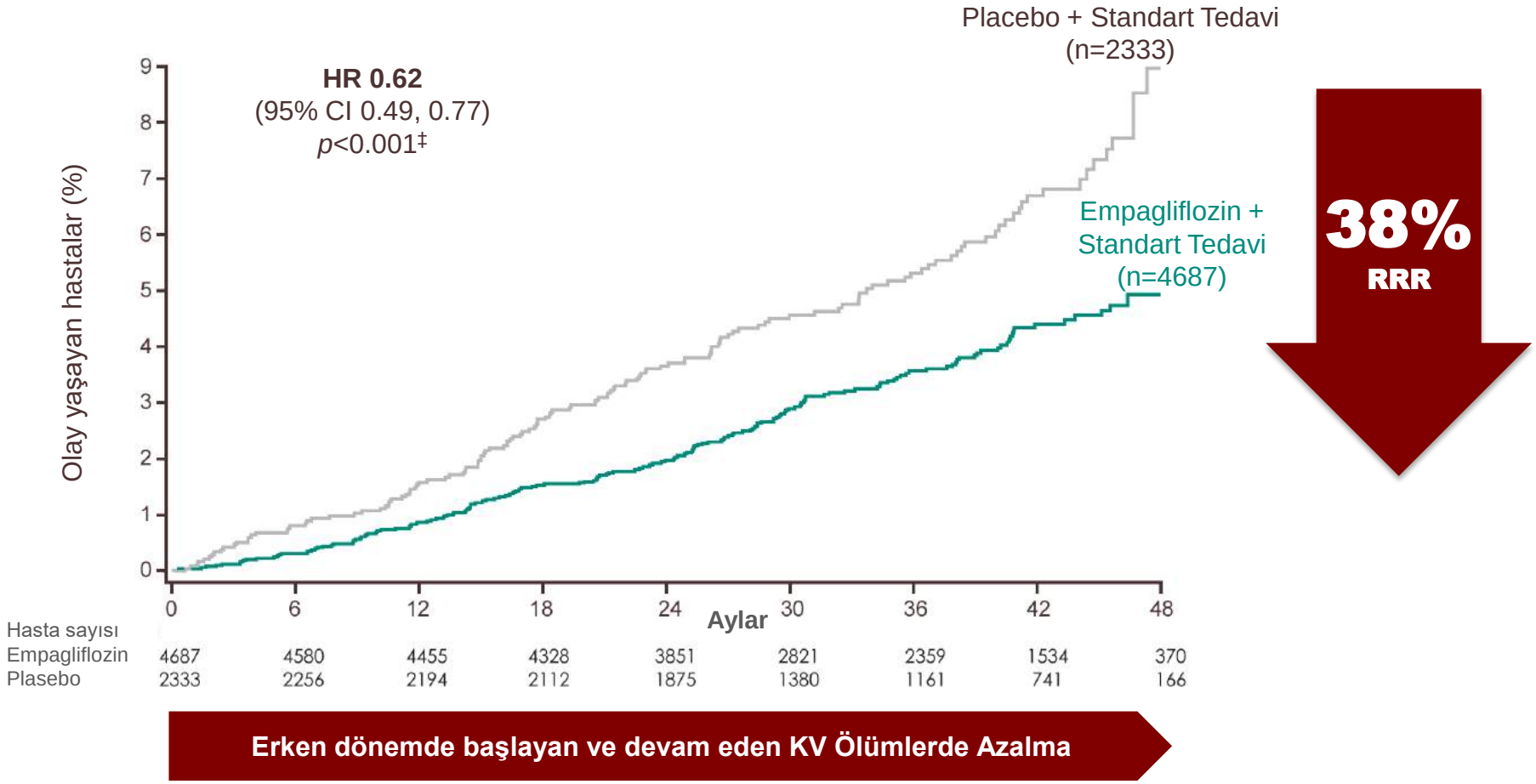
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Empagliflozin ile
3P MACE'te anlamlı azalma sağlanmıştır

3P-MACE için RRR: %14; 3P-MACE için ARR :%1.6

*Üstünlük için iki-yönlü testler yapılmıştır ($p \leq 0.0498$ ise istatistiksel anlamlılık gösterilmiştir)
3P-MACE, 3-noktalı majör advers KV olaylar; GA, güven aralığı; KV, kardiyovasküler; HR, tehlike oranı; MI, miyokart enfarktüsü; RRR, göreceli risk düşüşü; ARR, mutlak risk düşüşü

Empagliflozin
KV ölümleri azaltmıştır*

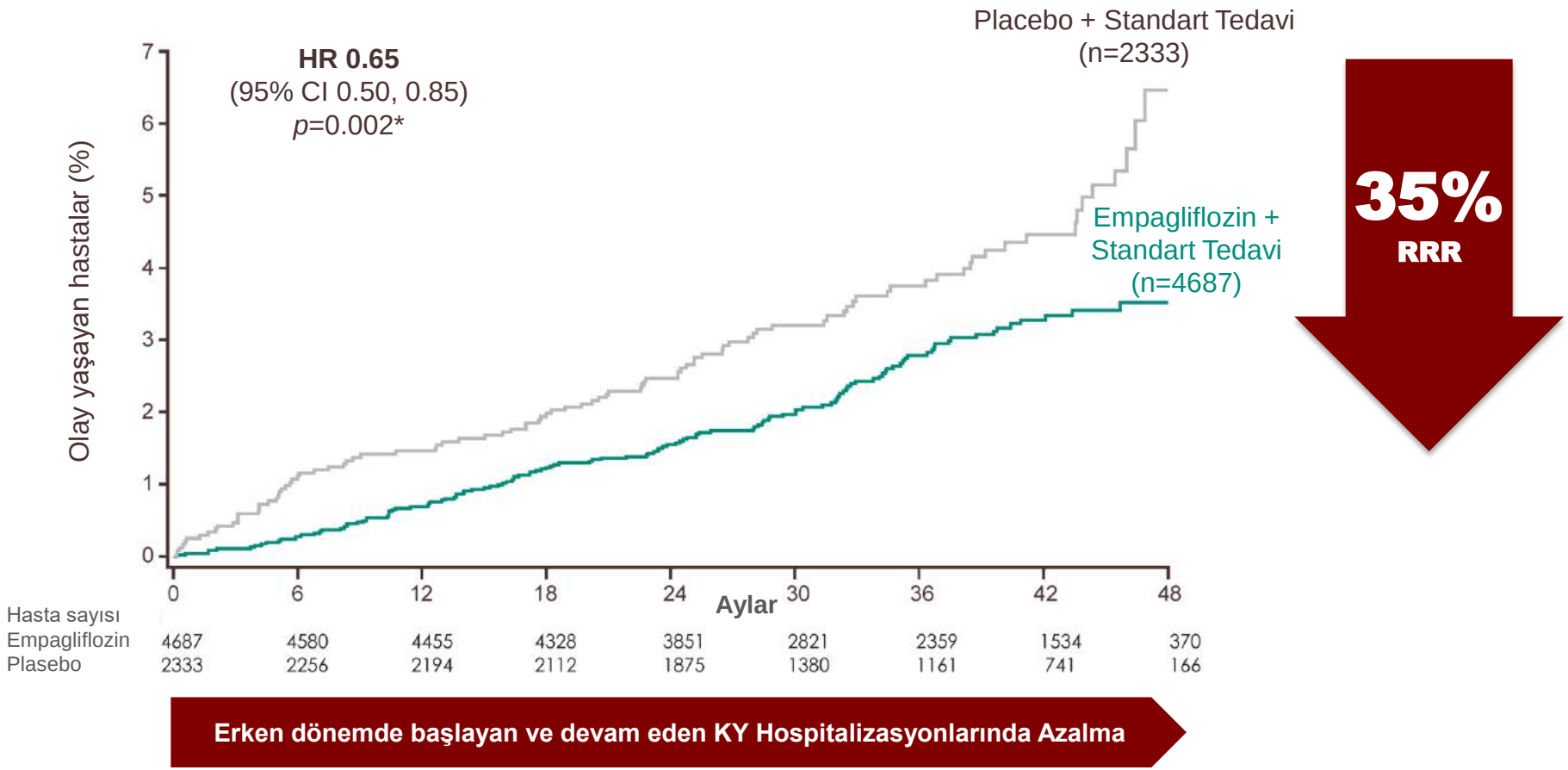


Erken dönemde başlayan ve devam eden KV Ölümlerde Azalma

*Empagliflozin, mevcut KV hastalığı olan T2D hastalarında standart tedaviye eklendiğinde, KV ölümler için plaseboya kıyasla %38 rölatif risk azalması sağlamıştır.

**plaseboya kıyasla KV, kardiyovasküler; HR, tehlike oranı; RRR, göreceli risk düşüşü

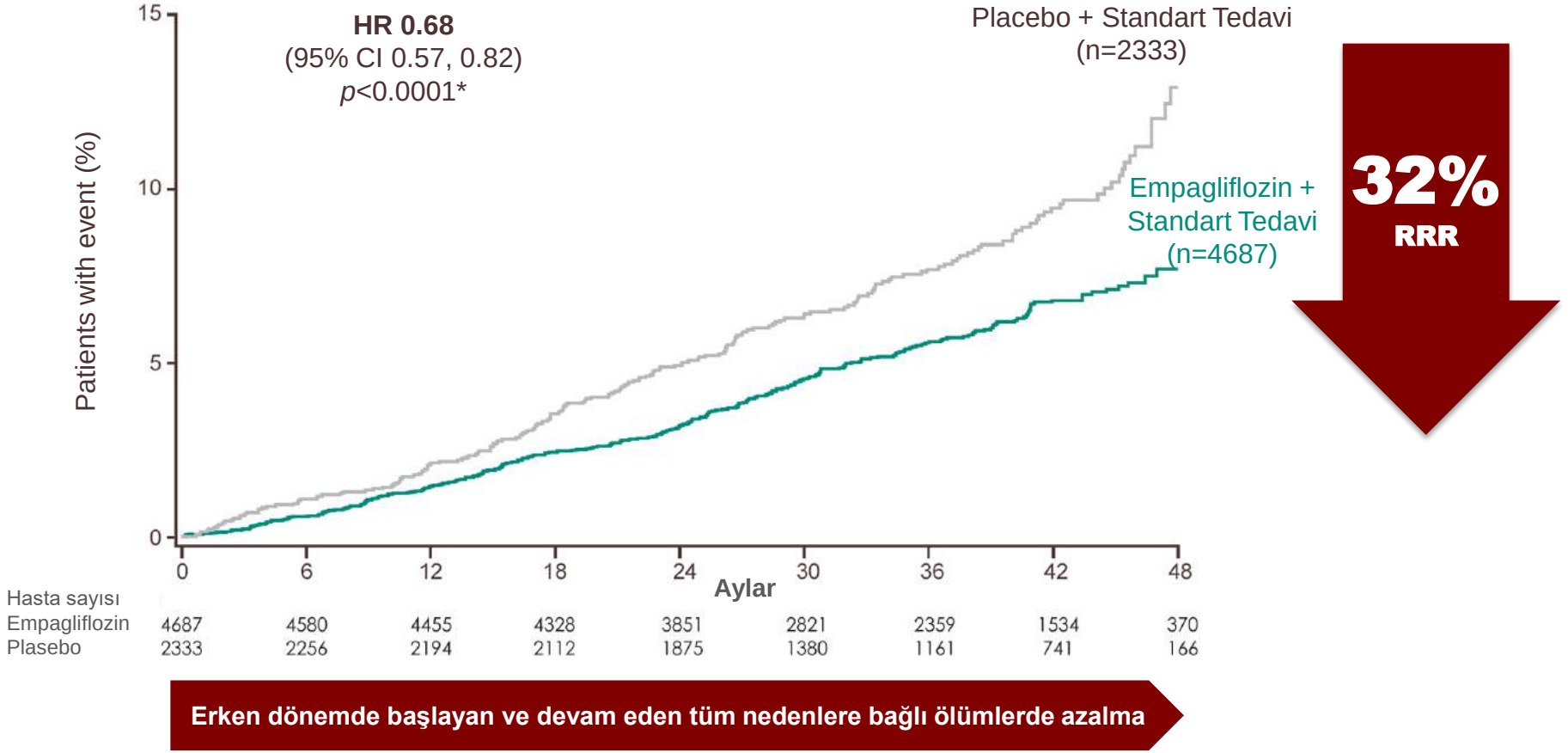
Empagliflozin
KY hospitalizasyonlarını azaltmıştır



Erken dönemde başlayan ve devam eden KY Hospitalizasyonlarında Azalma

*Empagliflozin, mevcut KV hastalığı olan T2D hastalarında standart tedaviye eklendiğinde, KY'ne bağlı hospitalizasyonlar için plaseboya kıyasla %35 rölatif risk azalması sağlamıştır.
*Nominal p-değeri. Kümülatif insidans fonksiyonu

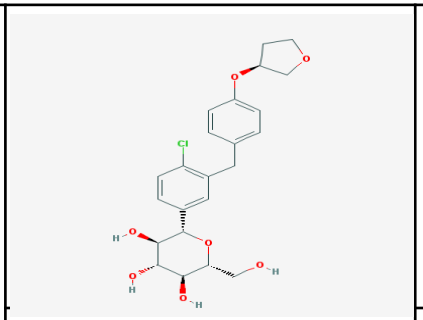
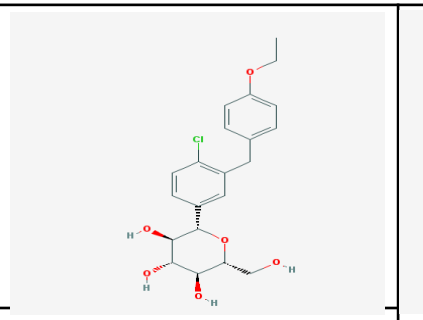
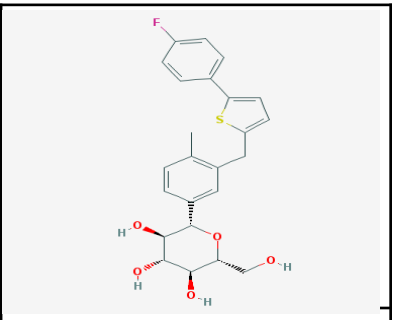
Empagliflozin
tüm nedenlere bağlı ölümleri azaltmıştır*



Erken dönemde başlayan ve devam eden tüm nedenlere bağlı ölümlerde azalma

*Empagliflozin, mevcut KV hastalığı olan T2D hastalarında standart tedaviye eklendiğinde, KY'ne bağlı hospitalizasyonlar için plaseboya kıyasla %35 rölatif risk azalması sağlamıştır.
*Nominal p-değeri. Kümülatif insidans fonksiyonu

SGLT2i'ler

			
	Empagliflozin	Dapagliflozin	Canagliflozin
Terapötik doz (mg/gün) Başlangıç dozu	10–25 10	5–10 10	100–300 100
Uygulama	qd Yemekle birlikte veya tek başına	qd Yemekle birlikte veya tek başına	qd İlk öğünden önce
Tepe plazma konsantrasyonu (doz sonrası saat)	1.5	2 saat içinde	1–2
Eliminasyon (yarılanma-ömrü, saat)	Hepatik:renal 43:57 [12.4]	Hepatik:renal 22:78 [12.9]	Hepatik:renal 67:33 [13.1]*
SGLT1'e kıyasla seçicilik	**1:5000**	**>1:1400**	**>1:160[1]**

300 mg dozu için. qd, günde bir defa; SGLT1, sodyum-glikoz eş-taşıyıcısı-1; SGLT2, sodyum-glikoz eş-taşıyıcısı-2

Veri kaynağı: www.ema.europa.eu (Jardiance KÜB, Forxiga KÜB, Invokana PI, Invokana KÜB, tümüne erişim 20 Şubat 2016); 1. Sha S *ve ark. Diab Obes Metab* 2015;17:188

1. Preclinical data; adapted from Grempler R. Diabetes Obes Metab 2012;14:83

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

ABSTRACT

- 10142 yüksek KVH riskli T2 DM li hasta,
- %65 inde KVH öyküsü
- Ort 188,2 hafta takip edilmişler
- P.O KV nedenleri, nonfatal MI ya da nonfatal inme nedeniyle ölüm

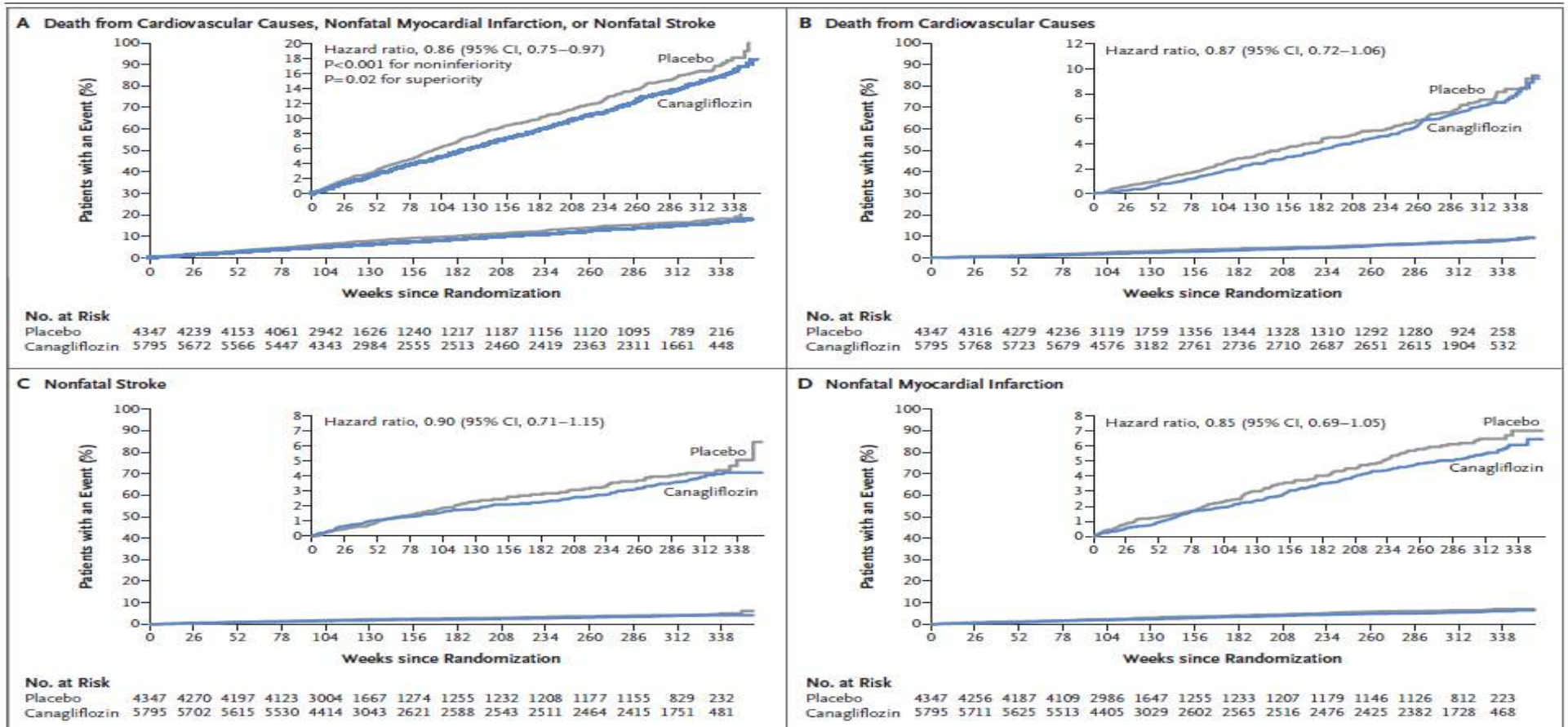


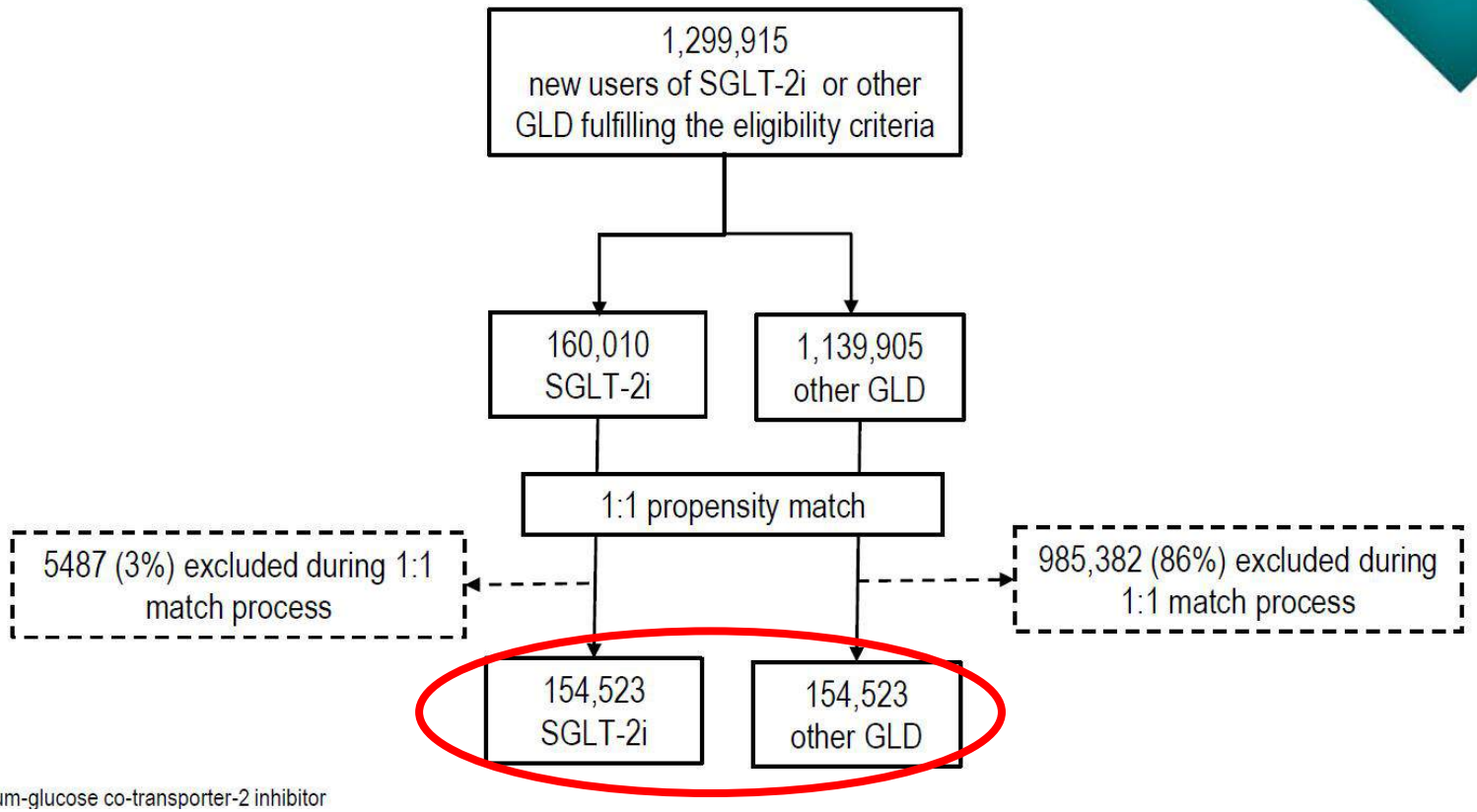
Figure 2. Cardiovascular Outcomes in the Integrated CANVAS Program.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratios and 95% confidence intervals for the primary outcome and the components of the outcome were estimated with the use of Cox regression models with stratification according to trial and history of cardiovascular disease for all canagliflozin groups combined versus placebo. Analyses are based upon the full, integrated data set comprising all participants who underwent randomization. The inset in each panel shows the same data on an enlarged y axis.

CVD-REAL Gözlemsel Çalışma

CVDREAL

Patient Population



SGLT-2i=sodium-glucose co-transporter-2 inhibitor

CVD-REAL Gözlemsel Çalışma

- Ortalama yaş 57, Saptanmış KVH % 13
- Kyh için (N=309.046): %41,8 Dapagliflozin, %52,7 Canagliflozin, %5,5 Empagliflozin
- Tüm nedenlere bağlı mortalite için (N=215.622): %51 dapagliflozin, %42,3 Canagliflozin, %6,7 Empagliflozin

Sonuçlar: Diğer OAD'ler (metformin, DPP-4i) ile karşılaştırıldığında SGLT-2i tedavisi:

- **KYh riskinde %39 azalma (p<0.001)**
- **Tüm nedenlere bağlı ölüm riskinde %51 azalma (p<0.001)**

MI, inme gibi diğer KV olaylar değerlendirilmemiştir

Received: 10 July 2017 | Revised: 29 July 2017 | Accepted: 31 July 2017

DOI: 10.1111/dom.13077

WILEY

ORIGINAL ARTICLE

Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study

Frederik Persson MD, DMSc[1] | Thomas Nyström MD PhD[2] | Marit E. Jørgensen MD PhD[1] | Bendix Carstensen MSc[1] | Hanne L. Gulseth MD PhD[3] | Marcus Thuresson PhD[4] | Peter Fenici MD PhD[5] | David Nathanson MD PhD[2] | Jan W. Eriksson MD PhD[6] | Anna Norhammar MD PhD[7,8] | Johan Bodegard MD PhD[9] | Kåre I. Birkeland MD PhD[3,10]

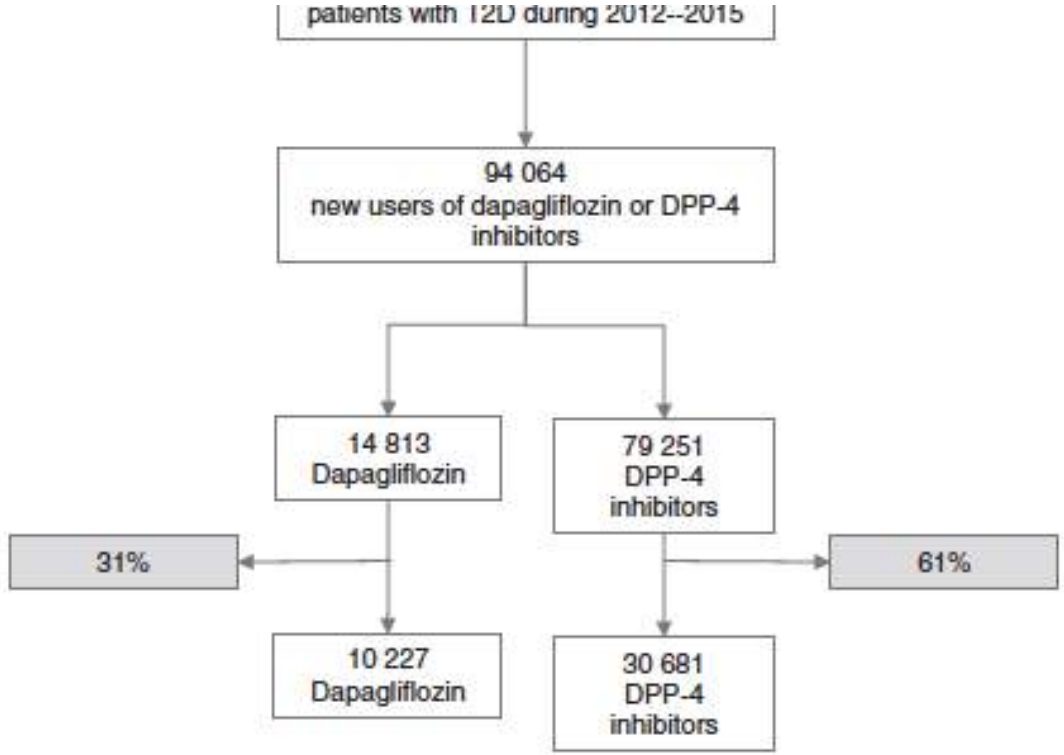


FIGURE 1 Patient flow charts for dapagliflozin vs DPP-4 inhibitor groups. Proportion of patients not fulfilling propensity matching 1:3

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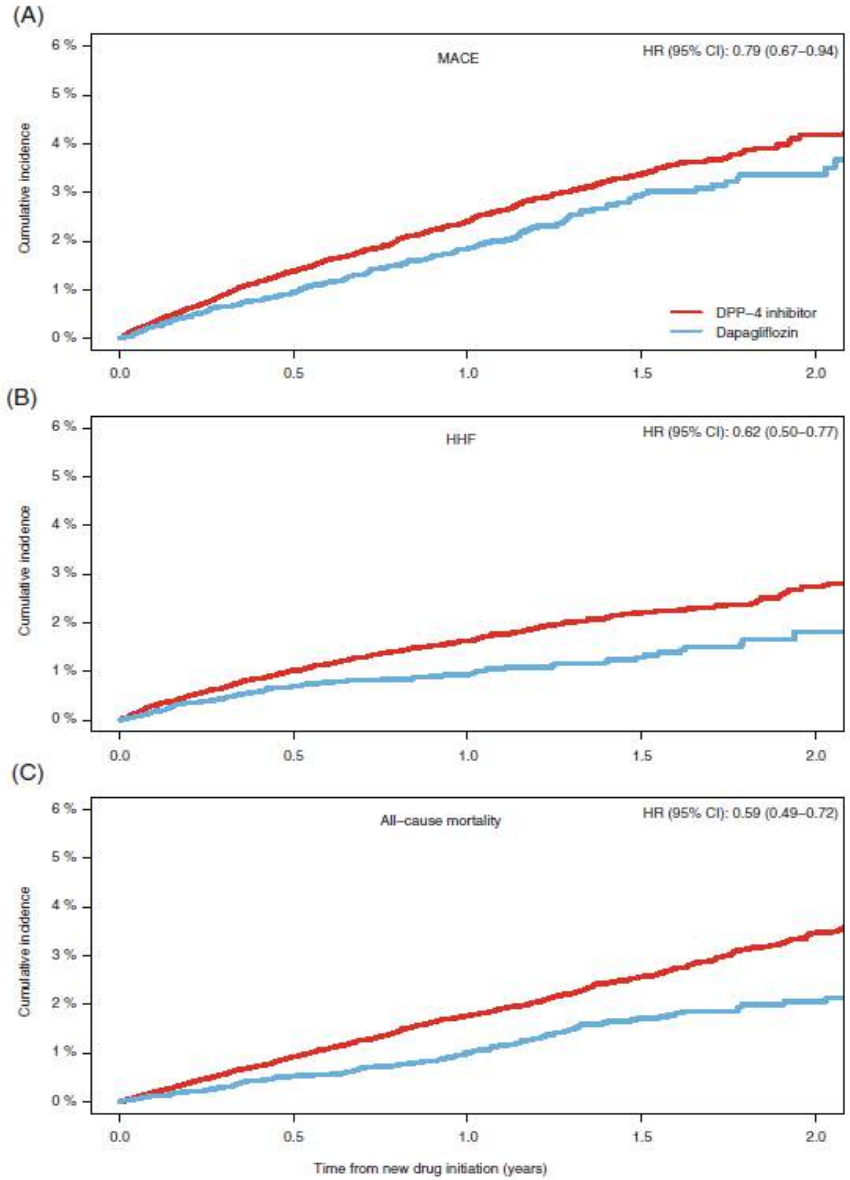
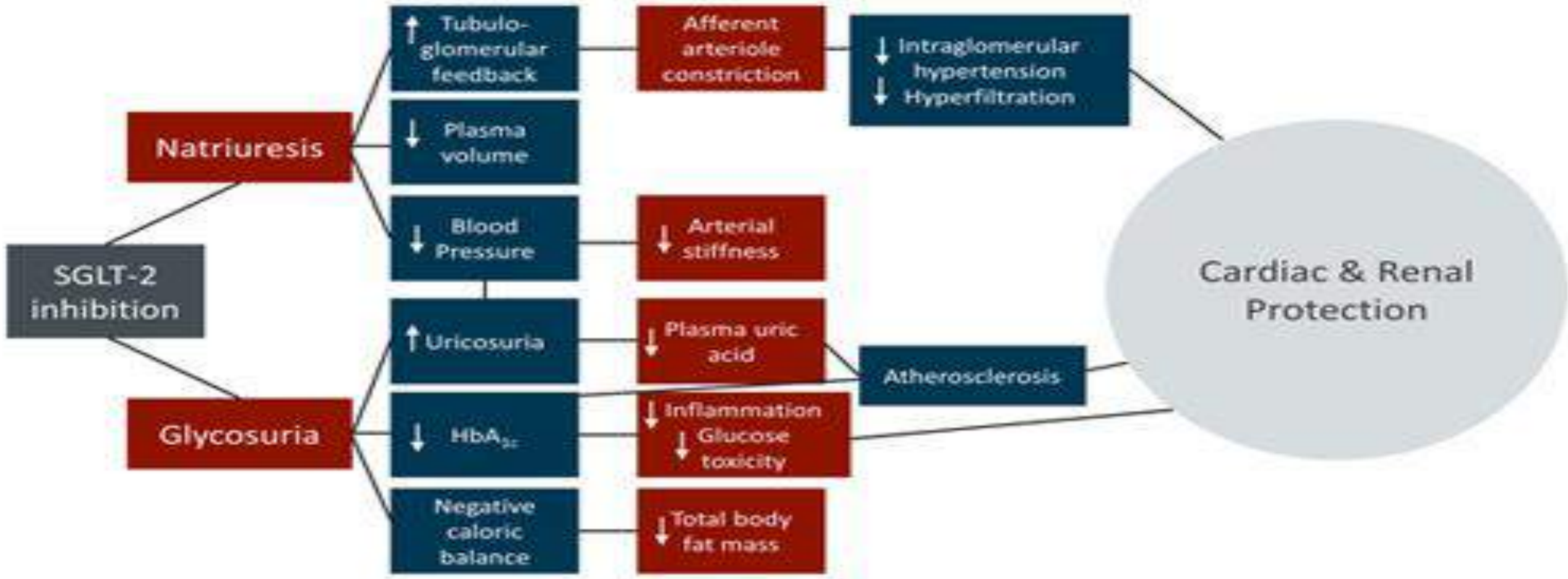


FIGURE 2 Pooled Kaplan–Meier curves from all 3 countries and HRs comparing propensity score-matched 1:3 groups of new users of dapagliflozin vs DPP-4 inhibitor treatment for MACE (A), HHF (B) and all-cause mortality (C) [Correction added on 18 September 2017 after first online publication: The label in Figure 2 (C) was previously incorrect and has been amended in this version]

SGLT2 inhibitörlerinin Kardiyovasküler Pleiotropik Etkileri



Rajasekeran H, et al. *Kidney Int*. 2016;89:524-526.

SGLT2 inhibitörleri ile yeni ortaya çıkan güvenlilik konuları
Alt ekstremite ampütasyonları

- **Empagliflozin**
- EMPA-REG OUTCOME® dahil olmak üzere bugüne kadar empagliflozin ile yapılmış olan tamamlanmış tüm Faz II ve III klinik çalışmaların birleşik analizi alt uzuv ampütasyonlarında artış olduğuna dair bir kanıt ortaya koymamıştır[1,2]

- **Canagliflozin**
- CANVAS ve CANVAS-R çalışmalarında alt uzuv ampütasyonu riskinde yaklaşık iki kat artış görülmesine dayalı olarak FDA Kara Kutu uyarısı vermiştir[3]

- **Dapagliflozin**
- Bugüne kadar dapagliflozin için yapılan analizlerde alt uzuv ampütasyonlarında bir artışa dair kanıt görülmemiştir[2]

- **EMA, canagliflozin ile görülen riskten ötürü bir önlem olarak, tüm SGLT2 inhibitörlerinin KÜB'lerini güncellemiştir[2]**

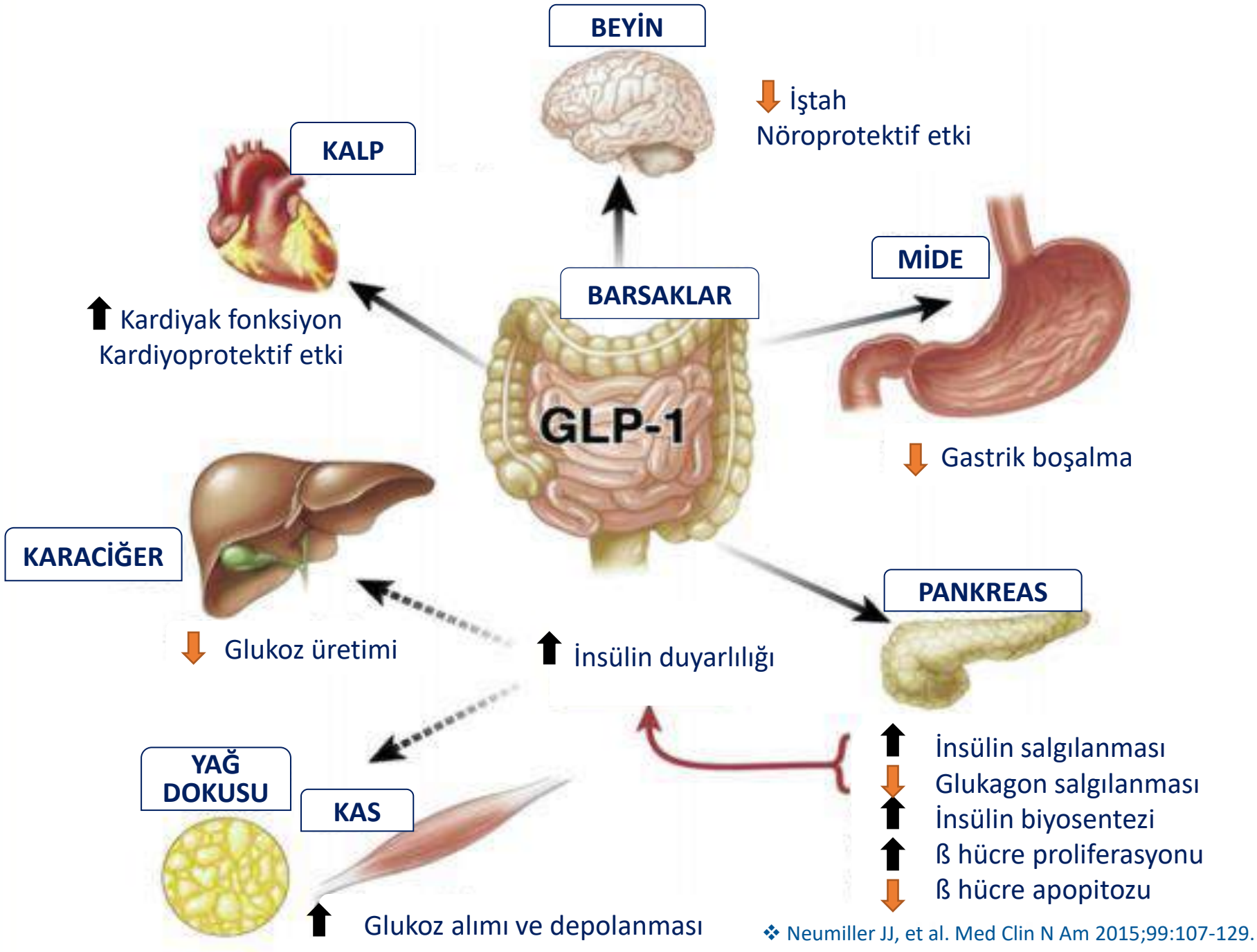
SGLT2 inhibitörleri arasında güvenlilik profili yorumlanırken dikkatli olunmalıdır.
Klinik çalışmalarda advers olayların kaydedilmesi için kullanılan metodolojik yaklaşım bileşikler arasında farklılık gösterebilir.
Ayrıca, reçetelenme hacimleri farklı olabileceğinden, pazarlama-sonrası güvenlilik bilgileri de dikkatle yorumlanmalıdır.

ADA 2017

SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High

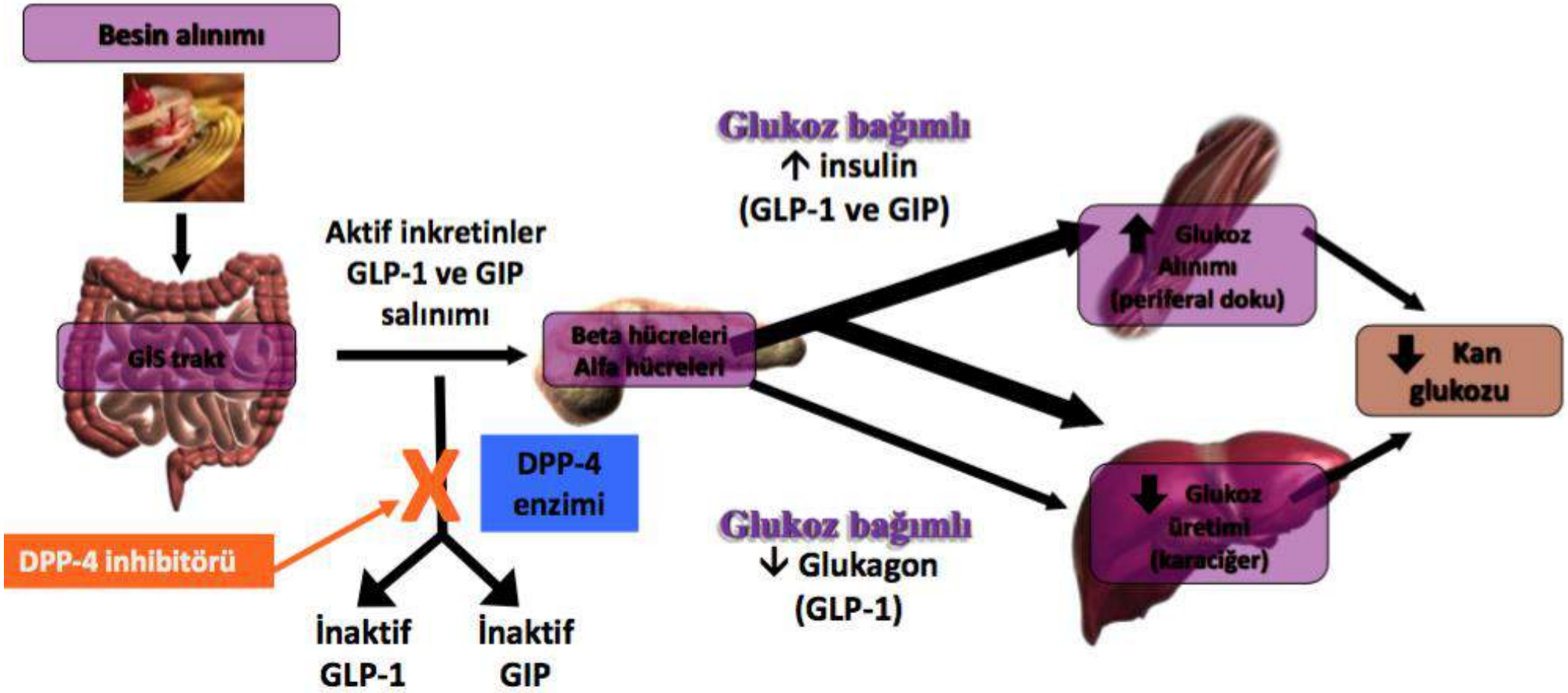
ADA 2018

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol

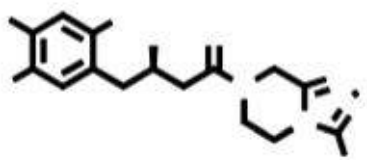
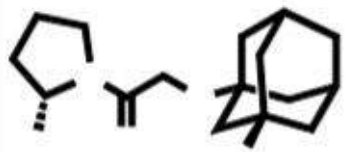
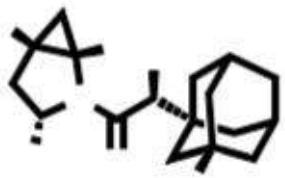
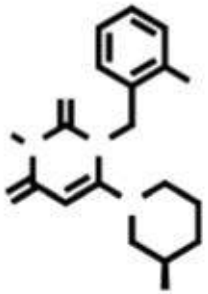


❖ Neumiller JJ, et al. Med Clin N Am 2015;99:107-129.

DPP4 İnhibitörleri



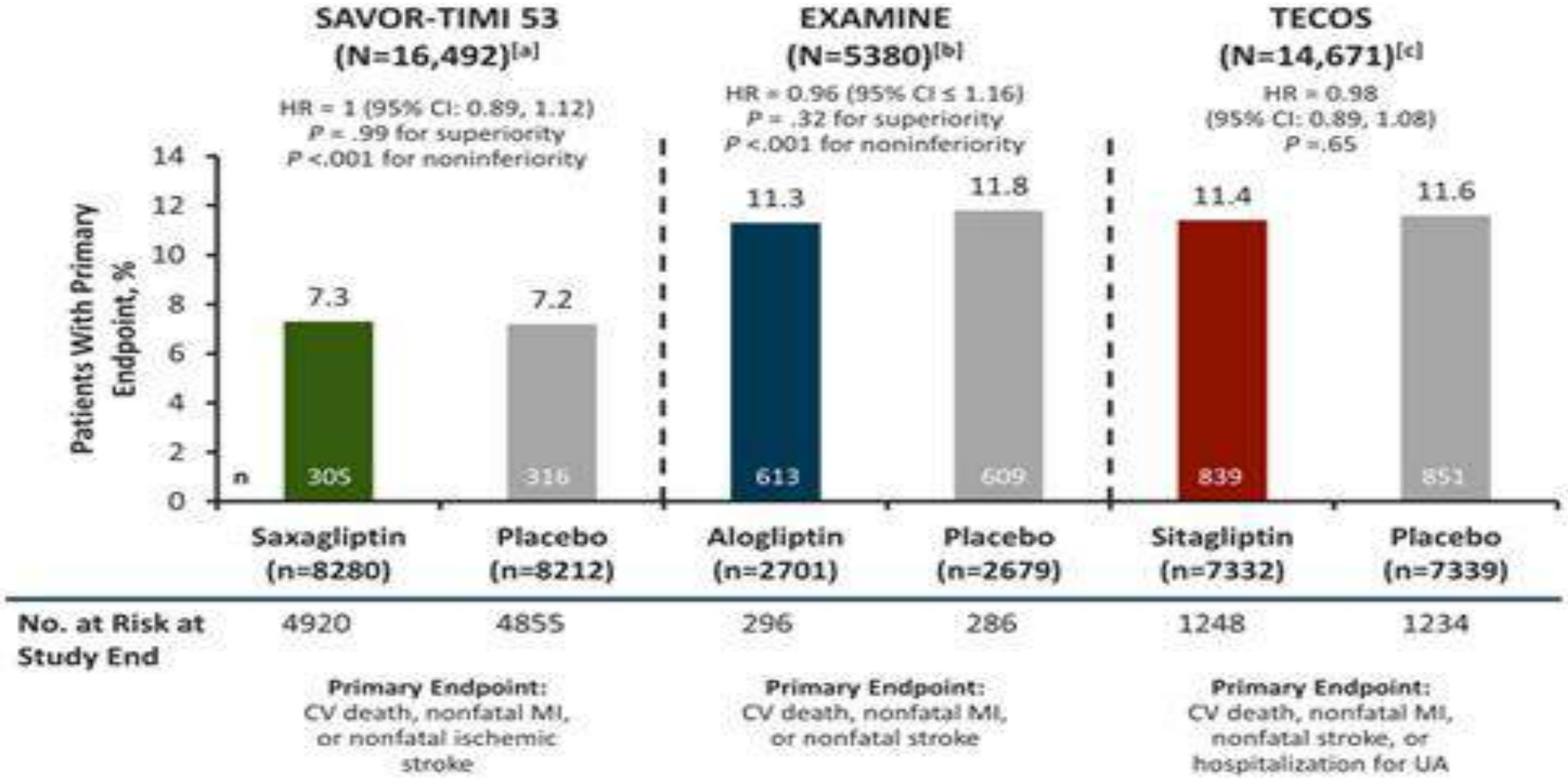
DPP-4 İnhibitörleri Molekül Yapıları ve Farmakolojik Özellikleri Bakımından Birbirlerinden Farklıdır

Kimyasal Sınıf	β-Fenetilaminler[1]	Siyanopirolidinler		Aminopiperidin[8]
Jenerik İsim	**Sitagliptin[2,3]**	**Vildagliptin[2,4,5]**	**Saksagliptin[2,6,7]**	**Alogliptin[9,10]**
Molekül Yapısı				
DPP-4 İnhibitör Aktivitesi (IC_{50})	9.96 ± 1.03 nM	5.28 ± 1.04 nM	3.37 ± 0.90 nM	6.9 ± 1.5 nM
Yarı-ömür	**12.4 saat**	**~2–3 saat**	**2.5 saat (ana ilaç)** **3.1 saat (metabolit)**	**12.4–21.4 saat**

DPP-4=dipeptidil peptidaz-4.

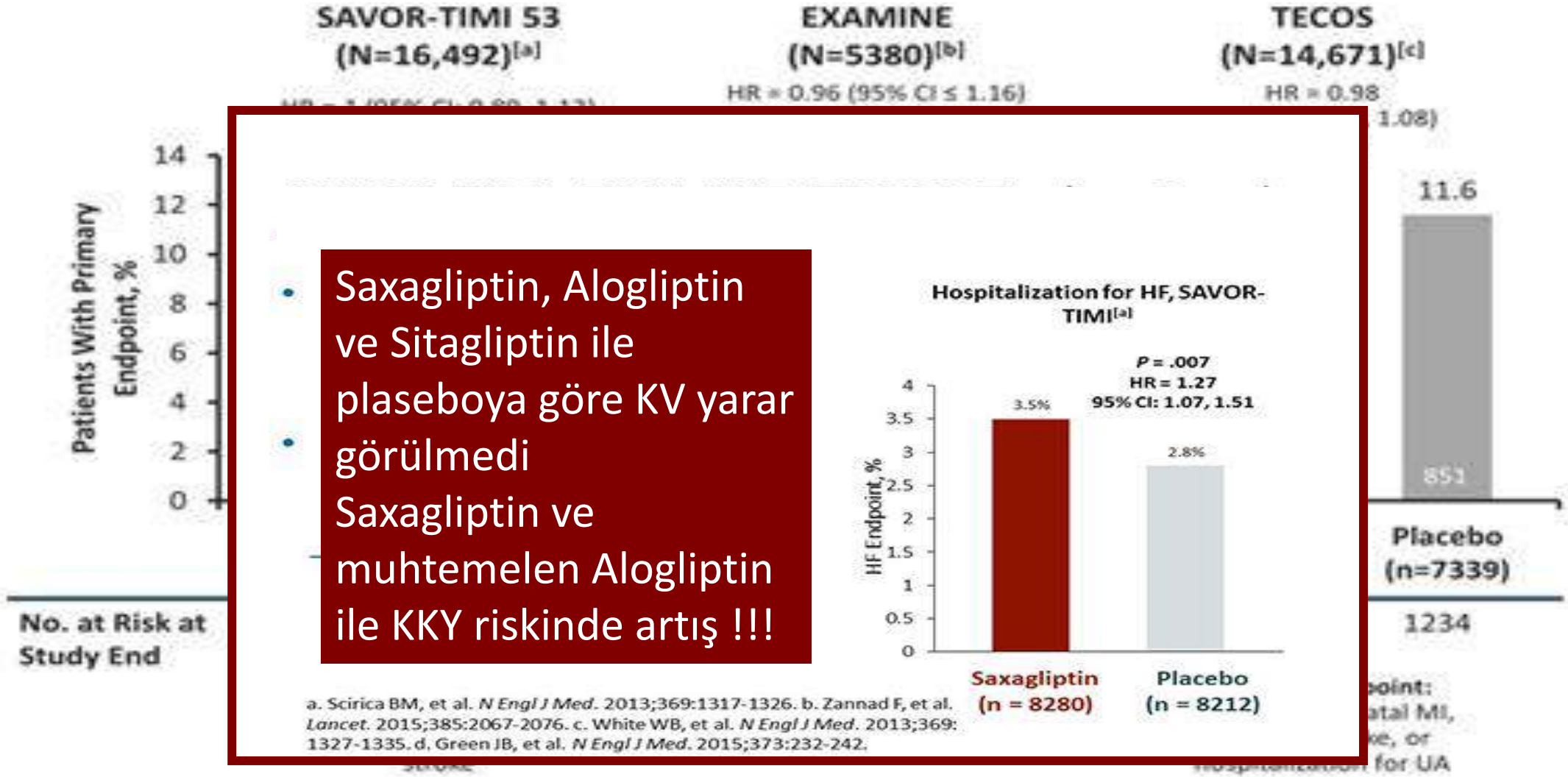
Chem. 2005;48(1):141–151. **2.** Matsuyama-Yokono A, et al. *Biochem Pharmacol*. 2008;76(1):98–107. **3.** JANUVIA EU-SPC 2010. **4.** Villhauer EB, et al. *J Med Chem.* 2003;46(13):2774–2789. **5.** Galvus EU-SPC 2010. **6.** Augeri DJ, et al. *J Med Chem.* 2005;48(15):5025–5037. **7.** Onglyza EU-SPC 2010. **8.** Feng J ,et al. *J Med Chem*. 2007;50(10):2297–2300. **9.** Lee B, et al. *Eur J Pharmacol*. 2008;589(1–3):306–314. **10.** Christopher R, et al. *Clin Ther*. 2008;30(3):513–527.

DPP4 İnhibitörleri Kardiyovasküler Güvenilirliğini Kanıtladı



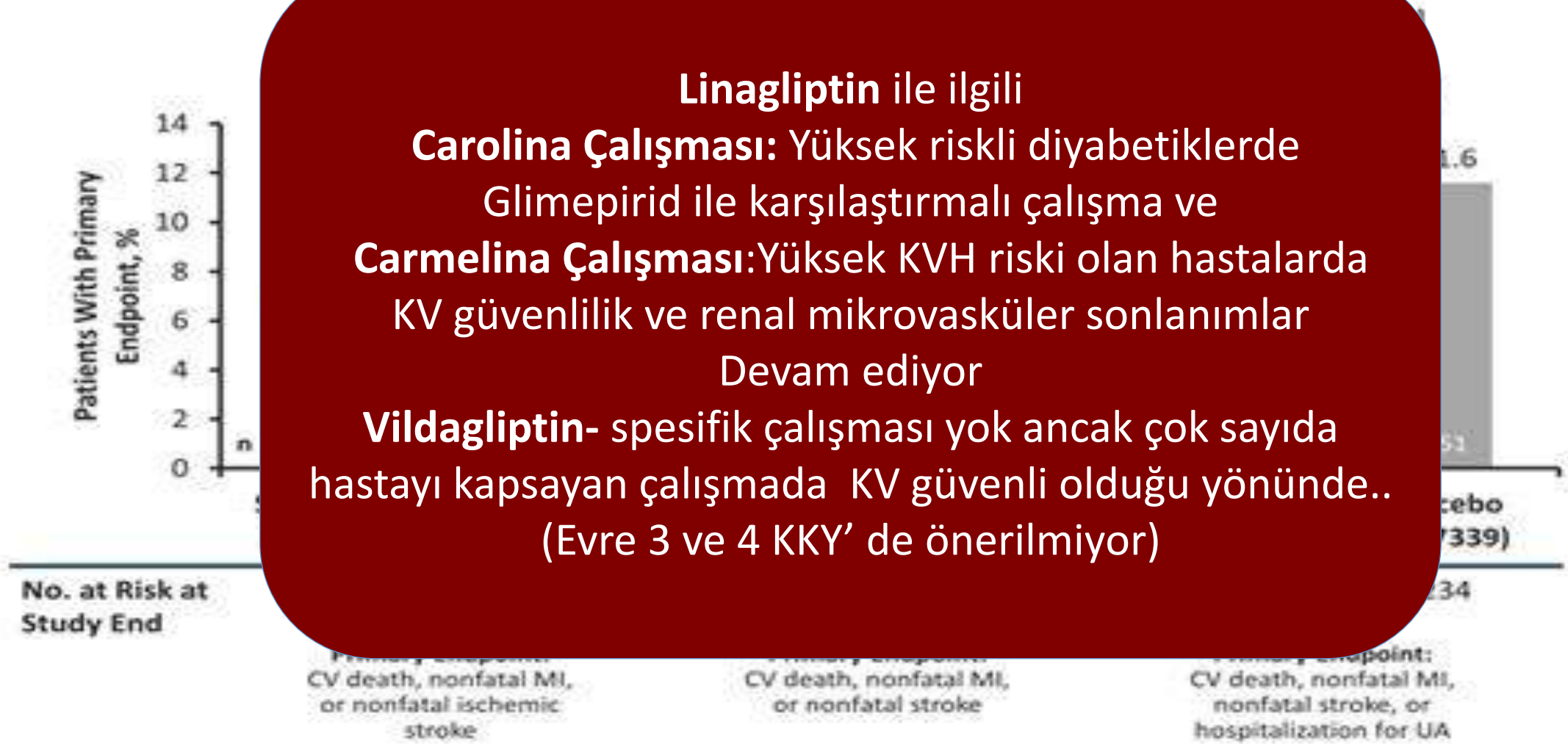
a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

DPP4 İnhibitörleri Kardiyovasküler Güvenilirliğini Kanıtladı



a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

DPP4 İnhibitörleri Kardiyovasküler Güvenilirliğini Kanıtladı



Linagliptin ile ilgili
Carolina Çalışması: Yüksek riskli diyabetiklerde Glimepirid ile karşılaştırmalı çalışma ve
Carmelina Çalışması:Yüksek KVH riski olan hastalarda KV güvenlilik ve renal mikrovasküler sonlanımlar Devam ediyor
Vildagliptin- spesifik çalışması yok ancak çok sayıda hastayı kapsayan çalışmada KV güvenli olduğu yönünde..
(Evre 3 ve 4 KKY' de önerilmiyor)

a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

ADA 2017

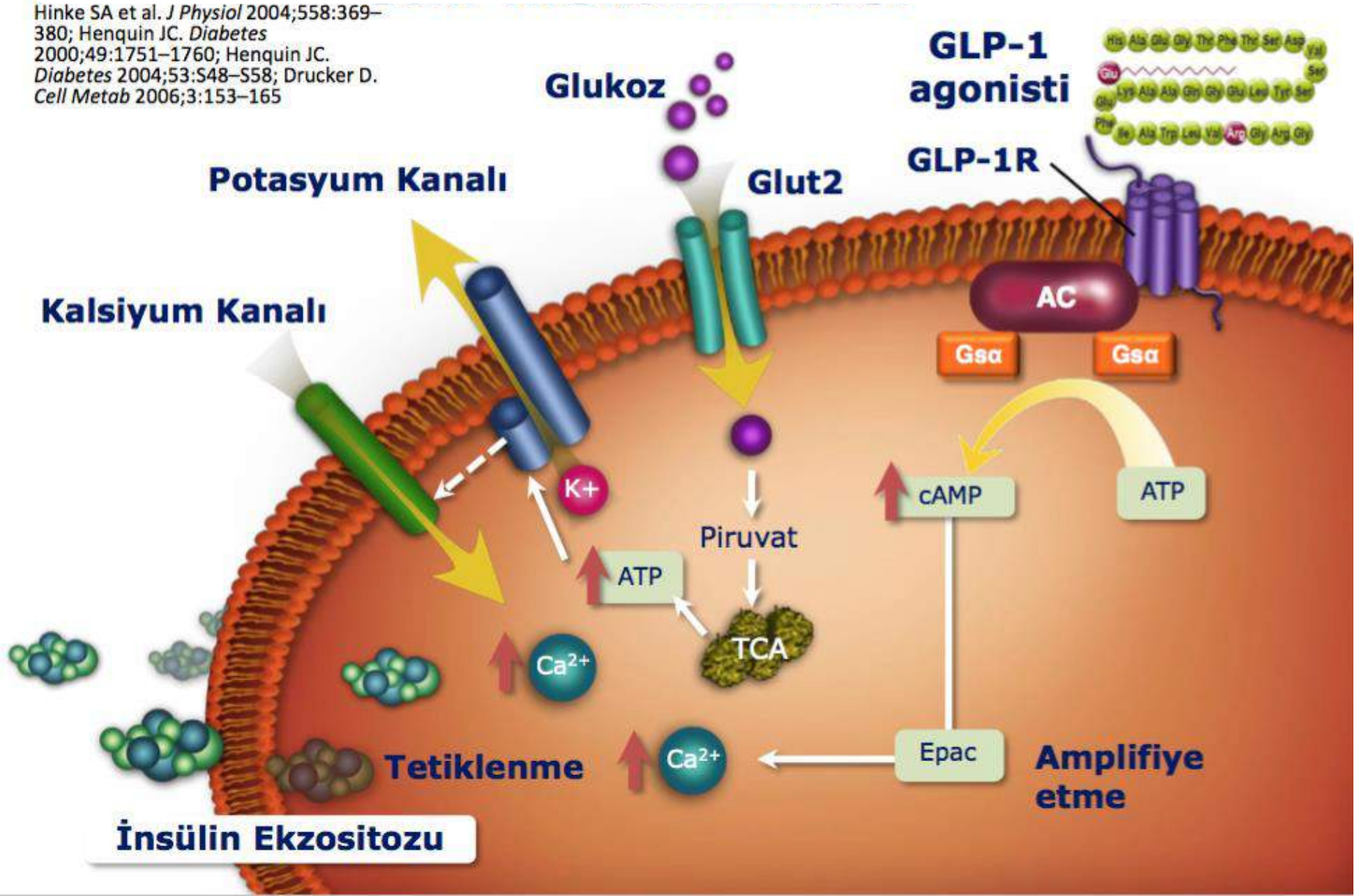
• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• Rare hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin; ? alogliptin)	High

ADA 2018

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain

GLP-1 Analogları

- Hinke SA et al. *J Physiol* 2004;558:369–380; Henquin JC. *Diabetes* 2000;49:1751–1760; Henquin JC. *Diabetes* 2004;53:S48–S58; Drucker D. *Cell Metab* 2006;3:153–165

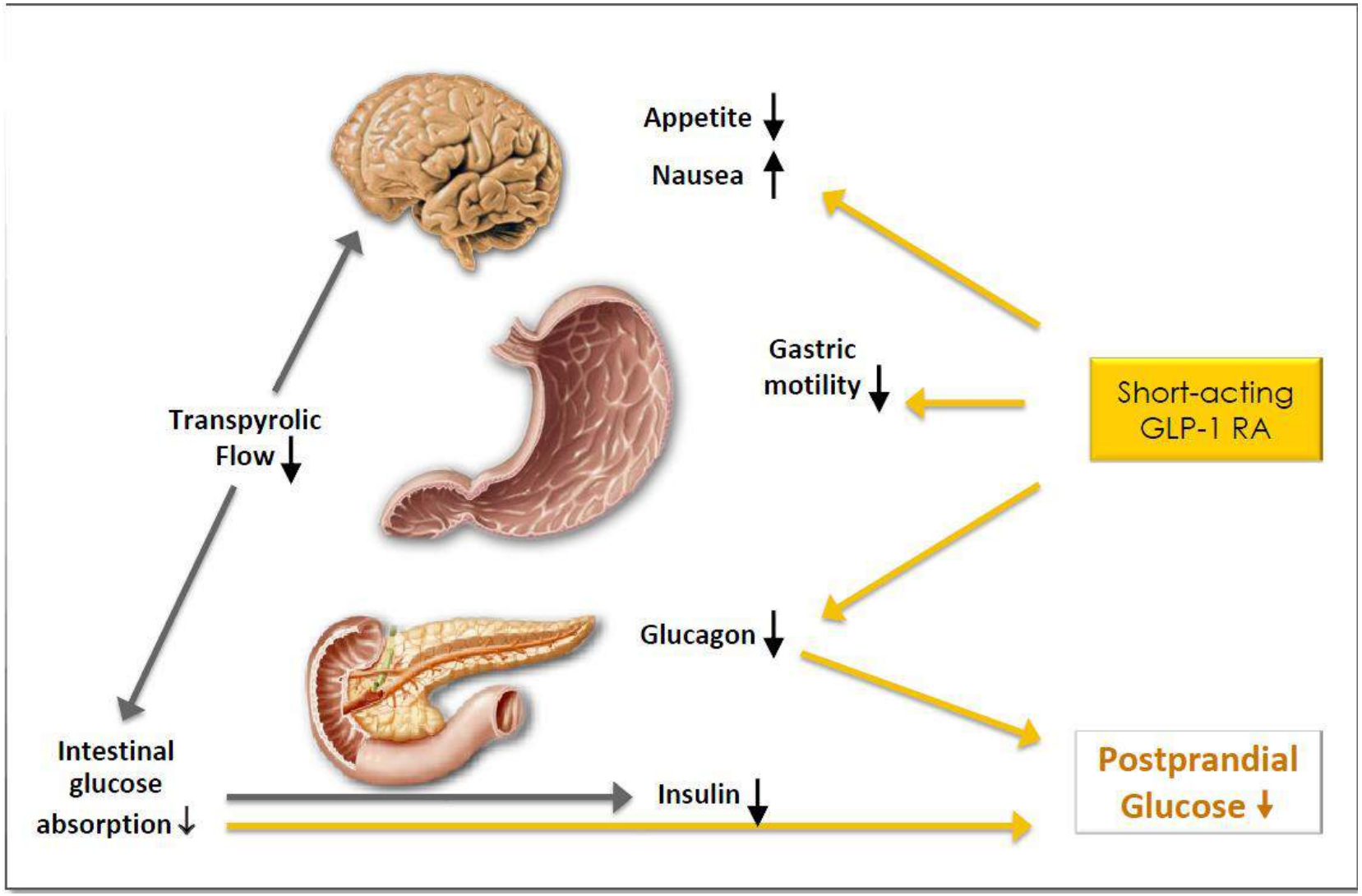


Glp-1 Analogları

Etken madde	Yarı ömür	T_{max}
Eksenatid	2.4 saat	2 saat
Liksisenatid	2–5 saat	1.25–2.25 saat
Liraglutid	13 saat	8–12 saat
Dulaglutid	90 saat (3.75 gün)	24–48 saat (1–2 gün)
Albiglutid	6–7 gün	3–5 gün
Semaglutid	155–184 saat (~7 gün)	24–36 saat (1–1.5 gün)
Eksenatide LAR	7–14 gün	6–7 hafta

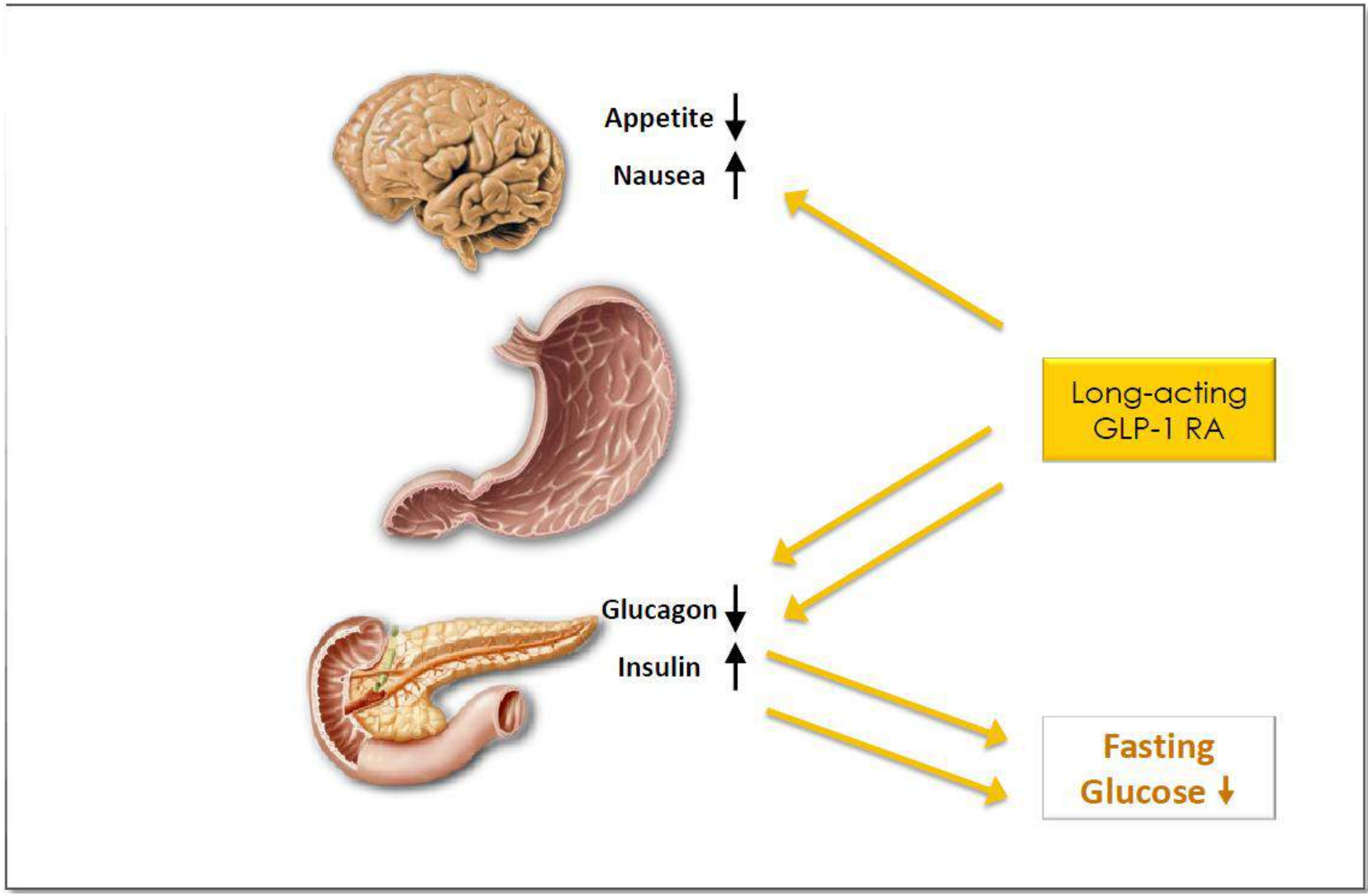
- Barrington et al. Diabetes Obes Metab 2011;13:434–438; Bush et al. Diabetes Obes Metab 2009;11:498–505.
- Matthews et al. J Clin Endo Metab 2008;93:4810–4817; Marbury T et al. Diabetes 2014;63(suppl 1):A260. Abst 1010-P.
- Kapitza C et al. J Clin Pharm 2015;55:497–504; Fineman et al. Clin Pharmacokinet 2011;50:65–74.

Kısa Etkili Glp-1 Analogları



❖ Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

Uzun Etkili Glp-1 Analogları



❖ Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

Kardiyovasküler Güvenlik

Table 2—Available GLP-1 analogs

Drug	Dosing	Use in renal impairment	Cardiovascular outcome trials
Exenatide	10 μg b.i.d.	- CrCl 30–50 mL/min (caution when escalating dose) - CrCl < 30 mL/min (avoid)	None
Exenatide QR	2 mg weekly	- CrCl 30–50 mL/min (caution) - CrCl 30 mL/min (avoid)	EXSCEL, *n* = 14,000: - June 2010–April 2018 - Inclusion criteria: HbA_{1c} ≥6.5 and ≤10.0%, age ≥18 years, and one of the following: *1*) Treatment with 0–3 oral antihyperglycemic agents and *2*) insulin therapy either alone or in combination with up to two oral agents - Primary outcome: time to first confirmed CV event in the primary composite of CV death, nonfatal MI, or nonfatal stroke
Liraglutide	1.2 mg OD 1.8 mg OD	- Mild–severe impairment - No dose adjustments (use with caution)	LEADER, *n* = 9,340: - August 2010–November 2015 - Inclusion criteria: ≥50 years old and concomitant CV, cerebrovascular, or peripheral vascular disease or chronic renal failure or chronic heart failure; ≥60 years old and other specified risk factors of vascular disease - HbA_{1c} ≥7%, age ≥50 years - Primary outcome: time from randomization to first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke
Lixisenatide	10 μg OD 20 μg OD	- eGFR 30–50 mL/min · 1.73 m^2 (caution) - eGFR <30 mL/min · 1.73 m^2 (avoid)	ELIXA, *n* = 6,000: - June 2010–February 2015 - Median follow-up 2 years - Inclusion criteria: patients with spontaneous ACS admitted to acute care facility within 180 days after ACS and prior to screening - HbA_{1c} 5.5–11%, age ≥30 years - Primary outcome: composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA
Dulaglutide	0.75 mg weekly 1.5 mg weekly	- No dose adjustments - Caution during initiation and dose escalation	REWIND, *n* = 9,622: - July 2011–April 2019 - Inclusion criteria: ≥50 years old with established clinical vascular disease, ≥55 years and subclinical vascular disease, or ≥60 years and at least ≥2 CV risk factors - HbA_{1c} ≤9.5%, age ≥50 years - Primary outcome: time to first occurrence of CV death, nonfatal MI, or nonfatal stroke (composite CV outcome)
Albiglutide	30 mg weekly 50 mg weekly	- No dose adjustments - Caution during initiation and dose escalation	None

❖ Wilding JPH, Rajeev SP, DeFronzo RA. Diabetes Care 2016;39 Suppl 2:S154-64.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

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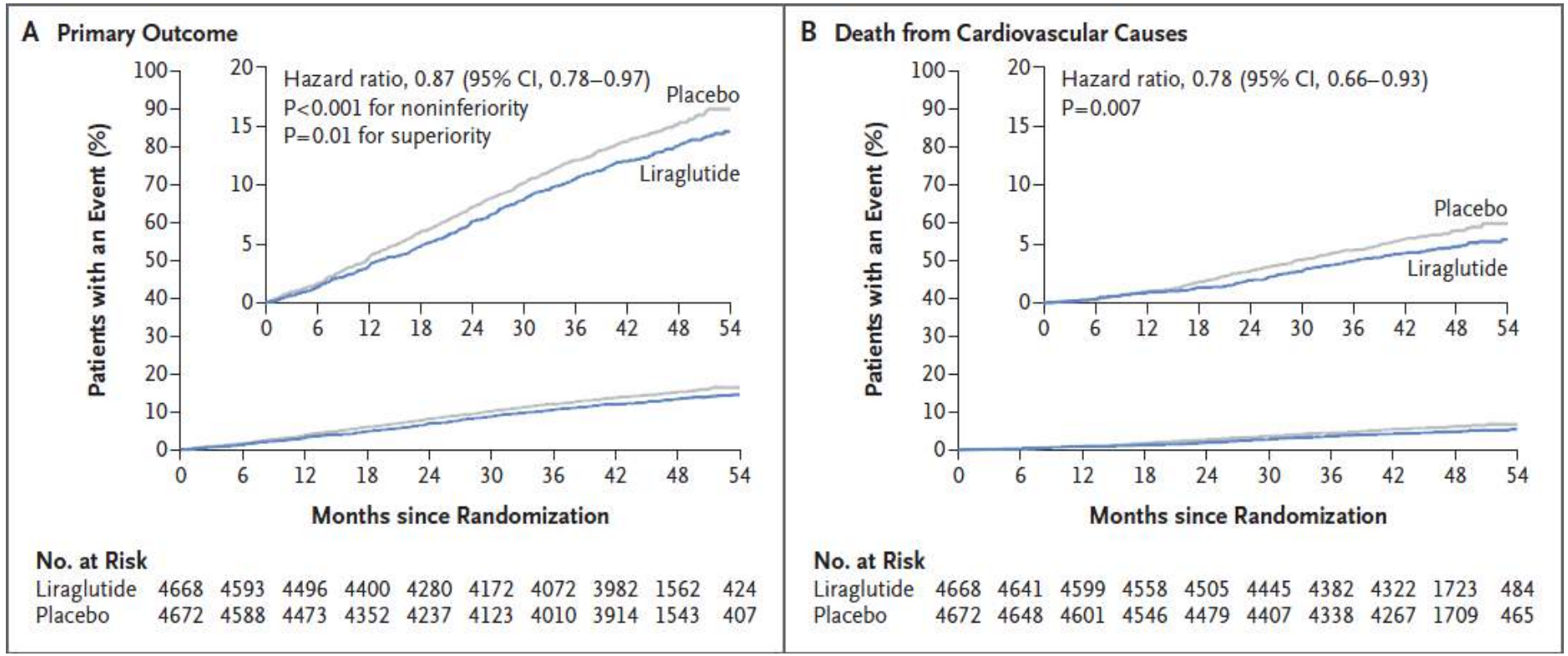

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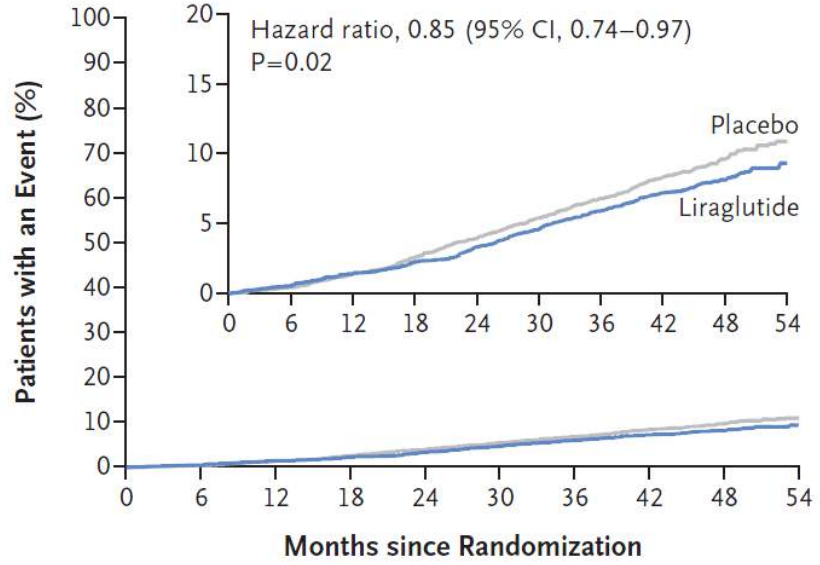
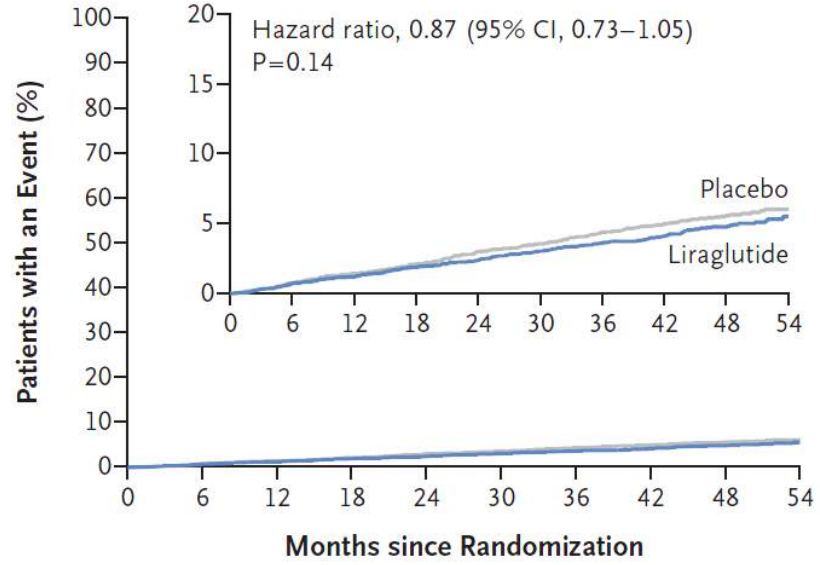
E Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F Hospitalization for Heart Failure

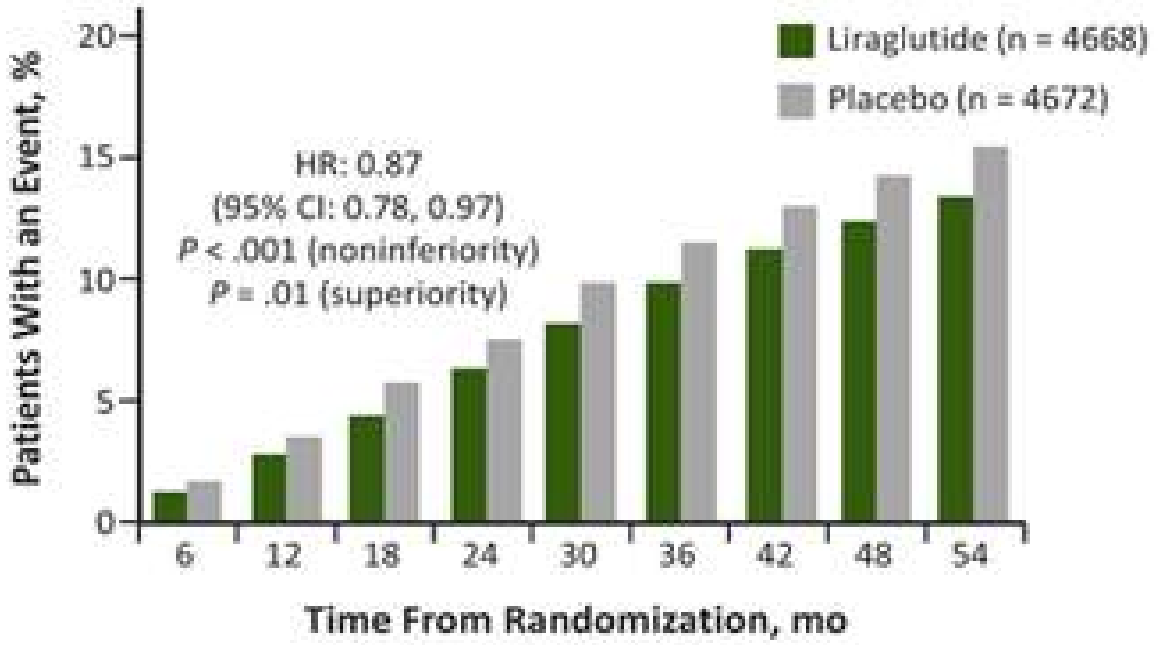


No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

LEADER: Liraglutide

Primary Outcome:

- CV death, MI, stroke, or hospitalization for UA



No. at Risk									
Liraglutide	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4588	4473	4352	4237	4123	4010	3914	1543	407

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

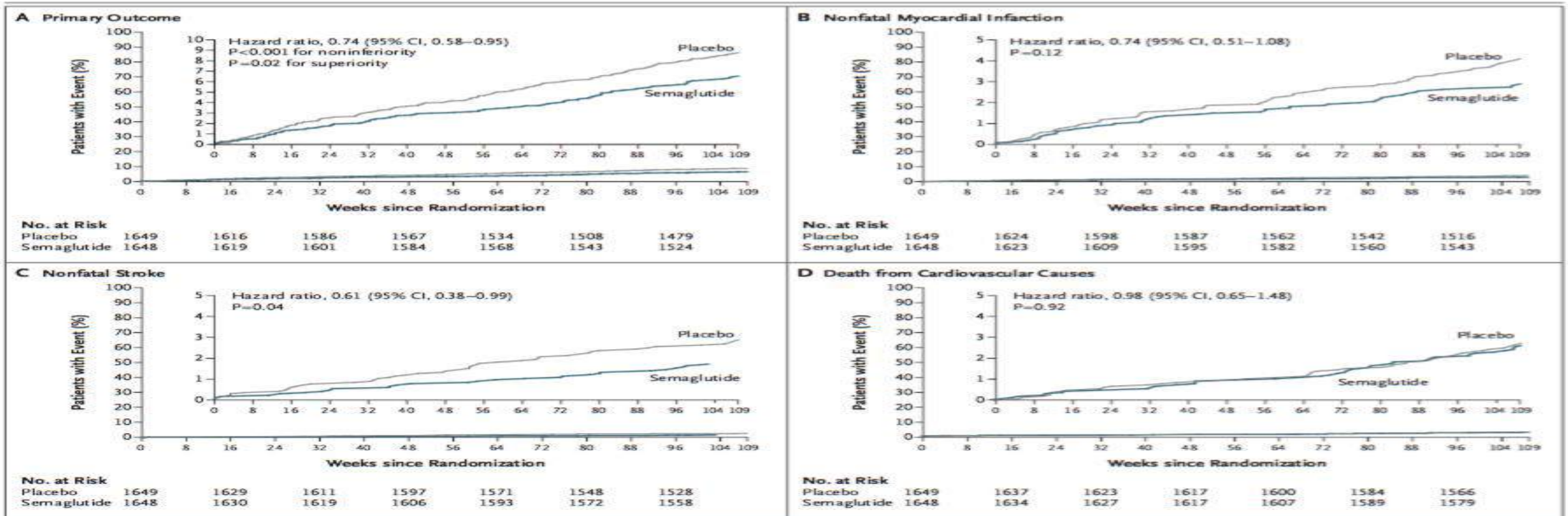


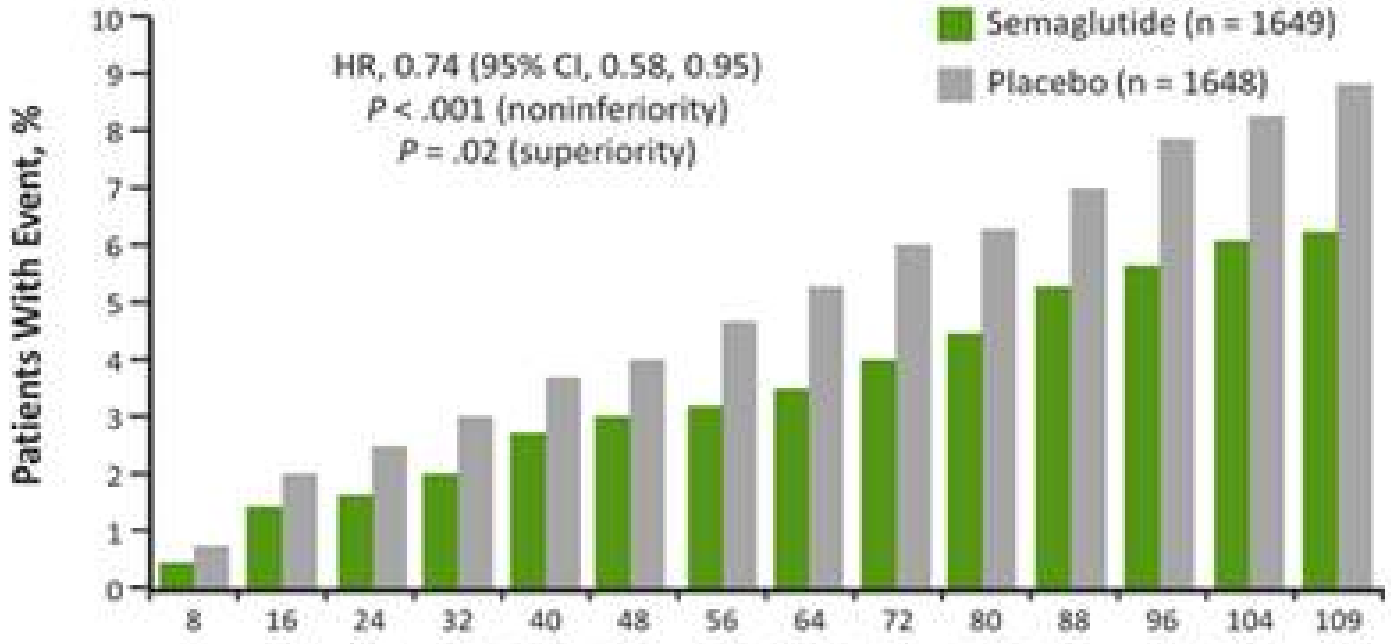
Figure 1. Cardiovascular Outcomes.

Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y axis.

SUSTAIN-6: Semaglutide*

Primary Outcome:

- First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke



No. at Risk							
Semaglutide	1648	1619	1601	1584	1568	1543	1524
Placebo	1649	1616	1586	1567	1534	1508	1479

*FDA has not yet approved this medication for use.

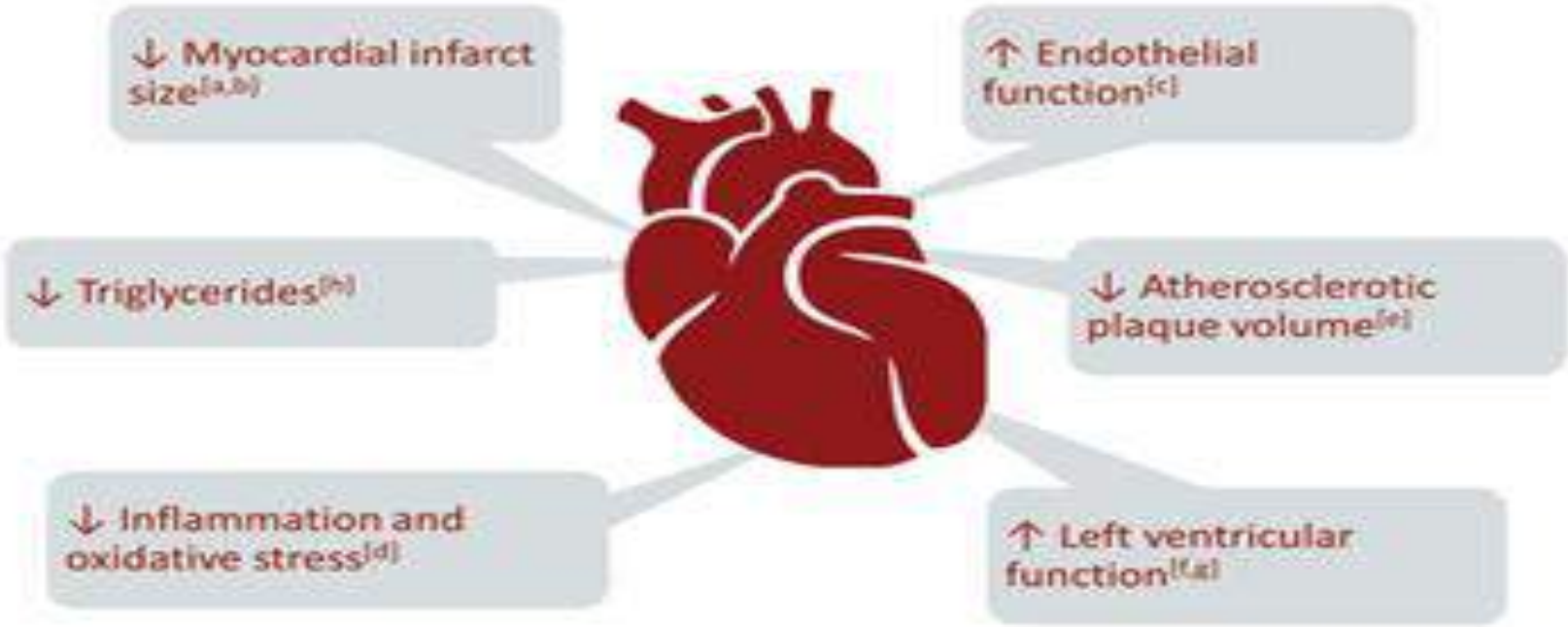
Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

ELIXA: Primer sonlanım: KV ölüm, nonfatal MI, nonfatal inme, USAP için hospitalizasyon

Subgroup interactions were analyzed, but none were significant.

Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.

GLP1 Reseptör Agonistlerinin Kardiyovasküler Pleiotropik Etkileri



a. Ye Y, et al. *Am J Physiol Heart Circ Physiol*. 2010;298:H1454-H465; b. Hocher B, et al. *Int J Cardiol*. 2013;167:87-93; c. van Poppel PC, et al. *Diabetes Care*. 2011;34:2072-2077; d. Kröller-Schön S, et al. *Cardiovasc Res*. 2012;96:140-149; e. Ta NN. et al. *J Cardiovasc Pharmacol*. 2011;58:157-166; f. Sauvé M, et al. *Diabetes*. 2010;59:1063-1073; g. Read PA, et al. *Circ Cardiovasc Imaging*. 2010;3:195-201; h. Matikainen et al. *Diabetologia*. 2006;49:2049-2057.

ADA 2017

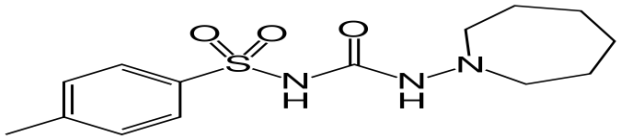
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER) (30)	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High

ADA 2018

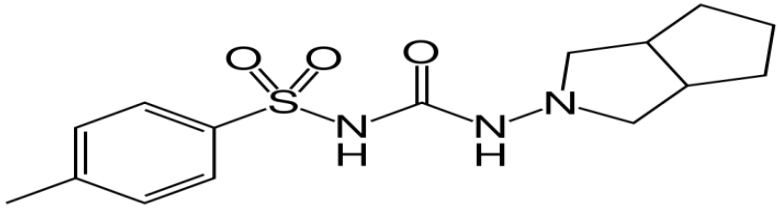
	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk

İnsülin salgılatıcılar

- 1. jenerasyon SUler
  - Asetohekzamid
  - Klorpropamid
  - Tolbutamid
  - Tolazamid

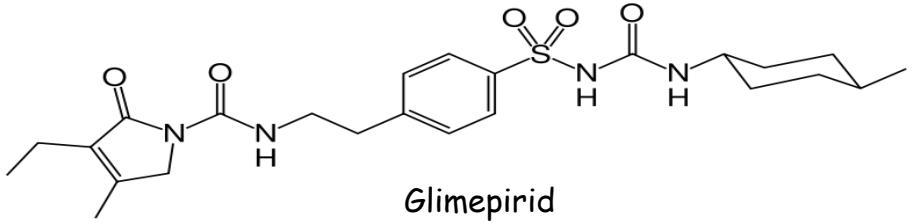


Tolazamid



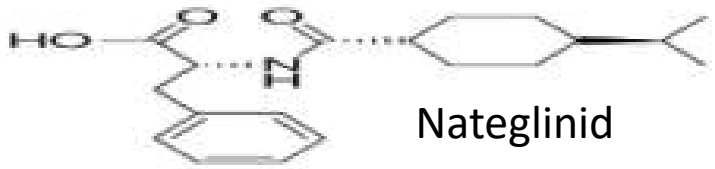
Gliklazid

- 2. jenerasyon SUler
  - Glipizid
  - Gliklazid
  - Glibenklamid (gliburid)
  - Glikuidon
  - Glibornurid
  - Glimepirid

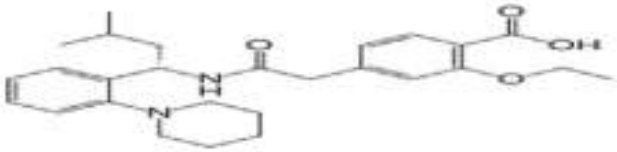


Glimepirid

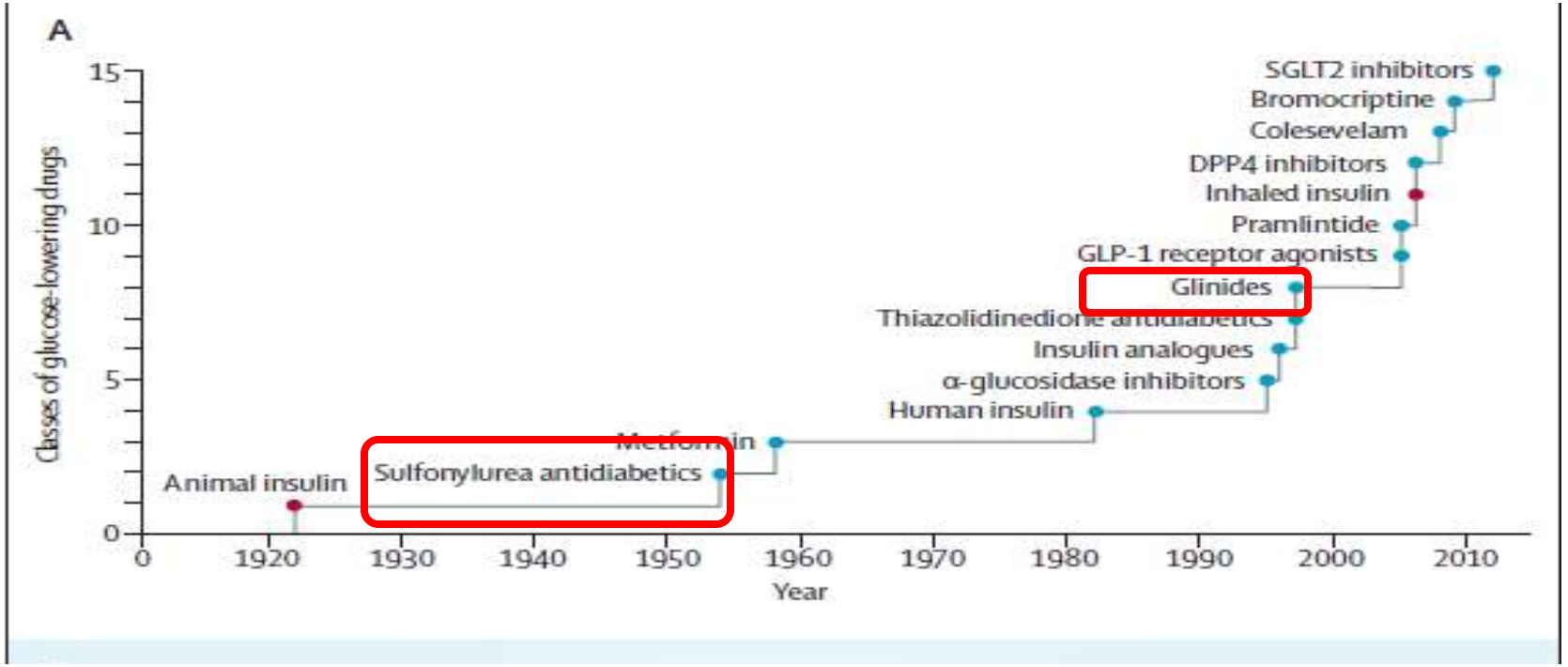
- Glinidler
  - Repaglinid
  - Nateglinid



Nateglinid



Repaglinid



SU'ler ilk kullanılan OAD'lerdir

1956 yılında ilk SU tolbutamid kullanıma girmiştir

1984 yılında 2. jenerasyon SU'ler (glibenklamid ve glipizid) USA'de kullanım onayı almıştır

1995 yılında da son SU glimepirid kullanım onayı almıştır

1988 yılında repaglinid ve 2001 yılında nateglinid kullanılmaya başlanmıştır

Lancet 2014; 383: 1068–83, Curr Diab Rep 2014; 14:473, Pharmacological Research 2016, 113: 636-674

- Ana etkileri: beta hücrelerinden insülin salınımını stimüle etmek
- Ekstrapankreatik etkileri:

  hepatik insülin klirensini azaltma

  glukagon sekresyonunu azaltma

  insülin sensitivitesini artırma (iskelet kası hücre kültürlerinde glibenklamid ve gliklazid)

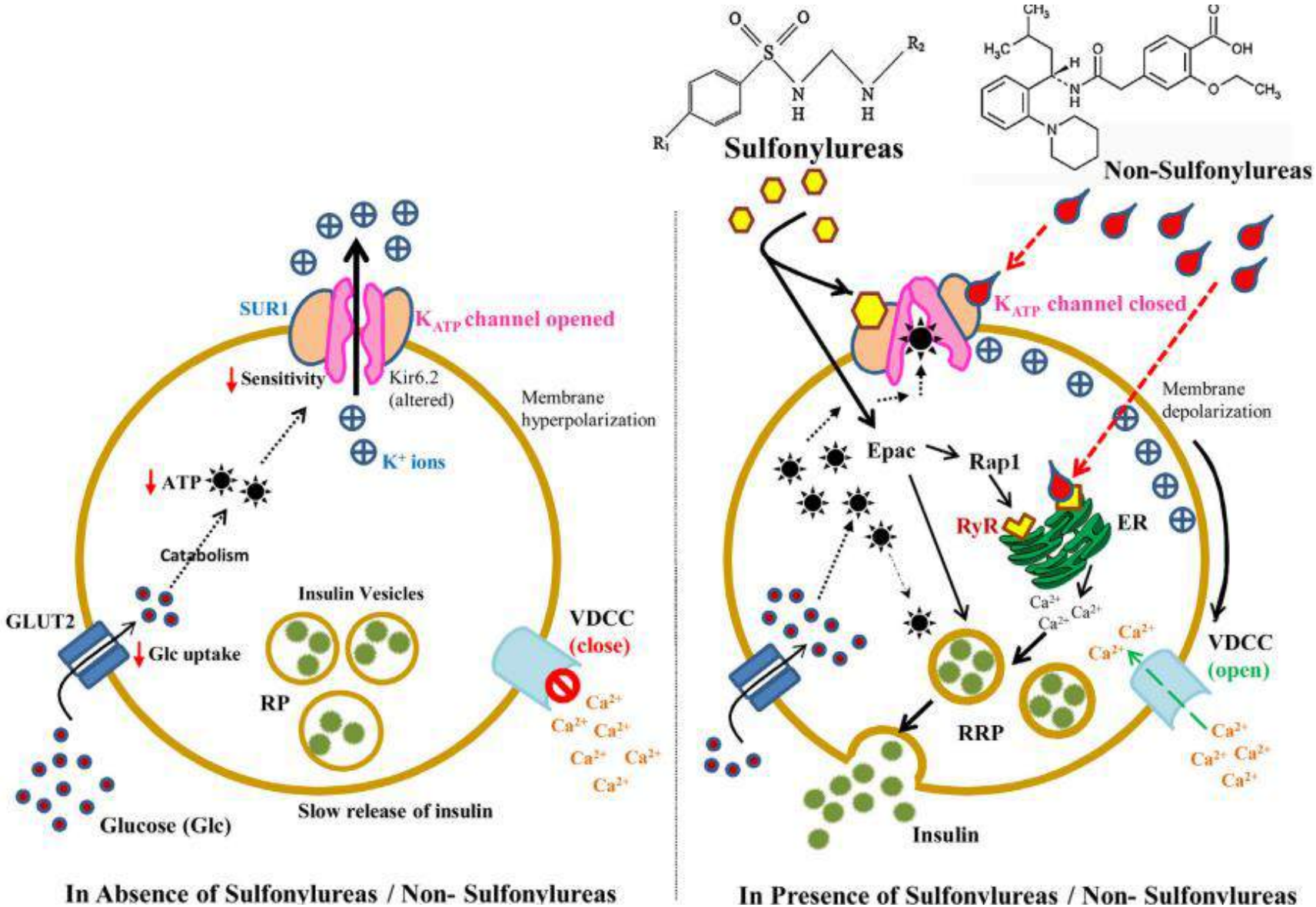
Curr Diab Rep 2014; 14:4

- ATP bağımlı K kanallarının 2 komponenti vardır

  Kir6.x ve SUR.x reseptörü

  - SUR1/Kir6.2: beta hücresi ve beyin
  - SUR2A/Kir6.2: kalp ve iskelet kası
  - SUR2B/Kir6.2: damar düz kası

- Gliklazid ve tolbutamid pankreatik beta hücre kanallarını bloke eder, glibenklamid üç kanalı (beta hücre, kalp ve düz kas) da bloke eder.



Pharmalogical Research 2016, 113: 636-674

SU- yan etkileri

Hipoglisemi(%2-5)

Kilo alma (2-5 kg)

SU-hipoglisemi

SU pankreastan glukoza bağlı olmayan bir mekanizma ile insülin sekresyonunu arttırır

Hipoglisemi beklenen bir durumdur

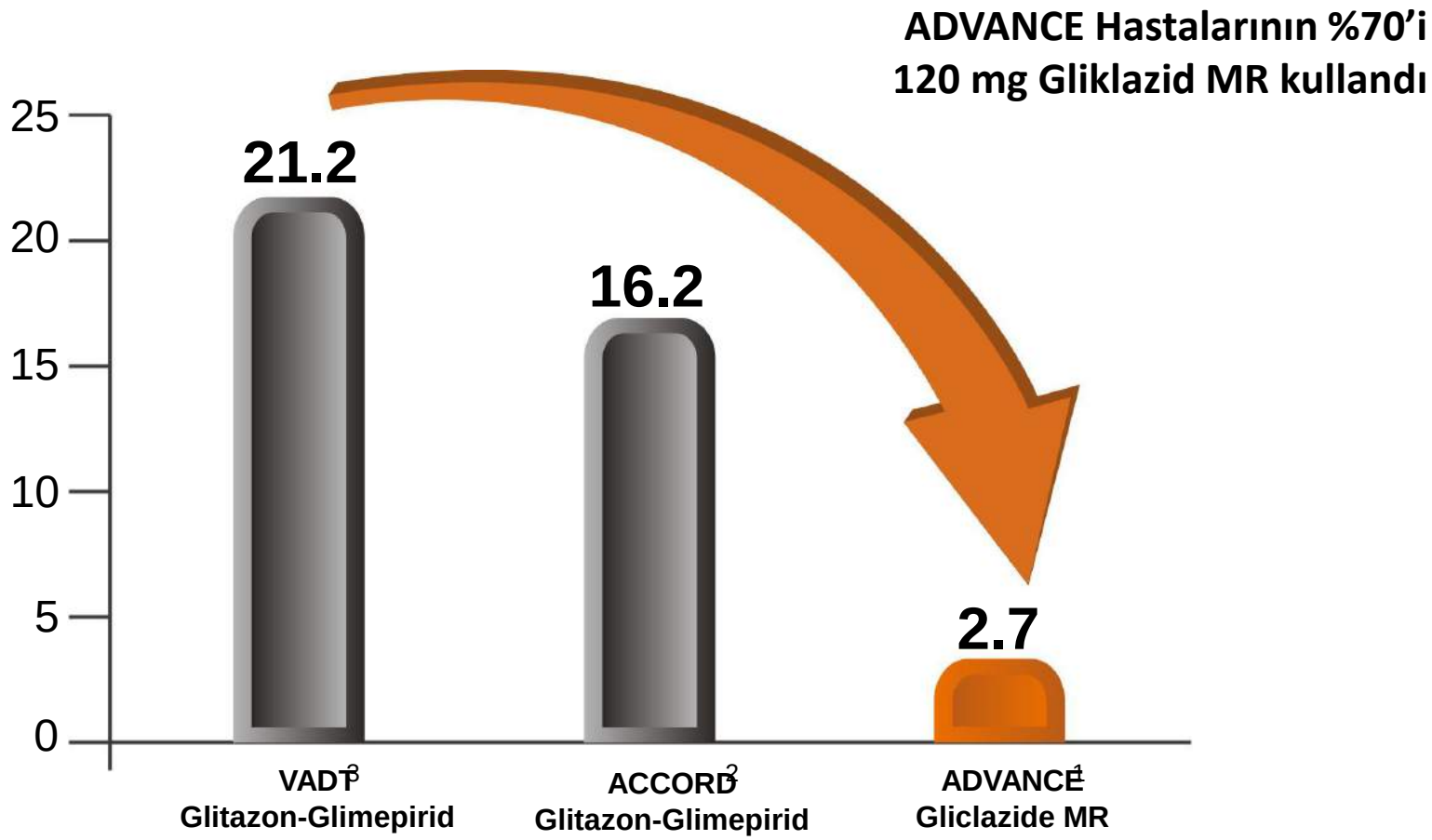
Hipoglisemi sıklığı tüm SU aynı değildir.

glibürid>glipizid>glimepirid>gliklazid

SU kullanan hastaların %10-20 si yılda bir veya daha fazla hafif-orta derecede, %0.5-1 ise ciddi hipoglisemi yaşar

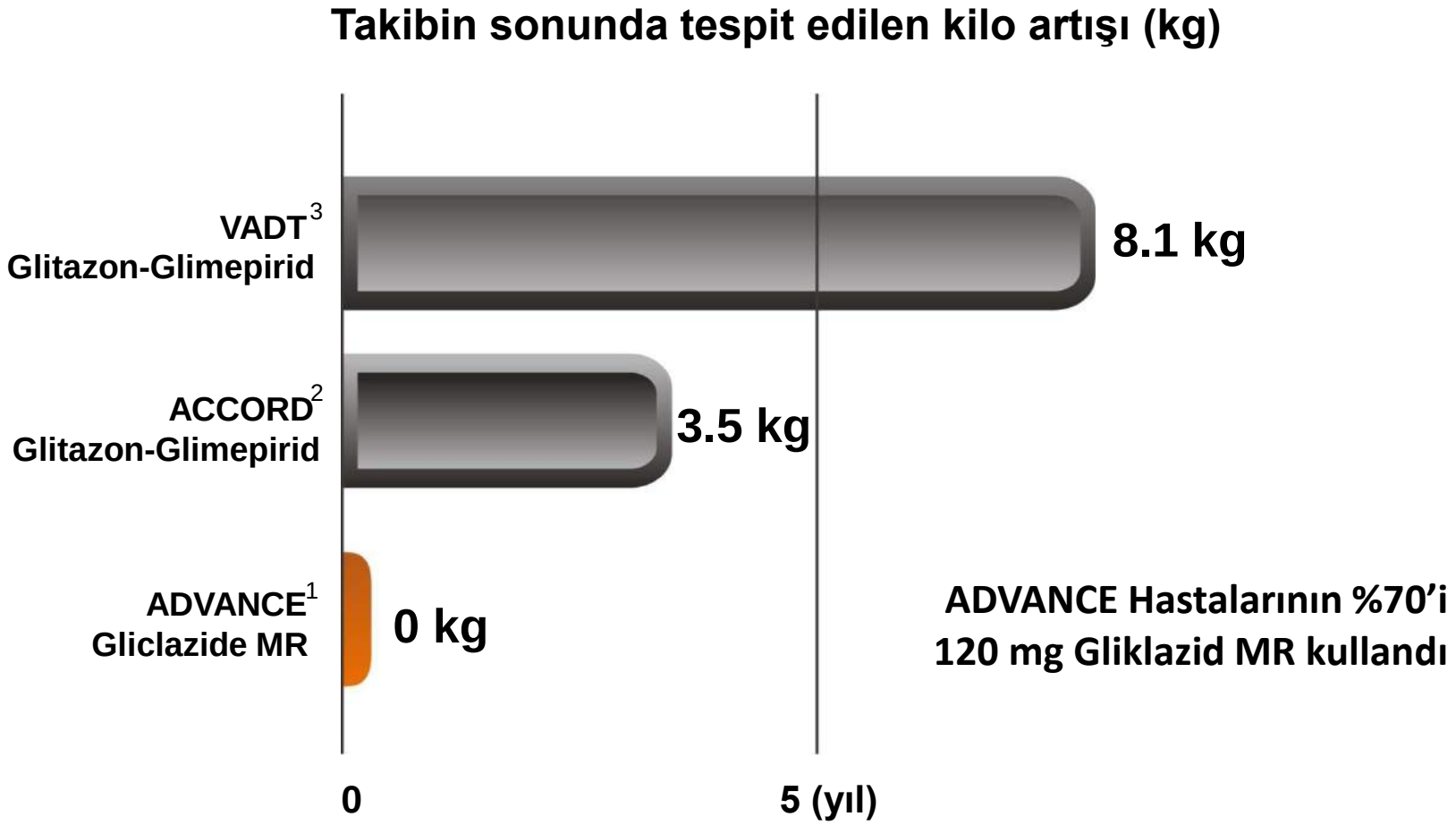
İnsülin ile tedavi edilenlerde SU ile tedavi edilenlere göre hipoglisemi daha sıktır (7.3% vs 0.8%)

ADVANCE/ACCORD/VADT
Ciddi hipoglisemi oranları



1. Advance Grubu. N Engl J Med 2008;358:2560-2572. 2. ACCORD Çalışması Grubu. N Engl J Med. 2008;358:2545-2559. 3. VADT Grubu. N Engl Med.2009;360:129-139.

ADVANCE/ACCORD/VADT
Kilo alımı

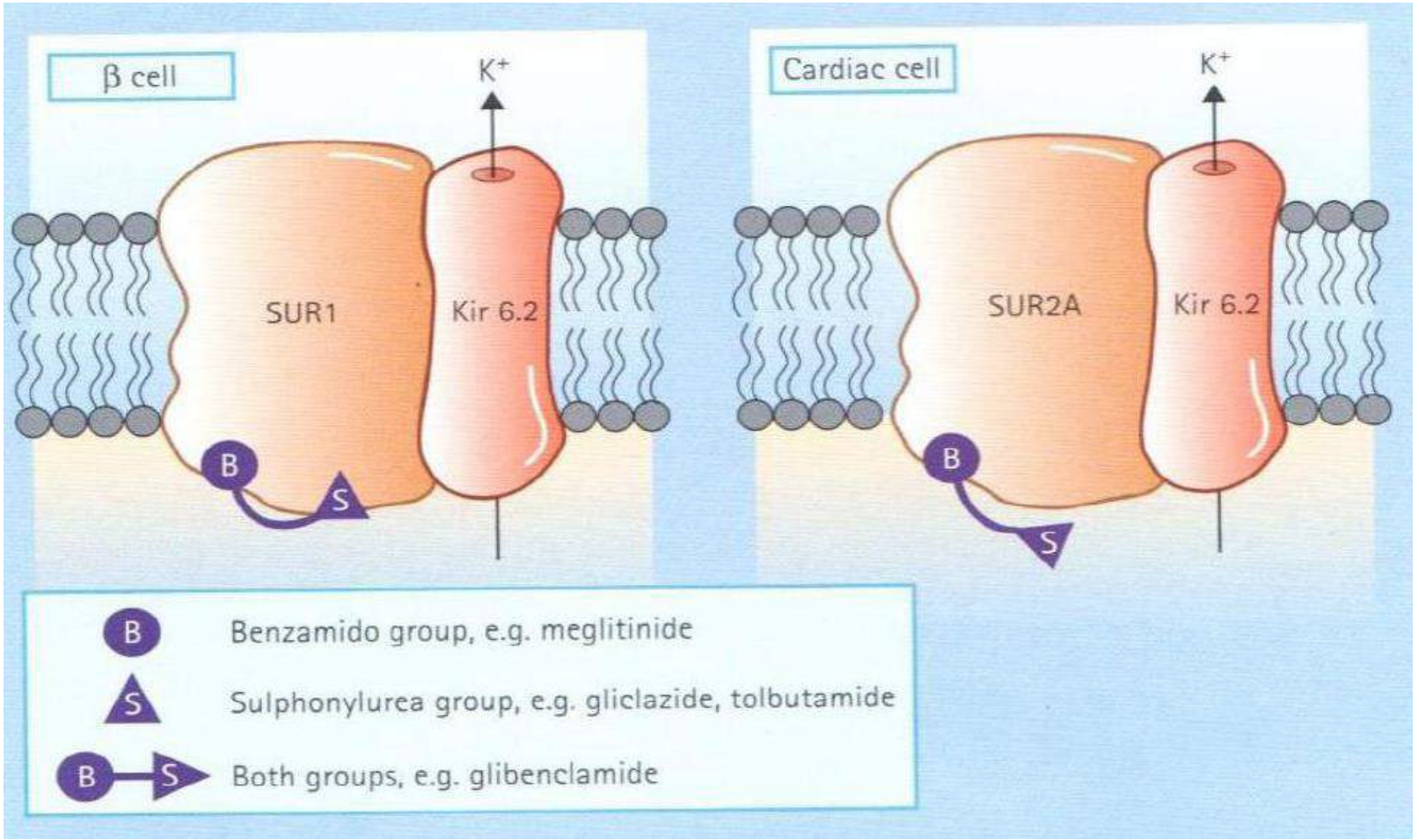


1. Advance Grubu. N Engl J Med 2008;358:2560-2572. 2. ACCORD Çalışması Grubu. N Engl J Med. 2008;358:2545-2559. 3. VADT Grubu. N Engl Med.2009;360:129-139.

SU lerin iskemik ön şartlanma(preconditioning) üzerindeki etkileri

- •SUR-1 ve SUR-2 etkilemesi eşit oranda olan SU ler özel durumlarda KV yanıtı etkileyebilir.
- •KATP kanalını kapatan bir ilacın KV yanıta zarar vereceği durum, geçici ya da uzamış iskemidir.
- •Etkiler daha büyük infarktüs alanı olarak ortaya çıkar
- •Glibenclamidin(gliburid) max dozunda bu etki belirgin
- **•Yeni geliştirilen sekretogoglarda(glimeprid ve gliclazid) bu etki az ya da hiç oluşmamaktadır**

Tolbutamid ve Gliclazid SUR 1 e spesifiktir; kardiyak hücredeki SUR 2 ye bağlanmaz ; Glibenclamid ve Glinidler, SUR 2 ye kısmen bağlanır



Sulfonilürelerin, vasküler düz kaslardaki KATP kanallarına afinitesi farklı

Differential effects of sulfonylurea derivatives on vascular ATP-sensitive potassium channels

Richard Engbersen, Rosalinde Masereeuw, Miriam A. van Gestel
Paul Smits, Frans G.M. Russel *

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Keywords:
ATP-sensitive potassium channel
Sulfonylurea drug
Vascular smooth muscle
Isolated perfused kidney

ABSTRACT

Sulfonylurea drugs exert their insulinotropi
pancreas. However, these channels are also e
possible detrimental cardiovascular effects. /
cy of various widely used sulfonylurea drug
arteries mounted in a myograph and isolate
cidil induced a dose-dependent relaxation
(pEC_{50} = 6.10 ± 0.01 and 5.66 ± 0.03, respec
enteric arteries in the presence of sulfonylurea antagonists revealed the following order of potency: glimepiride (pA_2 = 7.22) ≥ glibenclamide (pA_2 = 7.05) ≥ glipizide (pA_2 = 5.25) ≥ gliclazide (pA_2 = 4.31). The effects of glibenclamide in renal arteries were comparable. Furthermore, glibenclamide produced similar constrictive properties in isolated renal arteries as in isolated perfused whole kidneys. We conclude that sulfonylurea drugs exert differential effects on vascular smooth muscle K_{ATP} channels. Our results suggest that glibenclamide and glimepiride will interact with these channels at therapeutic concentrations.

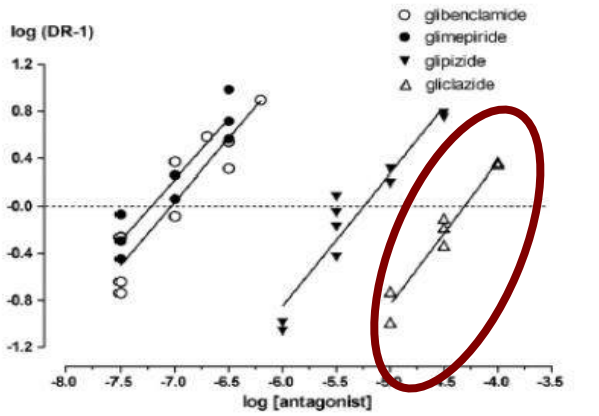
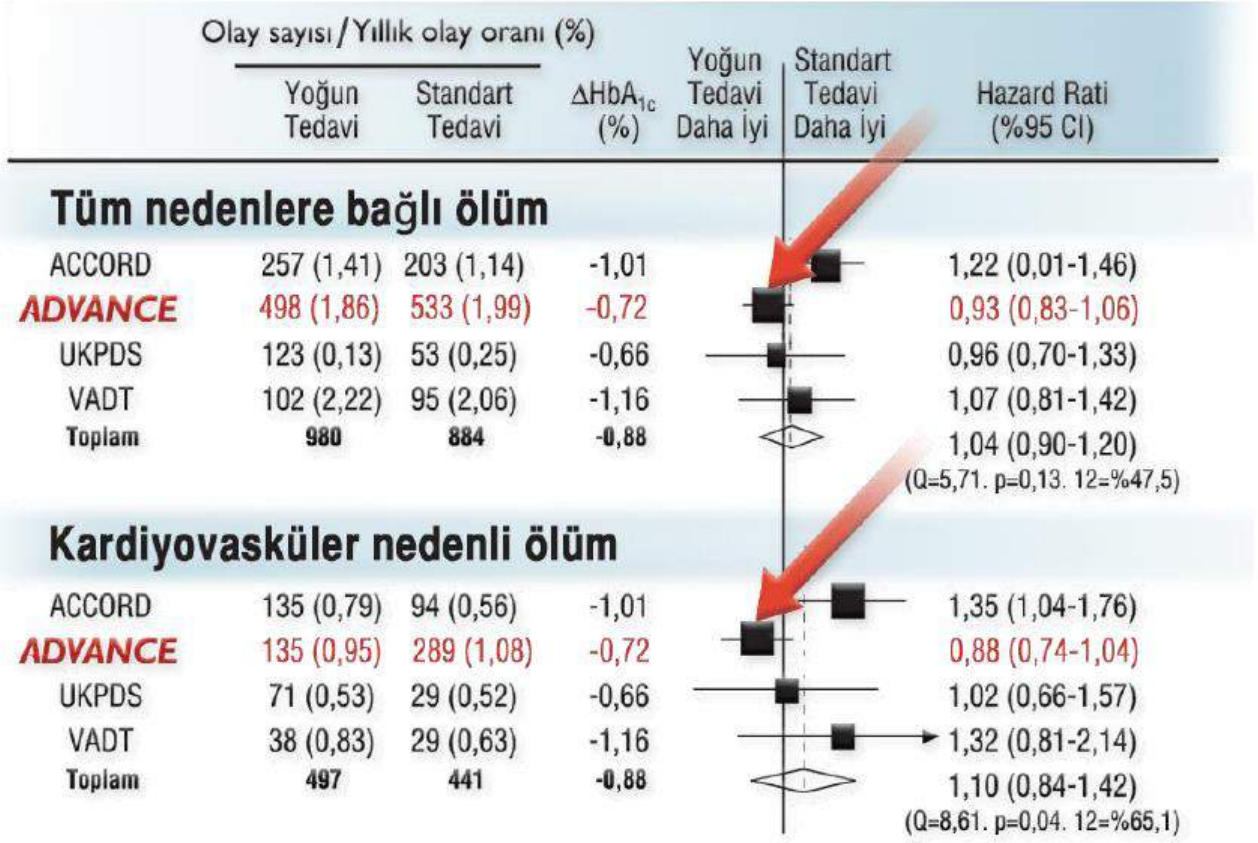


Fig. 3. Schild plots of pinacidil relaxation curves in mesenteric arteries in the presence of glibenclamide (closed circles), glimepiride (open circles), glipizide (closed triangles), and gliclazide (open triangles).

European Journal of Pharmacology

UKPDS, ACCORD,ADVANCE,VADT metaanalizi: KV nedenli ölümde azalma



CONTROL Meta-analysis-Turnbull FM. Diabetologia 2009;52:2288-2298

ADA 2017

Sulfonylureas	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Relatively higher A1C efficacy	• Hypoglycemia • ↑ Weight	Low

ADA 2018

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)

Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate

Tiazolidindionlar

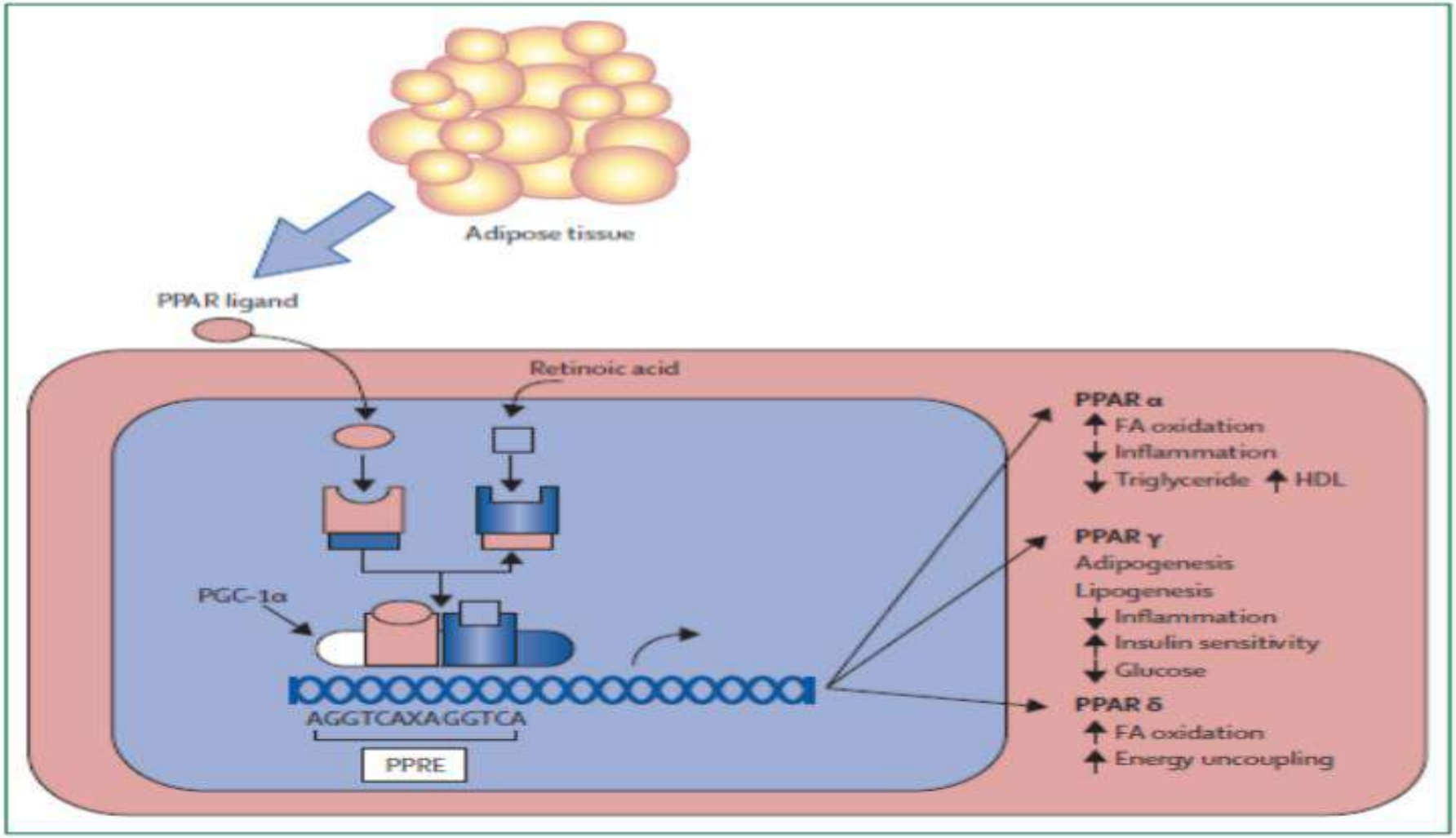


Figure 6: Summary of metabolic effects of PPAR agonists

- Tip 2 DM’nin ana patogenetik mekanizması üzerinden etkililer.
- Peroxisome proliferator-activated receptor (PPAR)
  - Nükleer transkripsiyon faktör ailesi..metabolik genlerin modifikasyonu
- Kas ve Yağ dokuda insülin duyarlılığında artış,
- Beta hücresinin glukoz yanıtında düzelme sağlar; koruyucu etki*.
- Yavaş glisemik düzelme
- Tip 2 DM’nin progresyonunu yavaşlatır.
- Tip 2 DM’nin gelişimini geciktirebilir.

* Rizos CV, ve ark. Expert Opin Pharmacother, 2008
Rizos CV, ve ark. Arch Tocixol, 2016

Glitazonlar; önemli KV etkiler

- Karotis intima/medya kalınlığında azalma
- Vasküler endotel fonksiyonunda düzelme
- Dislipidemide düzelme;
  - PİO; HDL↑ / TG↓ / LDL partikül boyutu↑
- KB düşmesi
- İnflamatuar belirteçlerde, fibrinolitik ve koagülasyon parametrelerinde düzelme

ATEROGENEZ KARŞITI ETKİLER

ÖZELLİKLE PİOGLİTAZON İLE KV RİSK ÜZERİNDE OLUMLU ETKİLER

Rizos ve ark, 2008
Goldberg ve ark, 2005

Pioglitazon / KV Etkiler

- CHICAGO Çalışması
  - 462 T2DM vakası; PIO vs glimepirid
  - PIO, 18 ayda, karotis intima/medya kalınlığının progresyonunu, glimepiride göre daha fazla azaltmıştır (p=0,02).
- PERISCOPE Çalışması
  - 360 T2DM vakası; glimepirid 1-4 mg vs PIO 15-45 mg, 18 ay
  - Koroner intravasküler USG ile ateroskleroz değerlendirmesi; öncesi ve sonrası
  - PIO, koroner ateroskleroz progresyonunu daha fazla azaltmış (p=0,002)
- Ateroskleroz progresyonunu azaltıcı direkt vasküler etki ? (Saremi ve ark, 2013)

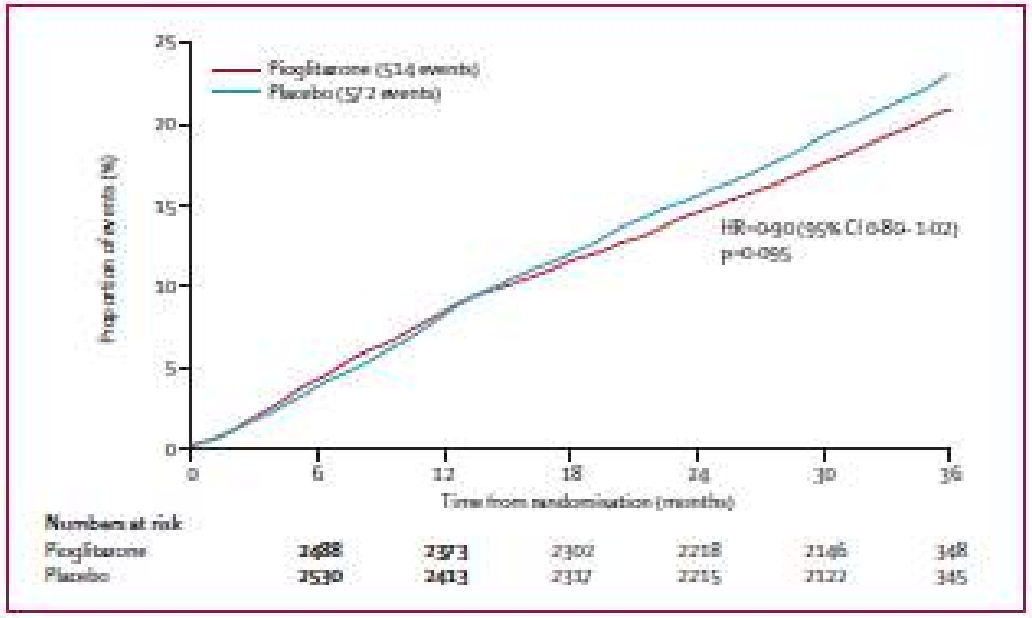
Mazzone ve ark, 2006
Nissen ve ark, 2008

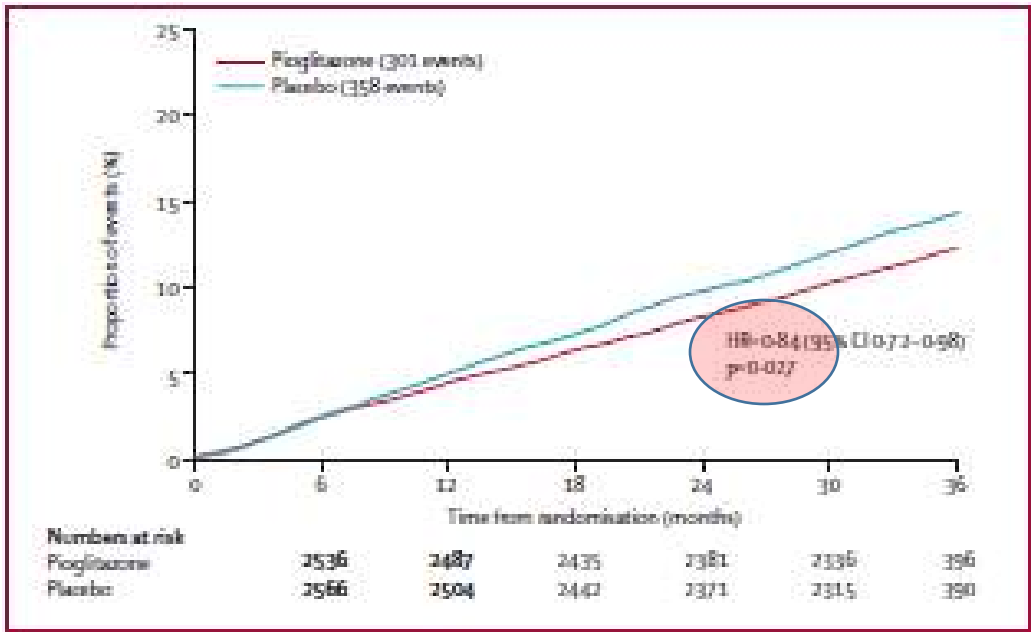
PROACTIVE
(PROspective pioglitAzone Clinical Trial In macroVascular Events)

- Prospektif, randomize, PCB kontrollü
- T2DM ve makrovasküler hastalıklı 5238 vaka; **sekonder önleme**..
- Gerekli tüm tedavilerine ek; PIO 15-45 mg vs PCB; ortalama 34,5 ay
- Birleşik olarak; tüm nedenlere bağlı ölüm, non-fatal MI, inme, akut koroner S, ampütasyon, vasküler cerrahi girişim; PIO %10 azaltmış (NS; 514 vs 572 vaka).
- Sekonder son nokta; **tüm nedenlere bağlı ölüm, non-fatal MI, inme; PIO grubunda daha az** (p=0,027; 301 vs 358 vaka).
- Kalp yetmezliği (p<0,0001) ve buna bağlı hospitalizasyon (p=0,007); PİO > PCB
  - KY bağlı mortalite benzer.
- PIO grubunda; glisemik kontrol daha iyi ve insülin ihtiyacı daha az (p<0,0001).

Dormandy JA, ve ark., Lancet 2005

PROACTIVE
(PROspective pioglitAzone Clinical Trial In macroVascular Events)



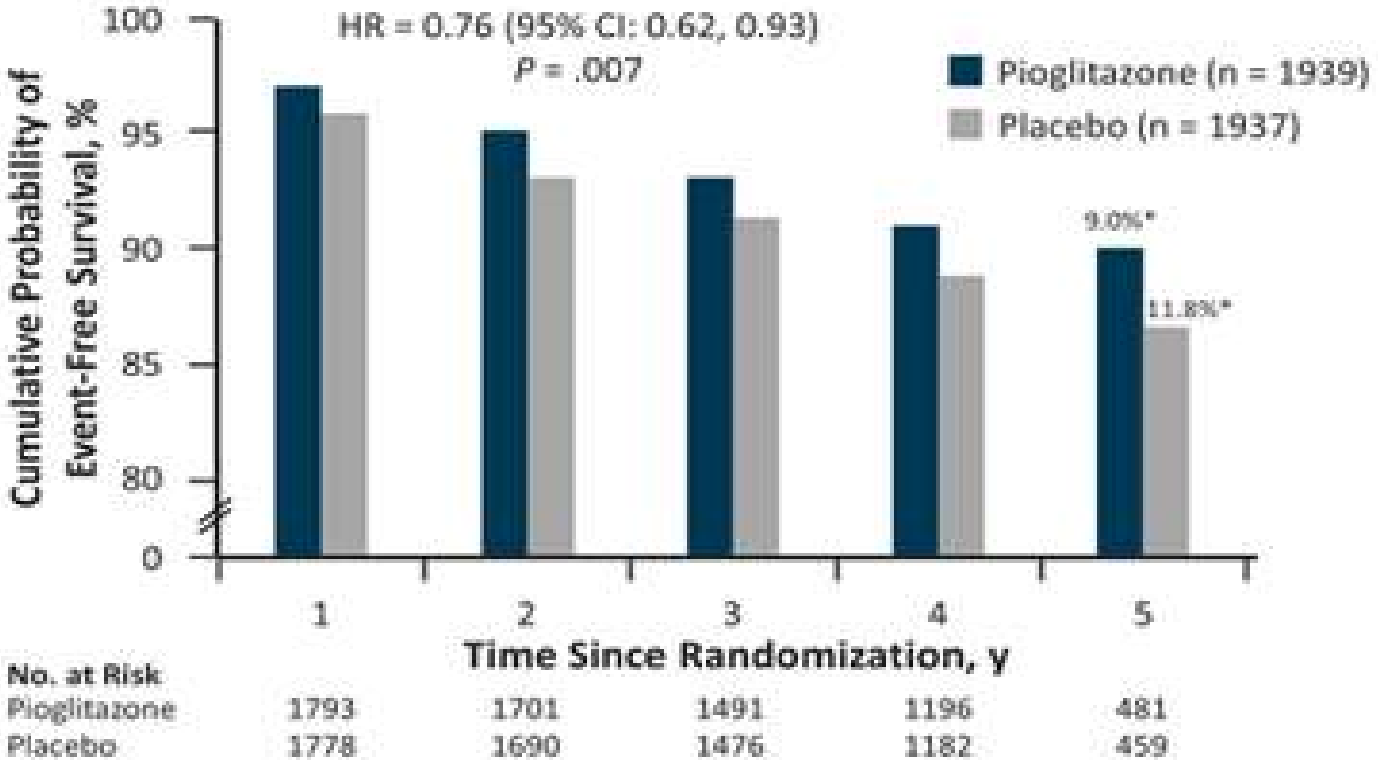


Dormandy JA, ve ark., Lancet 2005

IRIS: Pioglitazone

Primary outcome:

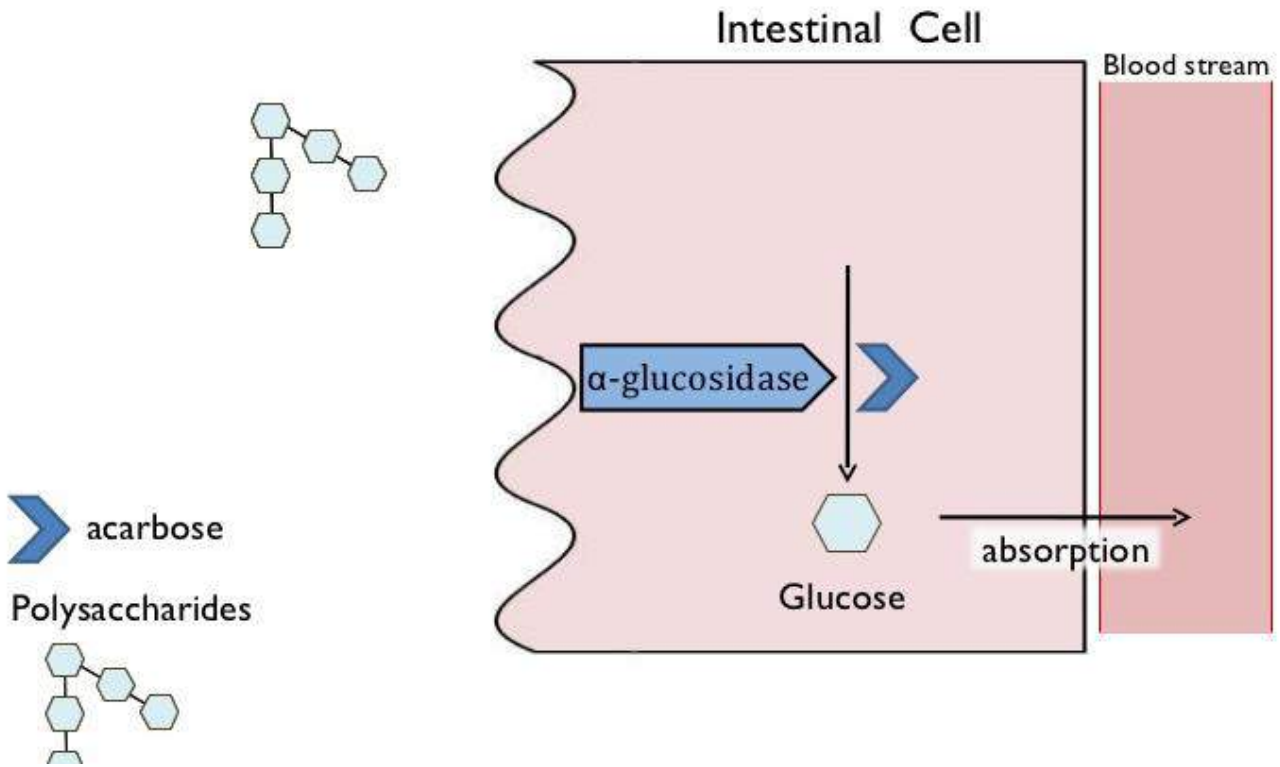
- First fatal or nonfatal stroke or fatal or nonfatal MI

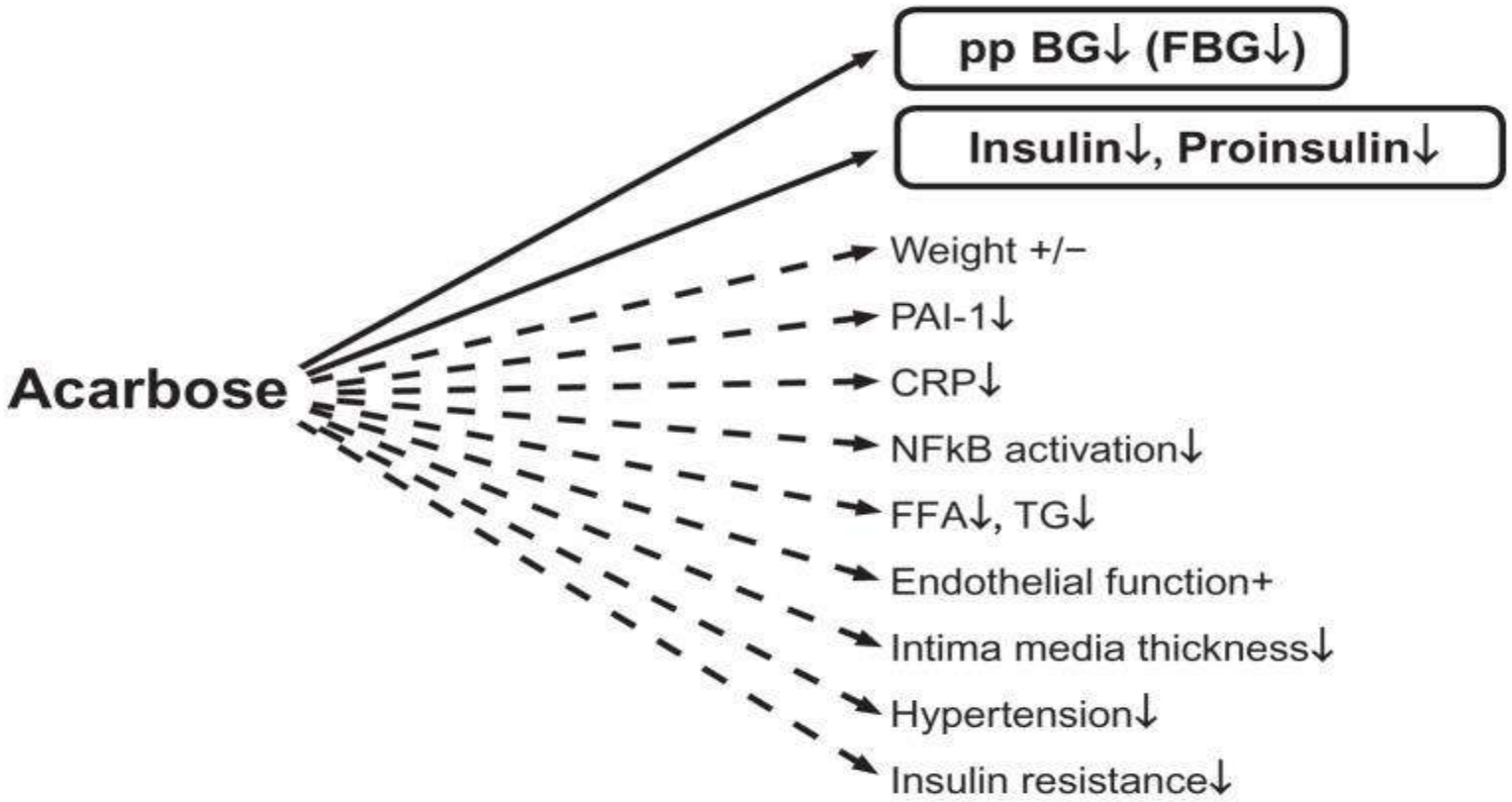


*Cumulative event rate.

Kernan WN, et al. *N Engl J Med.* 2016;374:1321-1331.

α- Glukozidaz İnhibitörleri





BG, blood glucose; CRP, C-reactive protein; FFA, free fatty acids; FBG, fasting blood glucose; NFκB, nuclear factor kappa B; PP, postprandial; PAI, PAI-1, plasminogen activator inhibitor-1; TG, triglycerides.

Curr Diabetes Rev. 2009;5:157–164

Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial

*Jean-Louis Chiasson, Robert G Josse, Ramon Gomis, Markolf Hanefeld, Avraham Karasik, Markku Laakso, for The STOP-NIDDM Trial Research Group**

Methods In a multicentre, placebo-controlled randomised trial, we randomly allocated patients with impaired glucose tolerance to 100 mg acarbose or placebo three times daily. The primary endpoint was development of diabetes on the basis of a yearly oral glucose tolerance test (OGTT). Analyses were by intention to treat.

Interpretation Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type 2 diabetes in patients with impaired glucose tolerance.

Lancet 2002; **359:** 2072–77

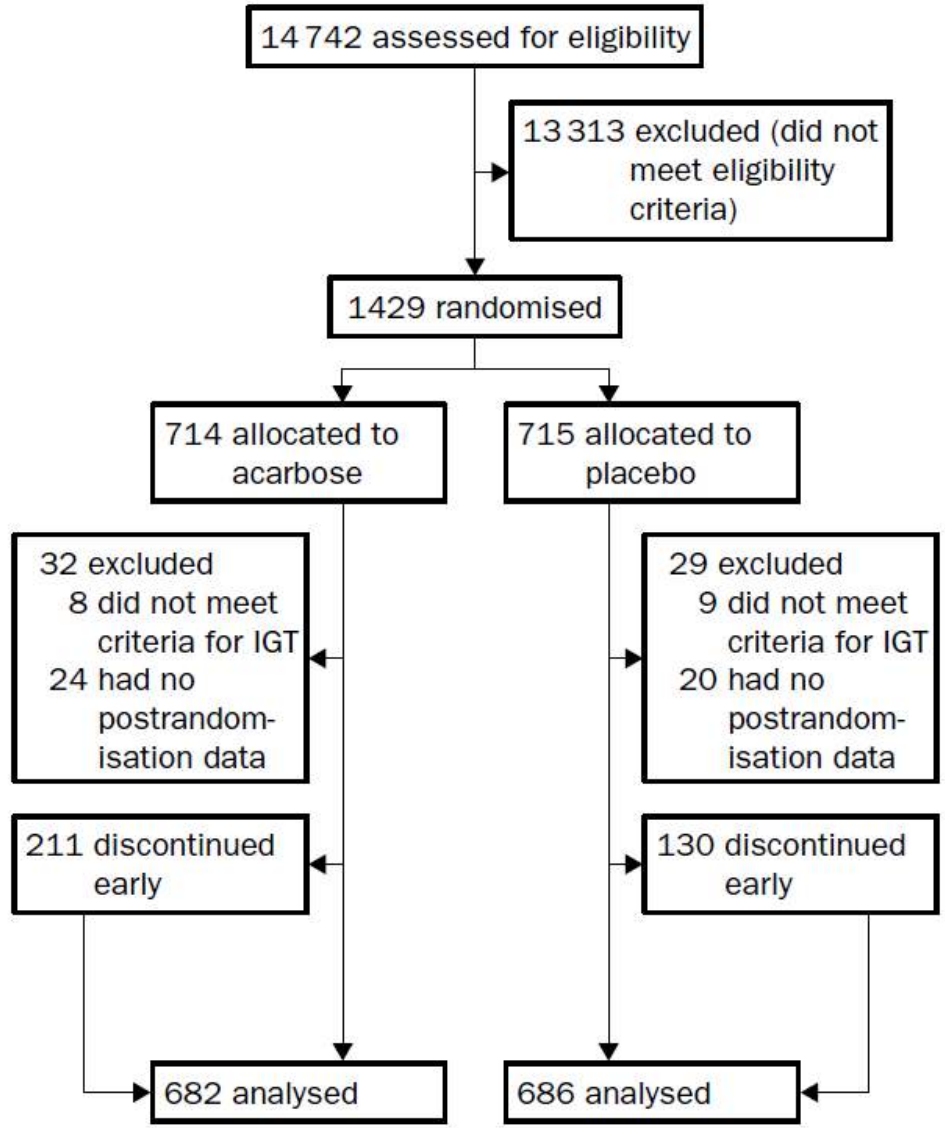
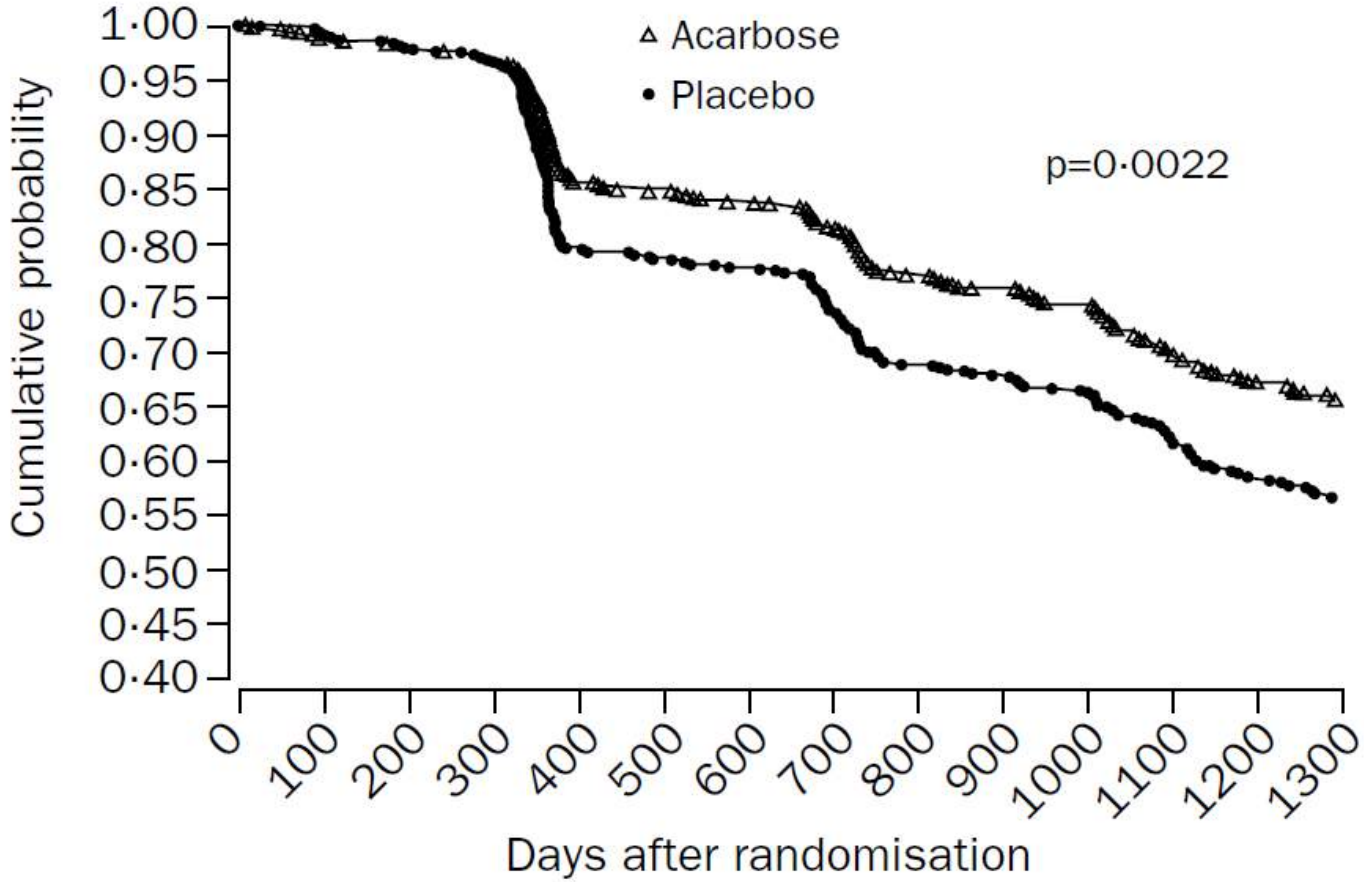


Figure 1: **Trial profile**
IGT=impaired glucose tolerance



Patients at risk

Acarbose	682	655	628	612	531	523	515	497	463	447	432	349	268	212
Placebo	686	671	655	640	512	505	497	470	434	427	414	331	255	208

Figure 3: **Effect of acarbose and placebo on cumulative probability of remaining free of diabetes over time**

Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial

Wenying Yang, Jie Liu, Zhongyan Shan, Haoming Tian, Zhiguang Zhou, Qiuhe Ji, Jianping Weng, Weiping Jia, Juming Lu, Jing Liu, Yuan Xu, Zhaojun Yang, Wei Chen

Lancet Diabetes Endocrinol 2014; 2: 46–55

Published Online October 18, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70021-4

This online publication has been corrected. The corrected version first appeared at thelancet.com/diabetes-endocrinology on February 3, 2014

See Comment page 6

China-Japan Friendship Hospital, Beijing, China (Prof W Yang MD, Prof Z Yang MD); Shanxi Province People's Hospital, Taiyuan, China (Prof J Liu PhD); The First Hospital of China Medical University, Shenyang, China (Prof Z Shan PhD); West China Hospital, Sichuan University, Chengdu, China (Prof H Tian MD); Xiangya Second Hospital of Central South University, Changsha, China (Prof Z Zhou PhD); Xijing

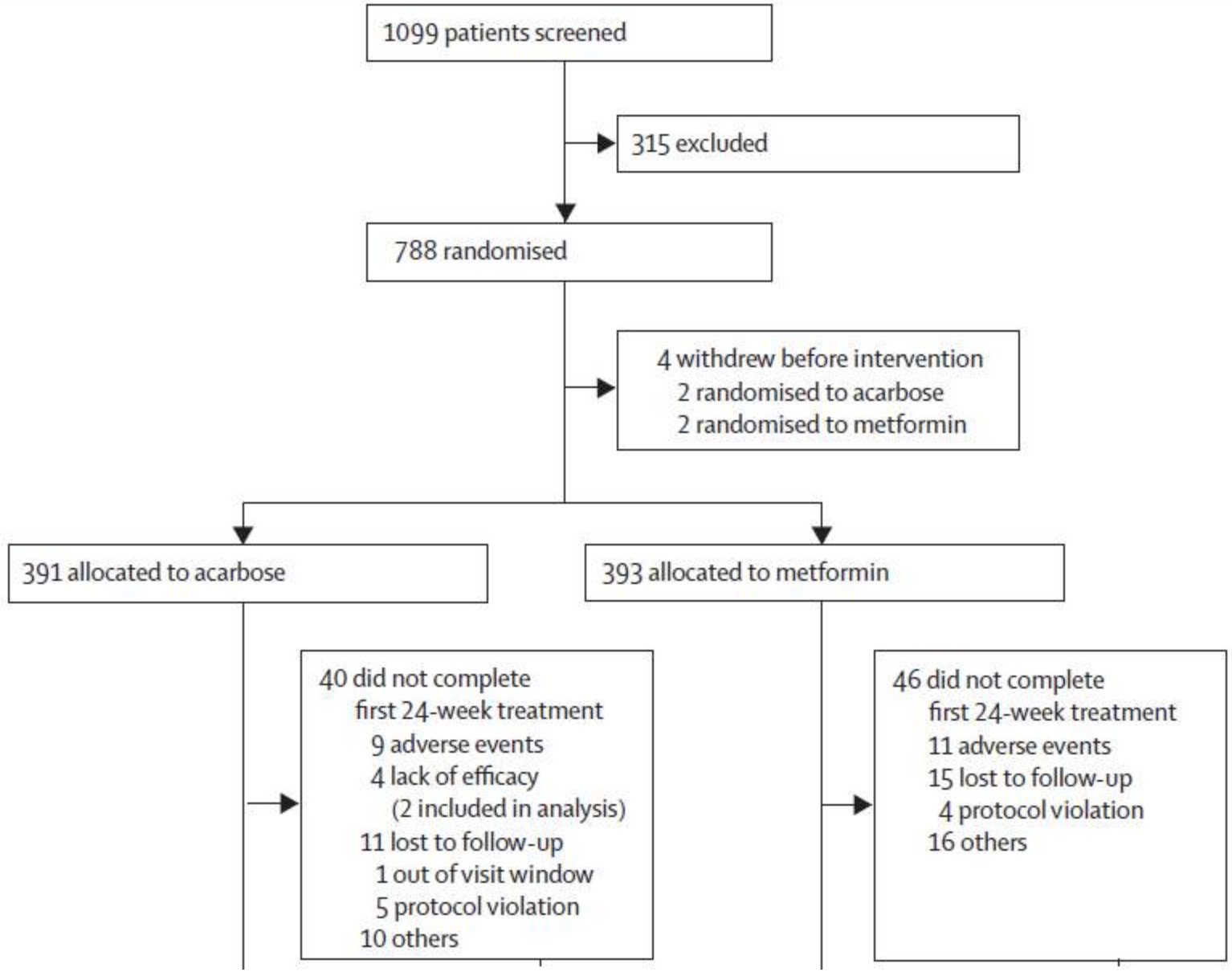
Summary

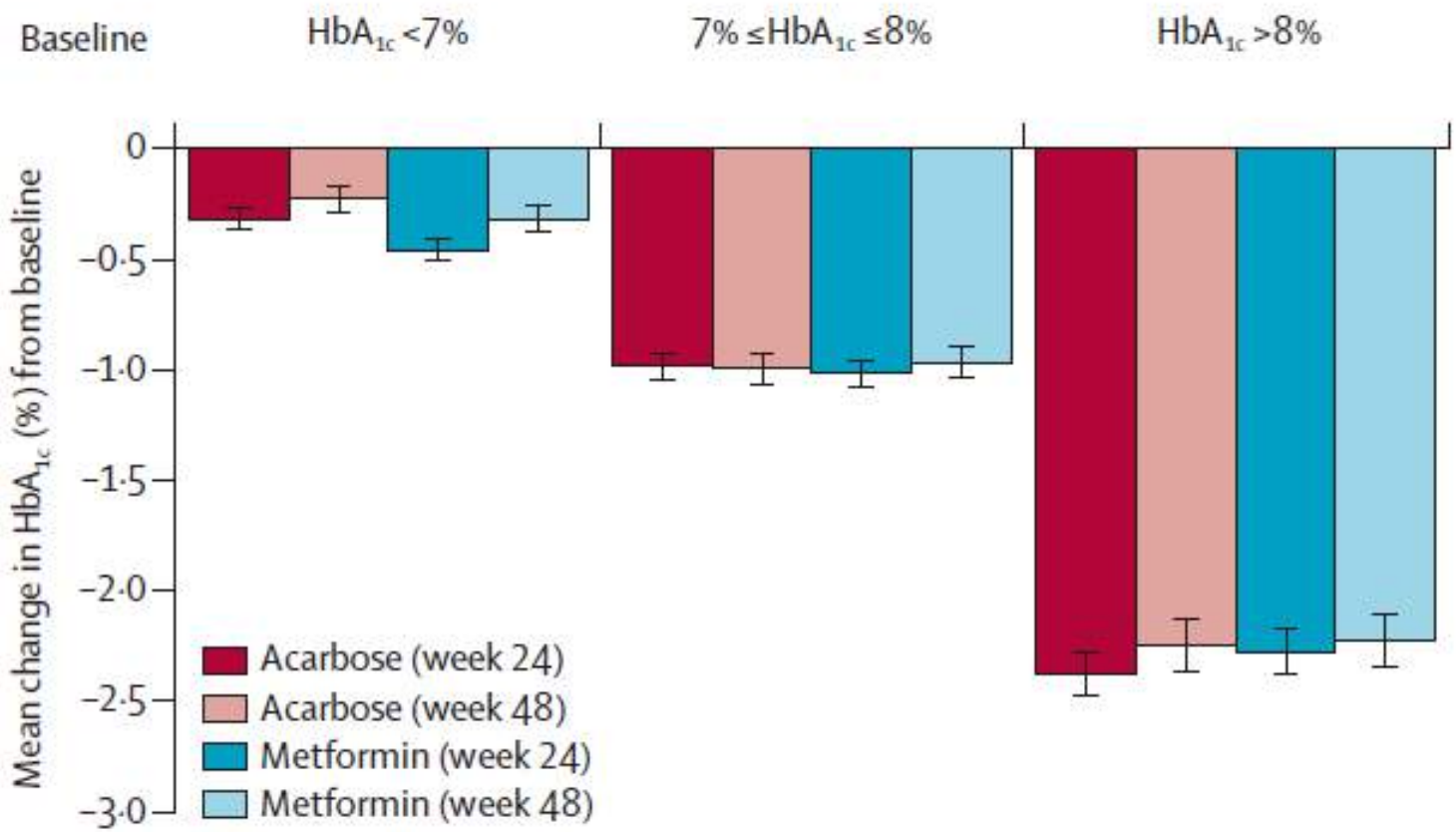
Background Metformin is the only first-line oral hypoglycaemic drug for type 2 diabetes recommended by international guidelines with proven efficacy, safety, and cost-effectiveness. However, little information exists about its use in Asian populations. We aimed to ascertain the effectiveness of the α-glucosidase inhibitor acarbose, extensively adopted in China, compared with metformin as the alternative initial therapy for newly diagnosed type 2 diabetes.

Methods In this 48-week, randomised, open-label, non-inferiority trial, patients who were newly diagnosed with type 2 diabetes, with a mean HbA_{1c} of 7·5%, were enrolled from 11 sites in China. After a 4-week lifestyle modification run-in, patients were assigned to 24 weeks of monotherapy with metformin or acarbose as the initial treatment, followed by a 24-week therapy phase during which add-on therapy was used if prespecified glucose targets were not achieved. Primary endpoints were to establish whether acarbose was non-inferior to metformin in HbA_{1c} reduction at week 24 and week 48 timepoints. The non-inferiority margin was 0·3%, with an expected null difference in the change from baseline to week 48 in HbA_{1c}. Analysis was done on a modified intention-to-treat population. This study was registered with Chinese Clinical Trial Registry, number ChiCTR-TRC-08000231.

Findings Of the 788 patients randomly assigned to treatment groups, 784 patients started the intended study drug. HbA_{1c} reduction at week 24 was –1·17% in the acarbose group and –1·19% in the metformin group. At week 48, the HbA_{1c} reduction was –1·11% (acarbose) and –1·12% (metformin) with difference 0·01% (95% CI –0·12 to 0·14, p=0·8999). Six (2%) patients in the acarbose group and seven (2%) patients in the metformin group had serious adverse events, and two (1%) and four (1%) had hypoglycaemic episodes.

Interpretation This study provides evidence that acarbose is similar to metformin in efficacy, and is therefore a viable choice for initial therapy in Chinese patients newly diagnosed with type 2 diabetes.


1099 patients screened
315 excluded
788 randomised
4 withdrew before intervention
2 randomised to acarbose
2 randomised to metformin
391 allocated to acarbose
393 allocated to metformin
40 did not complete
first 24-week treatment
9 adverse events
4 lack of efficacy
(2 included in analysis)
11 lost to follow-up
1 out of visit window
5 protocol violation
10 others
46 did not complete
first 24-week treatment
11 adverse events
15 lost to follow-up
4 protocol violation
16 others


Baseline
HbA1c <7%
7% ≤HbA1c ≤8%
HbA1c >8%
Mean change in HbA1c (%) from baseline
0
−0·5
−1·0
−1·5
−2·0
−2·5
−3·0
Acarbose (week 24)
Acarbose (week 48)
Metformin (week 24)
Metformin (week 48)

• COVER ARTICLE •

March 2017 Vol.60 No.3: 225–238
doi: 10.1007/s11427-016-0409-7

Efficacy and safety of metformin and sitagliptin based triple antihyperglycemic therapy (STRATEGY): a multicenter, randomized, controlled, non-inferiority clinical trial

Wen Xu[1†], Yiming Mu[2†§], Jiajun Zhao[3†], Dalong Zhu[4†], Qiuhe Ji[5], Zhiguang Zhou[6], Bin Yao[1], Anhua Mao[7], Samuel S. Engel[8], Bin Zhao[7], Yan Bi[4], Longyi Zeng[1], Xingwu Ran[9], Juming Lu[2], Linong Ji[10], Wenying Yang[11], Weiping Jia[12¶] & Jianping Weng[1*]

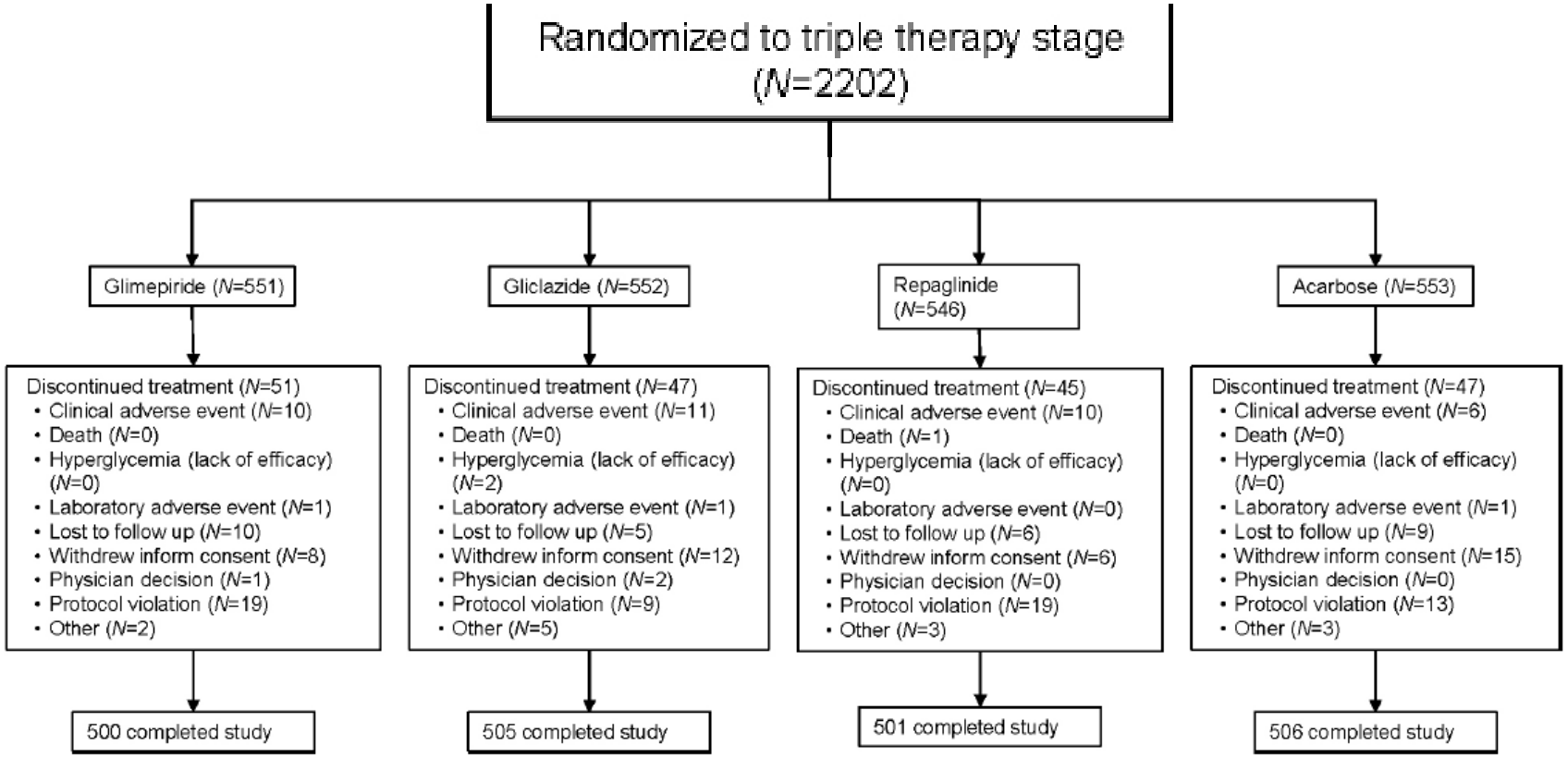
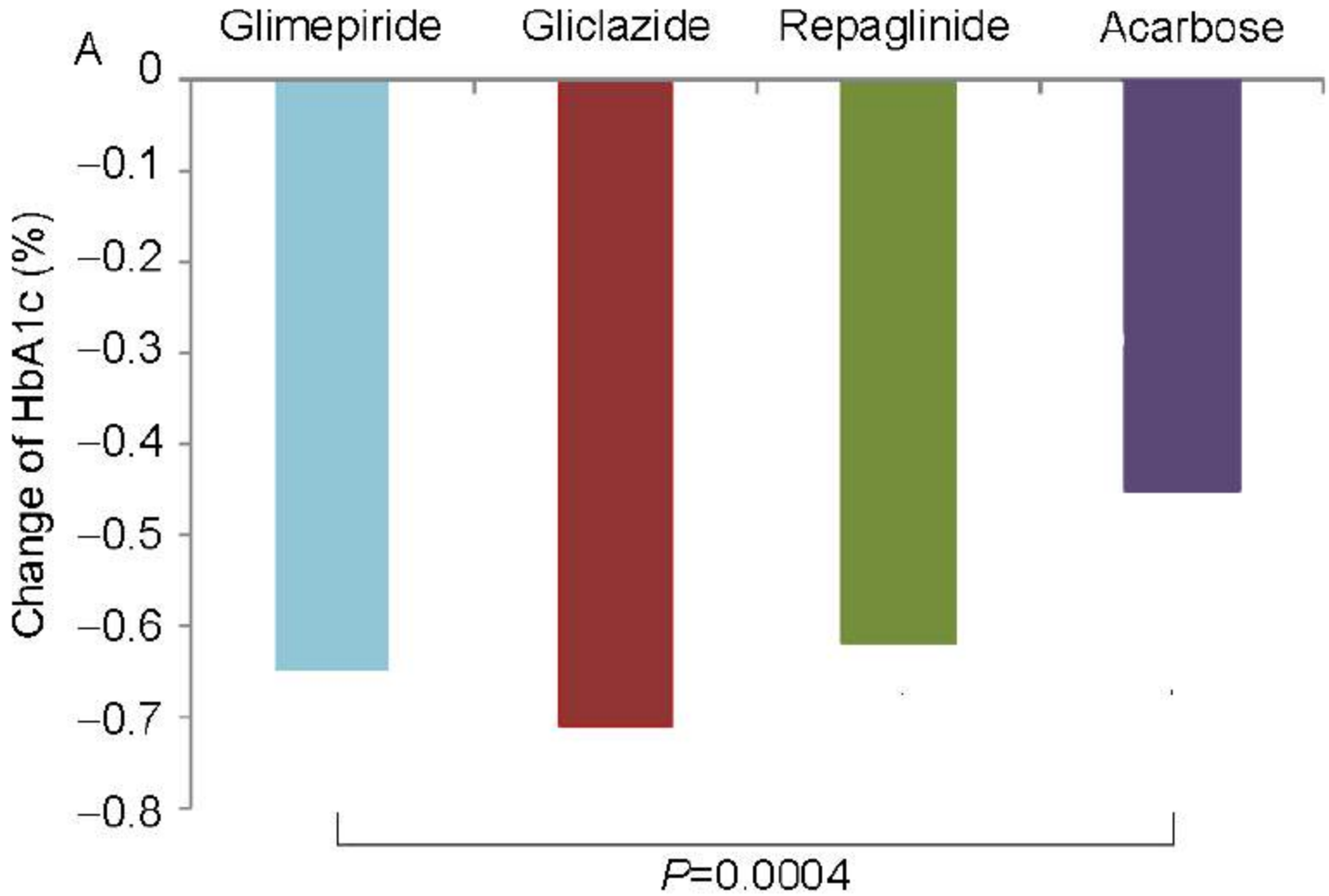
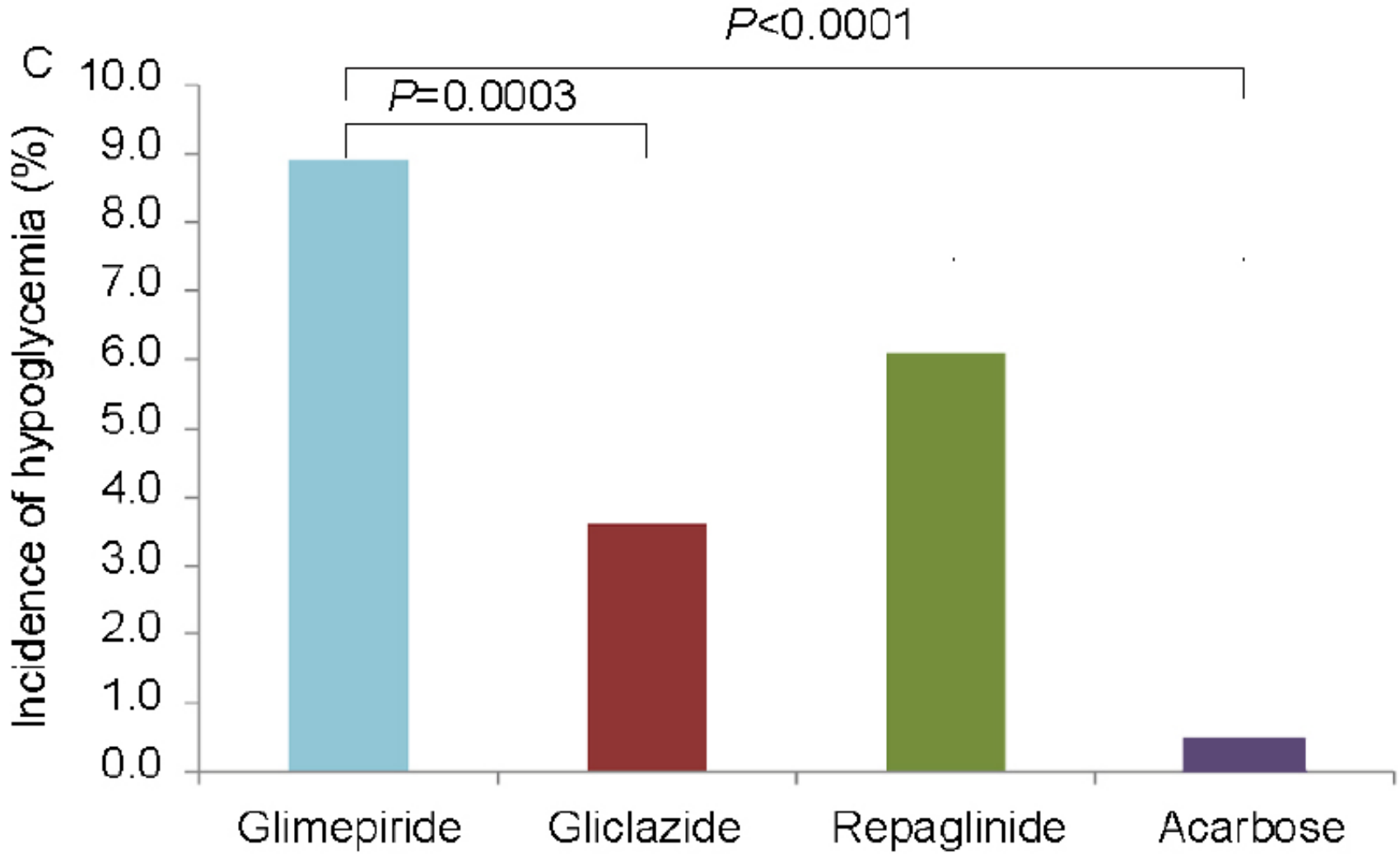
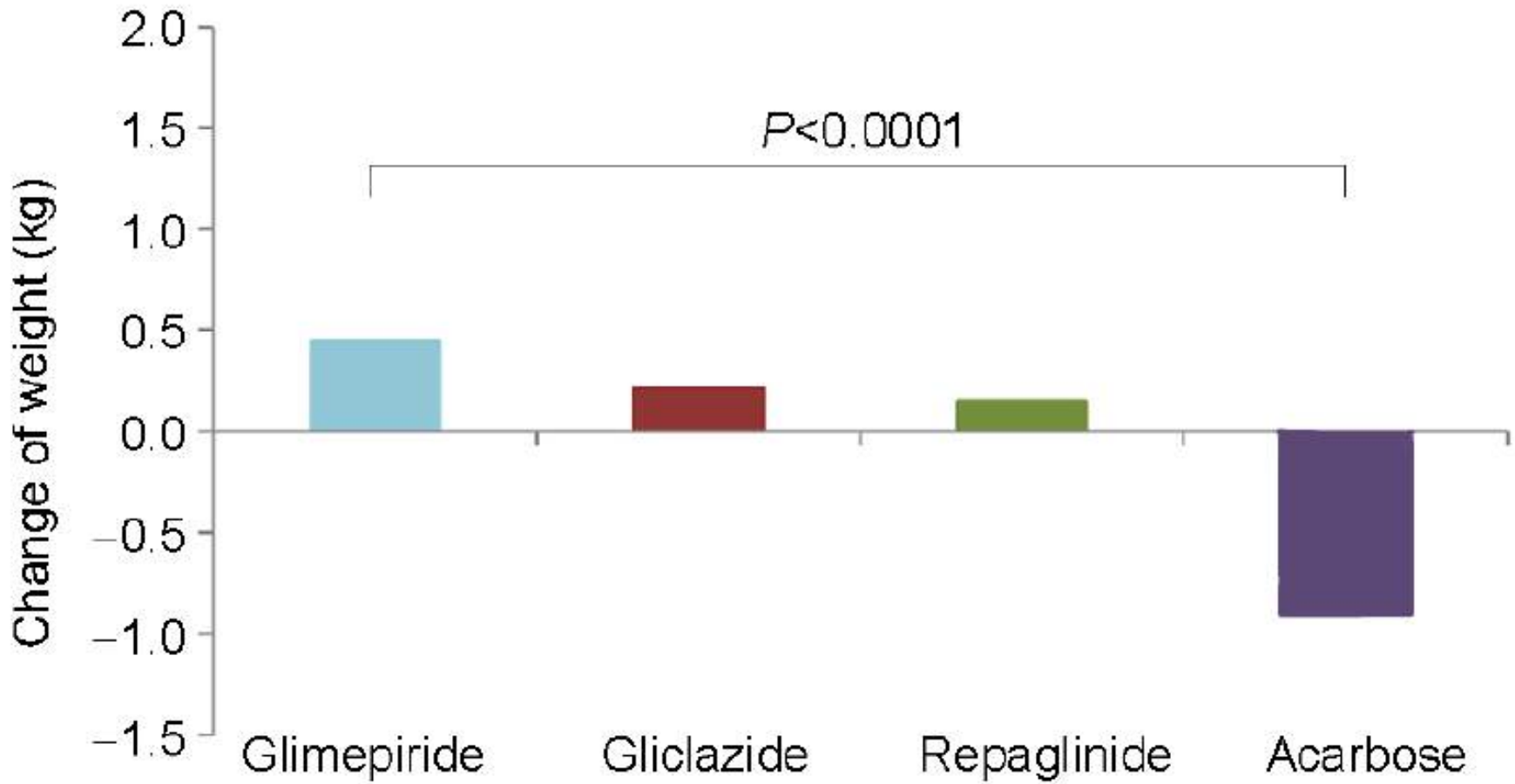


Figure 1 Trial profile. *, At Week 16, patients who achieved the recommended HbA1c target goal (<7.0%) were considered as early completers. #, 119 patients achieved the HbA1c goal (<7.0%) before they discontinued the treatment in the dual therapy stage.


A
Glimepiride
Gliclazide
Repaglinide
Acarbose
0
−0.1
−0.2
−0.3
−0.4
−0.5
−0.6
−0.7
−0.8
Change of HbA1c (%)
P=0.0004


C
Incidence of hypoglycemia (%)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
P=0.0003
P<0.0001
Glimepiride
Gliclazide
Repaglinide
Acarbose

D


2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
Change of weight (kg)
P<0.0001
Glimepiride
Gliclazide
Repaglinide
Acarbose

ADA 2017

• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate

ADA 2018

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	

Tabloda Yeralmıyor

Journal of Clinical Lipidology (2017) 11, 1126–1133

Journal of Clinical Lipidology

Review Articles

Cardiovascular disease leads to a new algorithm for diabetes treatment

Valentina Rodriguez, MD[1], Matthew C. Weiss, MD[1], Howard Weintraub, MD, Ira J. Goldberg, MD, Arthur Schwartzbard, MD*

Division of Endocrinology, Diabetes, and Metabolism, New York University School of Medicine, New York, NY, USA (Drs Rodriguez and Goldberg); and Center for Prevention of Cardiovascular Disease, New York University School of Medicine, New York, NY, USA (Drs Weiss, Weintraub, and Schwartzbard)

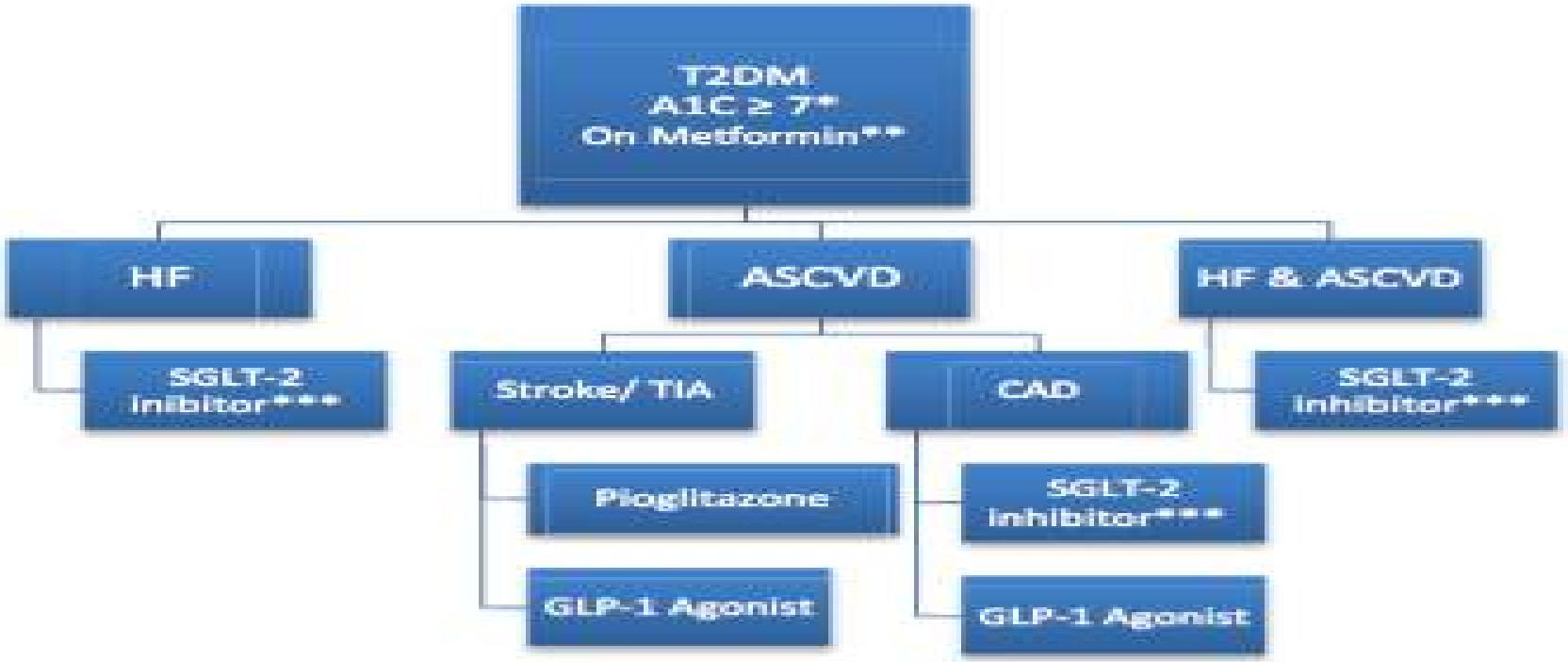


Figure 1 A new algorithm for choosing therapy for a patient with T2DM.

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

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

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

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

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

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

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

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

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND

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

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

PROGRESSION OF DISEASE

 DOI: 10.4158/EP161682.CS

Sonuç

- Diyabetik hastalarımız KVH nedeniyle kaybediliyor
- Yeni seçenek ilaçlar onlar için bir şans gibi görünüyor
- Yeni oldukları için riskleri konusunda dikkatli olmalı..
- Eski ajanlar konusunda tecrübemiz arttı, gerektiği yerde kullanılmalı..
- Hastalık yok hasta var prensibi unutulmamalı..

İlginiz İçin Teşekkür ederim