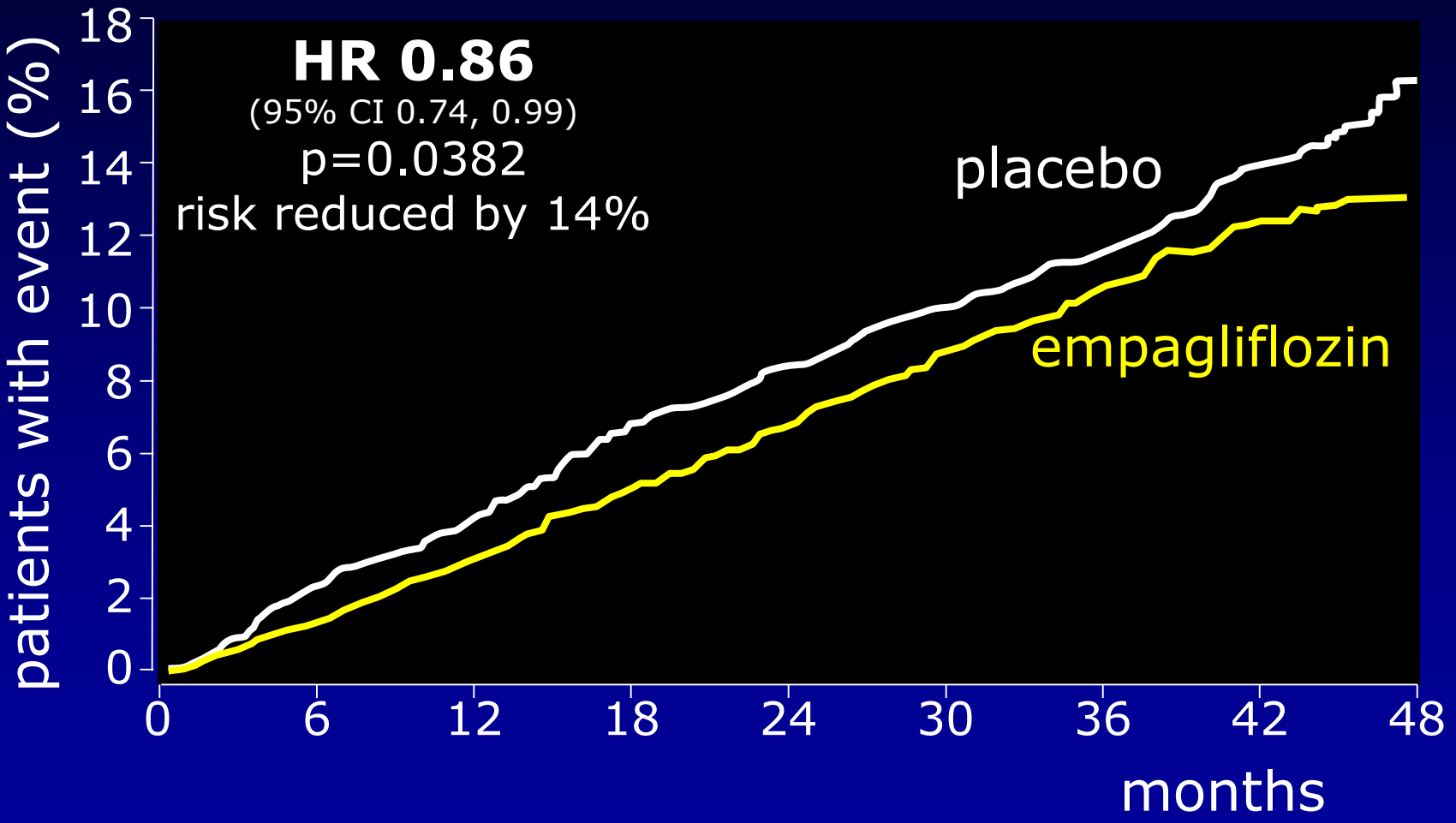
effetto degli SGLT-2i sul cuore

Gemelli

Andrea Giaccari
Centro per le Malattie Endocrine e Metaboliche
diabete@policlinicogemelli.it

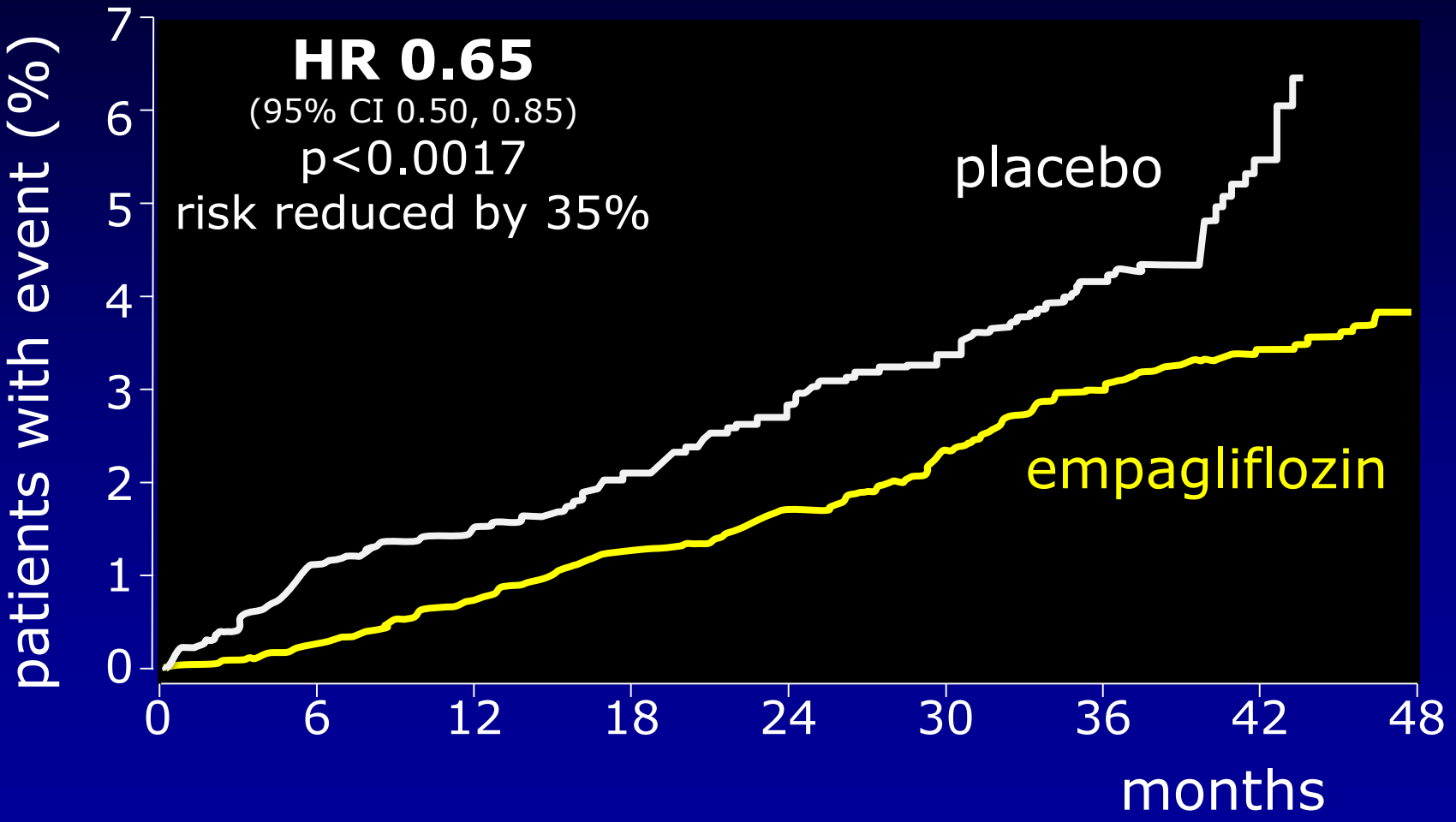
EMPAREG primary outcome: 3-point MACE



Zinman B et al.: NEJM 373:2117, 2015

gliflozins reduce HF Hospitalizations

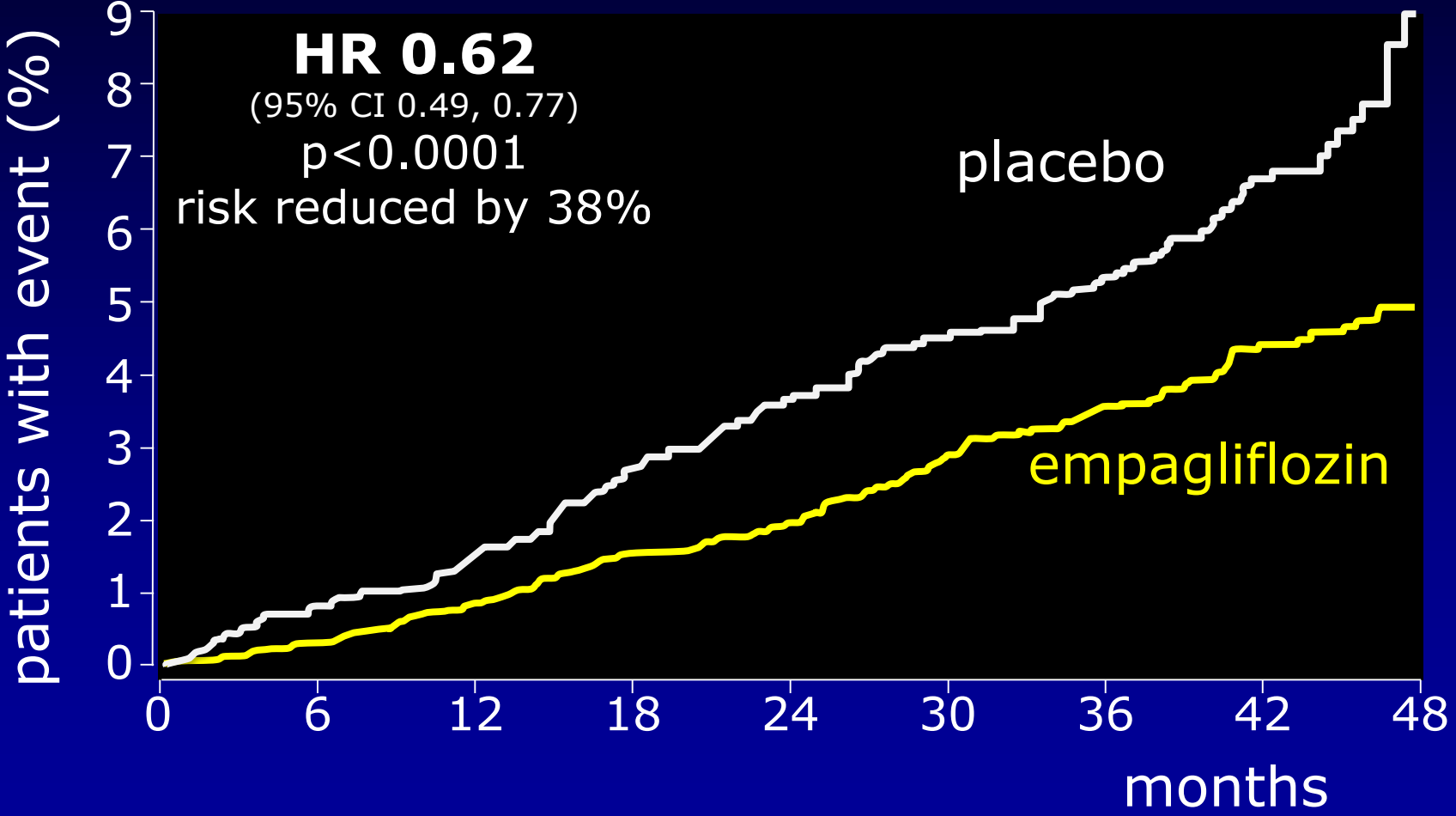
(EMPAREG secondary endpoint)



Zinman B et al.: NEJM 373:2117, 2015

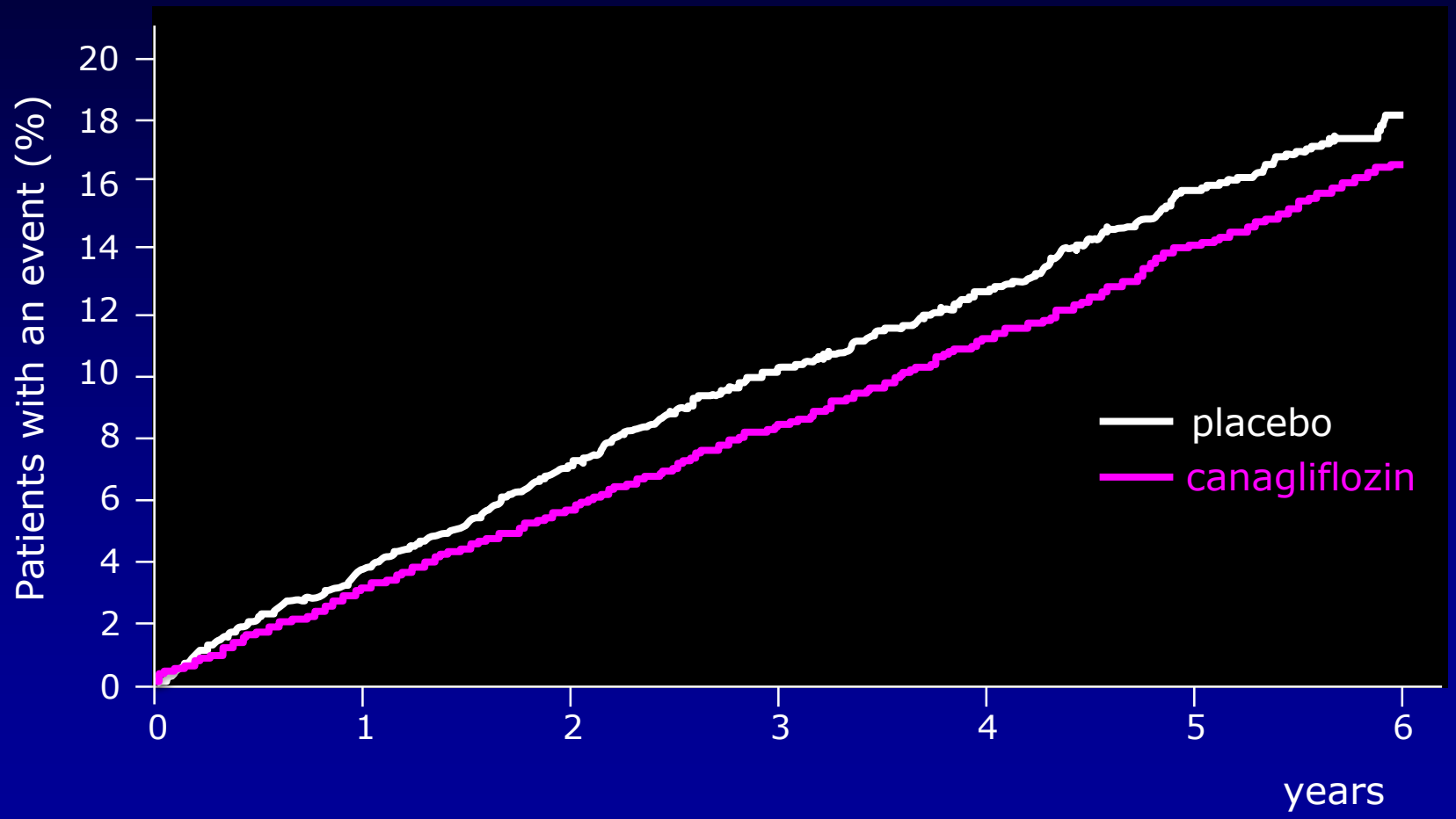
gliflozins reduce CV deaths

(EMPAREG secondary endpoint)



Zinman B et al.: NEJM 373:2117, 2015

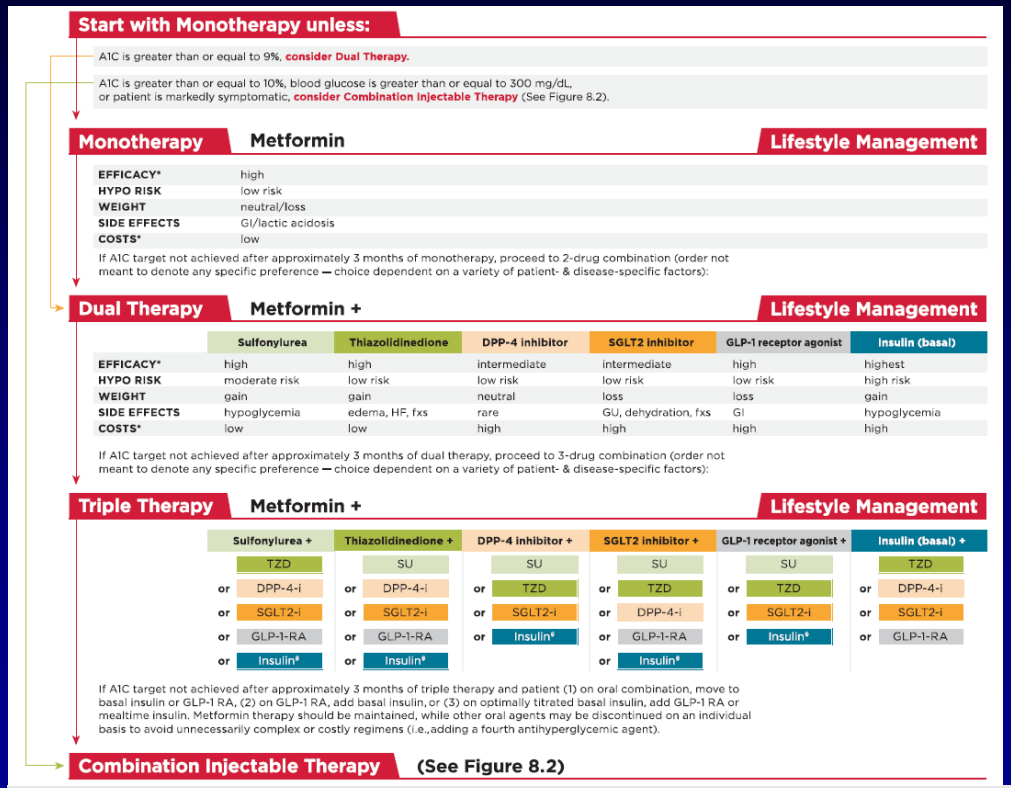
CANVAS
primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



CANVAS, Neal B et al.: NEJM Jun 12, 2017

ADA Standards of Medical Care in Diabetes

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES (p: S65-S71)
CV DISEASE AND RISK MANAGEMENT (p: S84)



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#	or GLP-1-RA	or Insulin*	or GLP-1-RA
or Insulin#	or Insulin#		or Insulin#		

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).

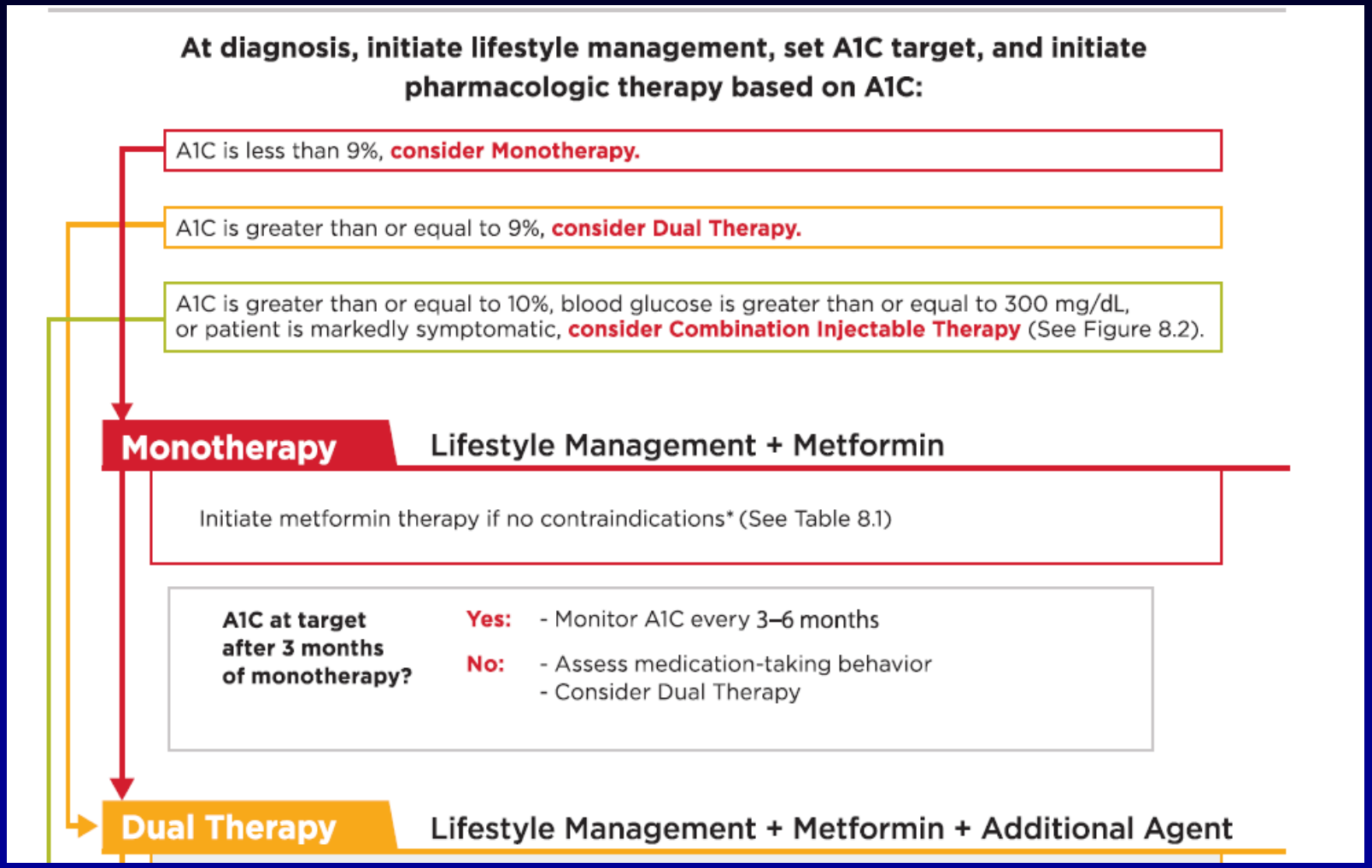
Combination Injectable Therapy **(See Figure 8.2)**

EMPA-REG OUTCOME Study

The BI10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a SGLT2 inhibitor, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI,
stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38%(absolute rate 3.7% vs. 5.9%) (29). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

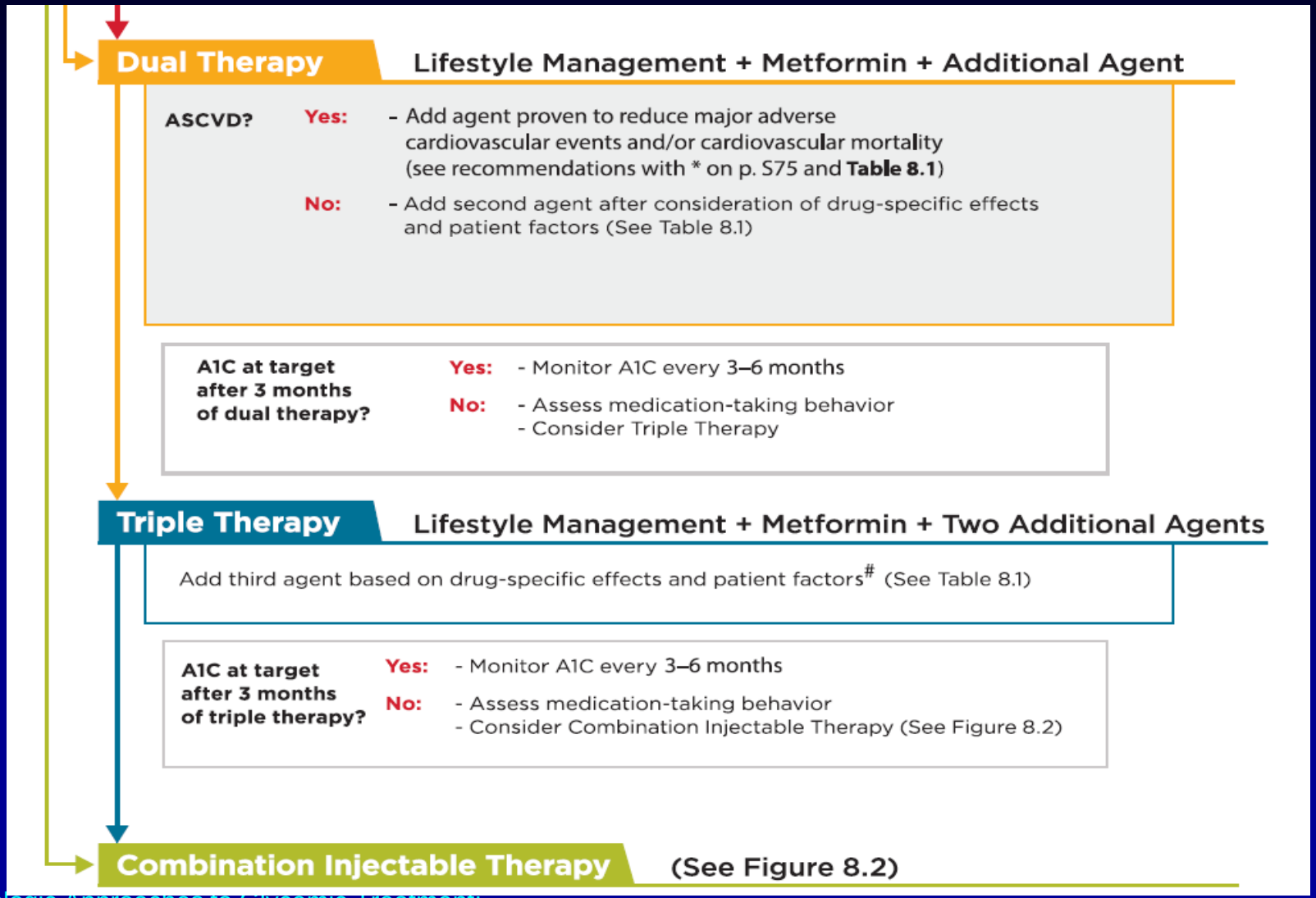
Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ 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

Antihyperglycemic Therapy in Adults with T2DM



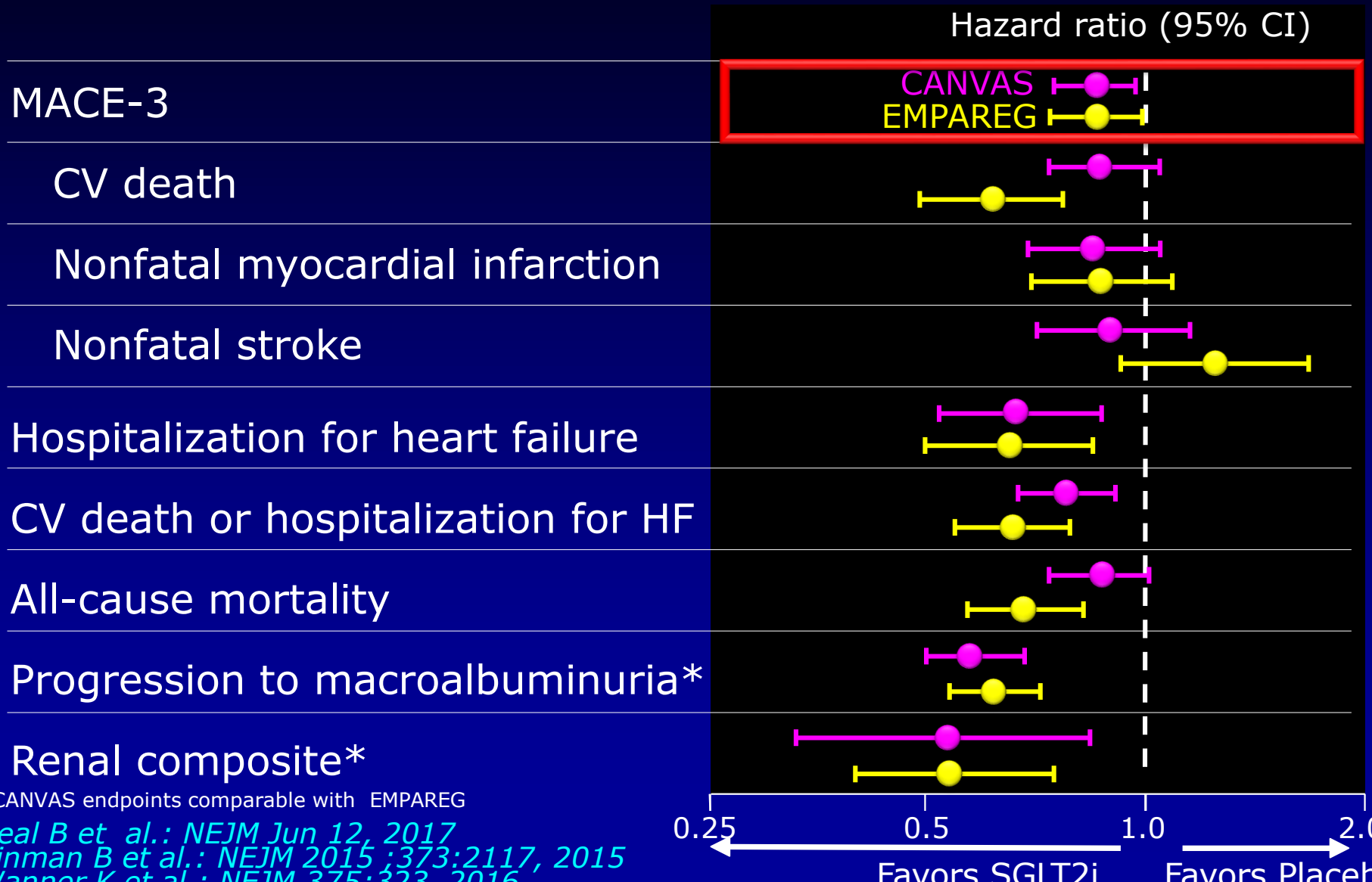
Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85

Antihyperglycemic Therapy in Adults with T2DM



Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85

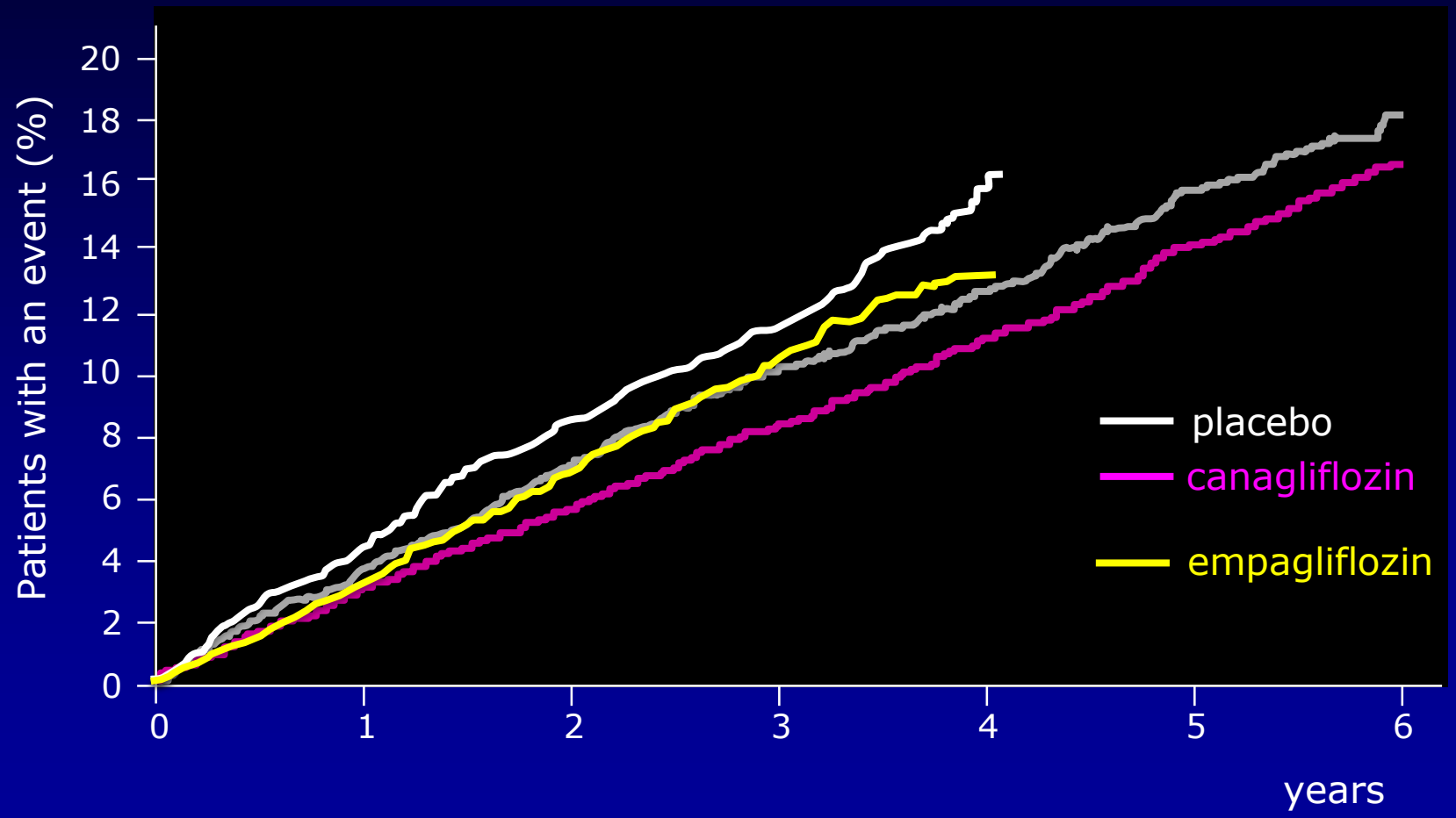
CANVAS & EMPAREG
key outcomes compared



*CANVAS endpoints comparable with EMPAREG

Neal B et al.: NEJM Jun 12, 2017
Zinman B et al.: NEJM 2015 ;373:2117, 2015
Wanner K et al.: NEJM 375:323, 2016

CANVAS & EMPAREG
primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017

CVOT: different populations

	SGLT-2i		GLP-1 RA			DPP-4 i		
Trial	EMPA-REG	CANVAS	ELIXA	LEADER	SUSTAIN	SAVOR	EXAMINE	TECOS
Baseline	empa	cana	lixi	lira	sema	saxa	alo	sita
n	7020	10142	6068	9340	3297	16492	5400	14671
Age (yr)	63	63.3	60	64	65	65	61	66
Diabetes (yr)	57%>10	13.5	9.3	12.8	13.9	10	7.2	9.4
BMI (kg/m2)	30.6	32	30.1	32.5	32.8	31	29	29
Insulin (%)	48	50	39	44	58	41	30	23
Prior CV disease (%)	99	65	100	81	83	78	100	100
Type of prior CV disease	MI, CHD, CVD, PVD	MI, CHD, CVD, PVD	ACS < 180 days	≥ 50 yr + CVD or CKD; ≥ 60 yr + ≥1 risk factor		≥ 40 yr + CVD or CKD; ≥ 55 yr + ≥1 risk factor	ACS < 90 days	CHD, CVD, PVD
Hypertension (%)	94	90	76	92	93	81	83	86
Follow-up (yr)	3.1	3.6	2.1	3.8	2.1	2.1	1.5	2.8

agent or placebo tested as add-on to usual care, aiming for glycemic equipoise

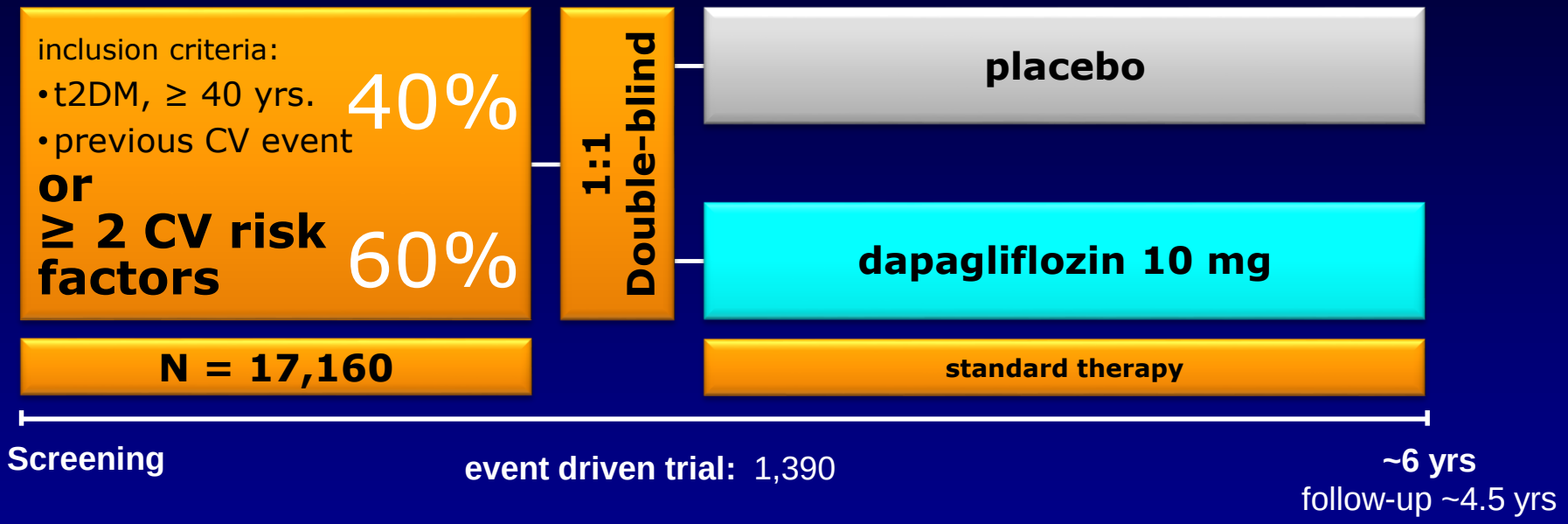
the burdening clinical point

le gliflozine prevengono CVD in prevenzione secondaria.

devono essere utilizzate

ma in prevenzione primaria?

DECLARE: Dapagliflozin Effects on CardiovascuLAR Events
the only trial with primary CV prevention data

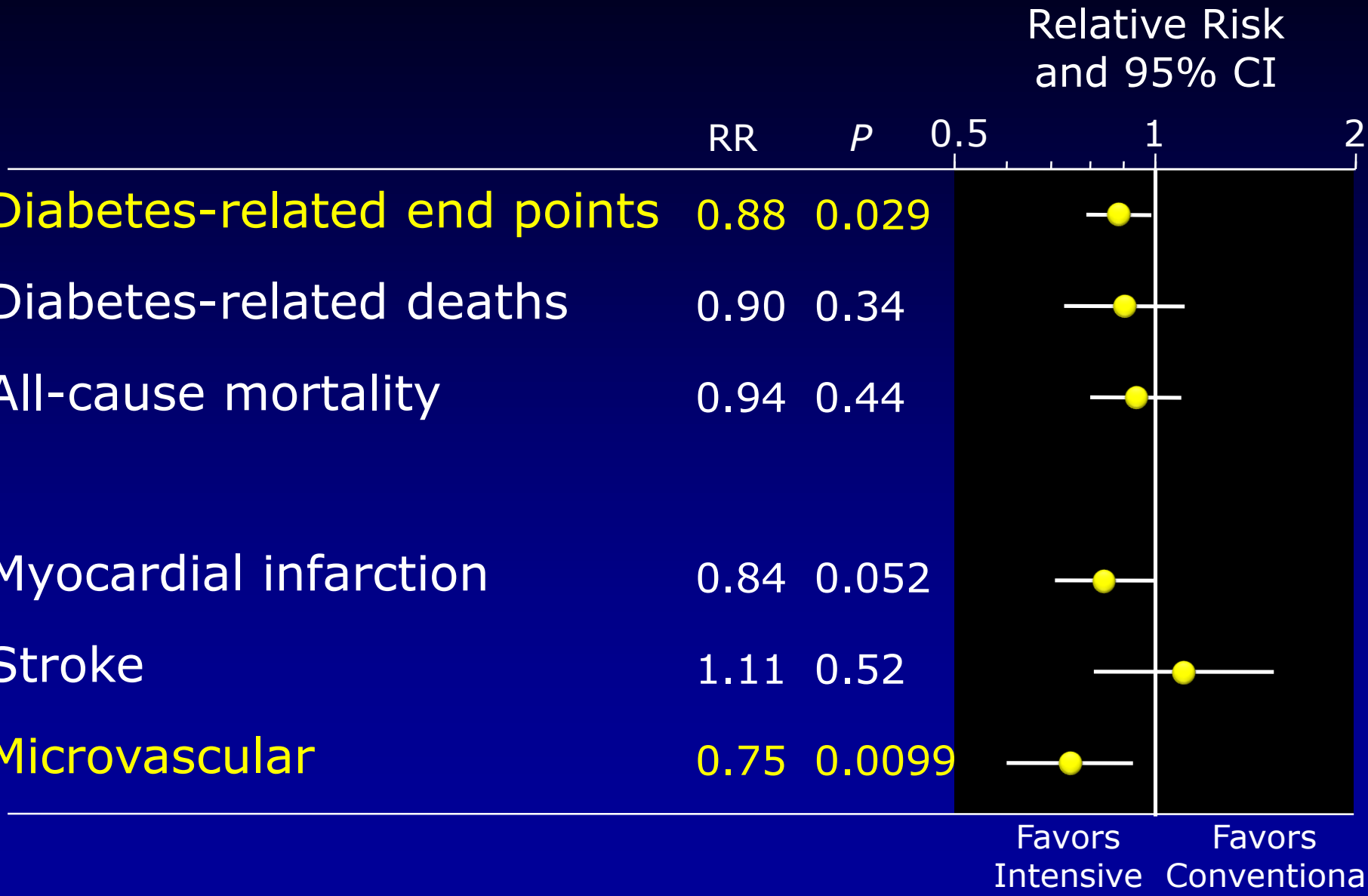


Primary Endpoint

- 3 MACE: CV death + non fatal MI or stroke

Raz I et al. DOM 2018 in press
doi: 10.1111/dom.13217
clinicaltrials.gov/ct2/show/NCT01730534
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM379659.pdf

UKPDS: Clinical End Points



UKPDS Group. Lancet 352:837, 1998

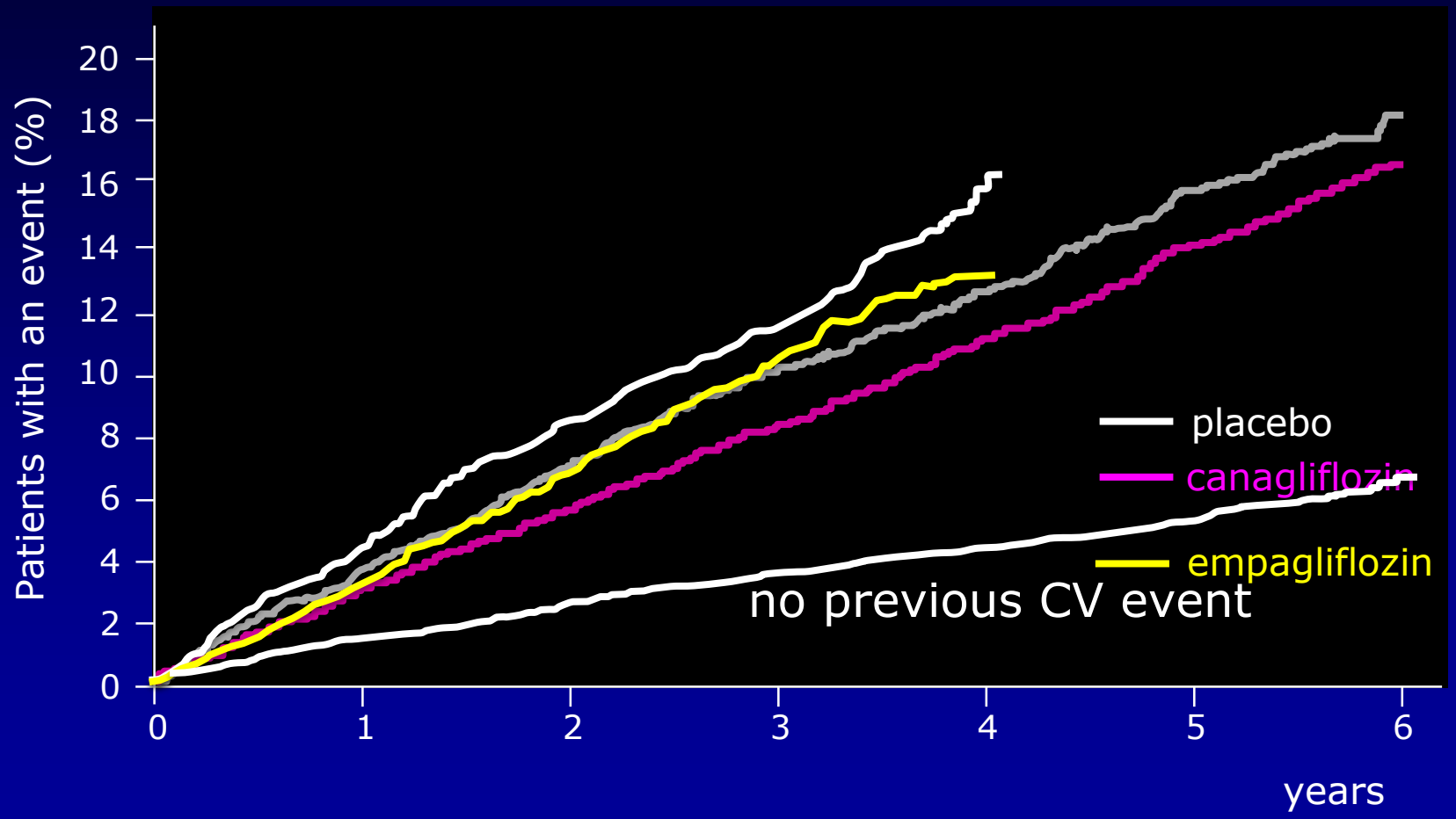
Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

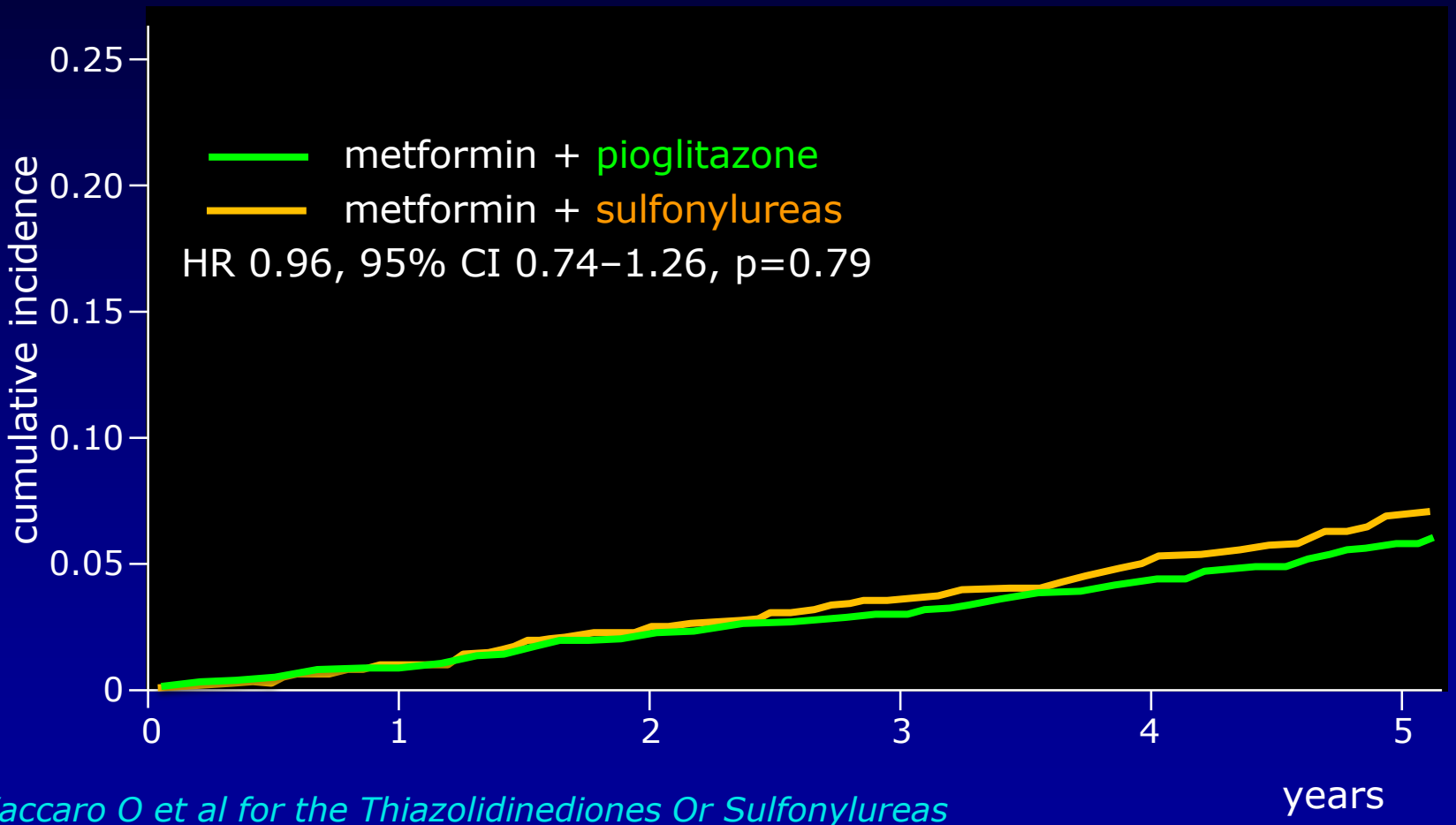
CANVAS & EMPAREG
primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017

TOSCA.IT: primary outcome

all-cause death, non-fatal MI (including silent), non-fatal stroke, or urgent coronary revascularisation



Vaccaro O et al for the Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) study group and Italian Diabetes Society. Lancet DE 5:887, 2017

the burdening clinical point

le gliflozine prevengono CVD in prevenzione secondaria.

devono essere utilizzate

trial in prevenzione primaria **non** è fattibile

come facciamo con i nostri pazienti?

FDA toward RWE

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

The term "real-world evidence" is widely used by those who develop medical products or who study, deliver, or pay for health care, but its specific meaning is elusive. We believe it refers to information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and dis-

shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions. Accordingly, if we are to realize the full promise of such evidence, we must be clear about what it is and how it can be used most effectively, and we must have appropriate expectations about what it can tell us.

Circulation 18:249, 2017

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

Mikhail Kosiborod, MD
Matthew A. Cavender, MD, MPH
Alex Z. Fu, PhD
John P. Wilding, MD, PhD
Kamlesh Khunti, MD, PhD
Reinhard W. Holl, MD, PhD
Anna Norhammar, MD
Kåre I. Birkeland, MD, PhD
Marit Eika Jørgensen, MD, PhD
Marcus Thuresson, PhD
Niki Arya, MSc
Johan Bodegård, MD, PhD
Niklas Hammar, PhD
Peter Fenici, MD, PhD

BACKGROUND: Reduction in cardiovascular death and hospitalization for heart failure (HHF) was recently reported with the sodium-glucose cotransporter-2 inhibitor (SGLT-2i) empagliflozin in patients with type 2 diabetes mellitus who have atherosclerotic cardiovascular disease. We compared HHF and death in patients newly initiated on any SGLT-2i versus other glucose-lowering drugs in 6 countries to determine if these benefits are seen in real-world practice and across SGLT-2i class.

METHODS: Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

RESULTS: After propensity matching, there were 309 056 patients newly initiated on either SGLT-2i or other glucose-lowering drugs (154 [redacted] in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin

Data Sources: Health Records Across Six Countries

Truven MarketScan Claims & Encounters and linked Medicare

National full-population registries

National full-population registries

National full-population registries

Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)

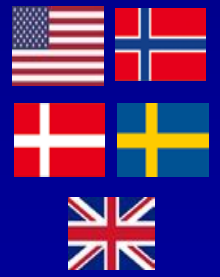
Diabetes Patienten Verlaufsdokumentation (DPV) initiative

cohort 1
HHF

cohort 2

all cause death

composite HHF + all cause death



CVDREAL

Kosiborod M. et al.: Circulation 18:249, 2017

propensity match

SGLT-2i

search a
patient similar
for 42 different
criteria

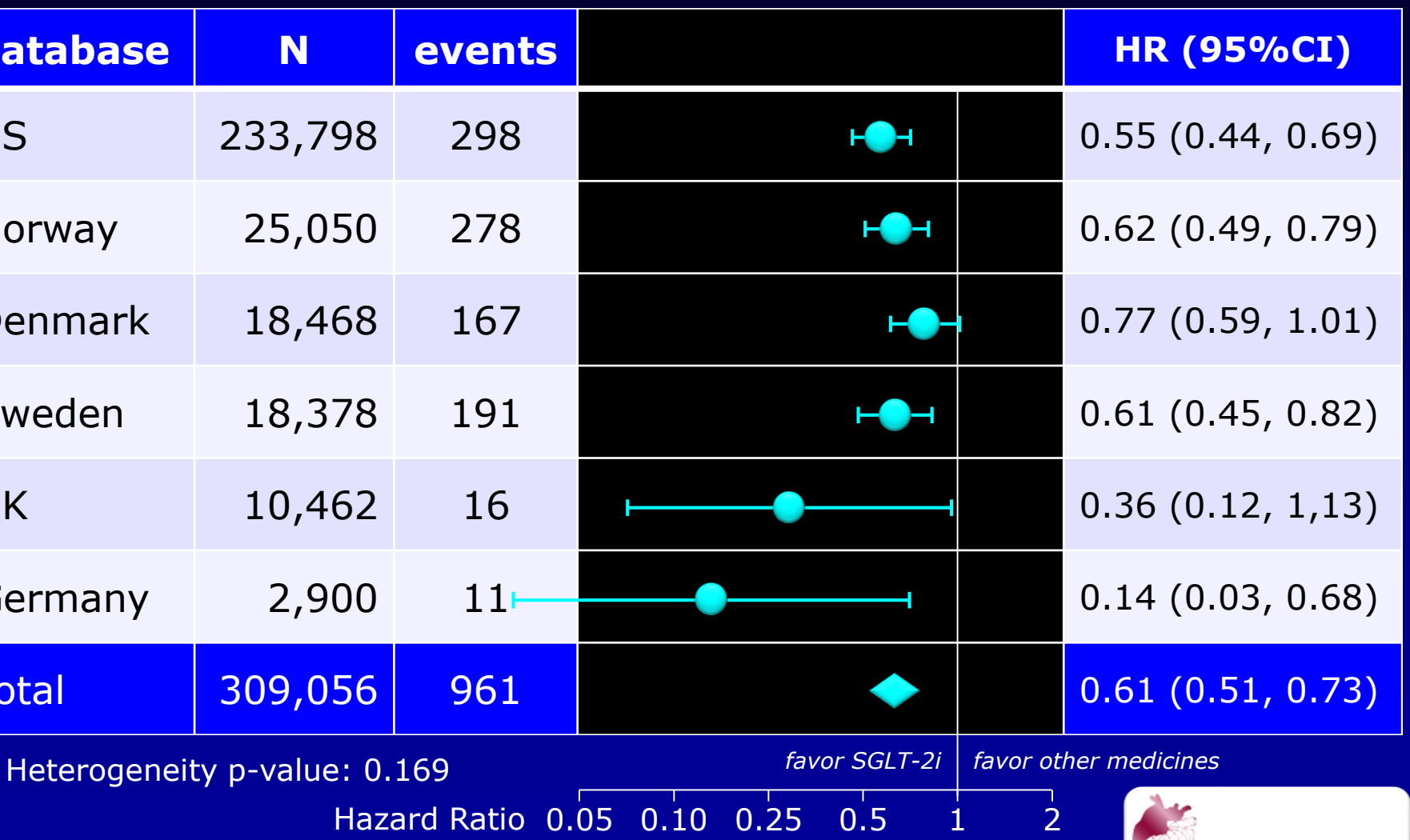
other glucose lowering drugs

other glucose
lowering drugs
compared 1:1

Kosiborod M. et al.: Circulation 18:249, 2017

HHF: primary analysis (N=309,046)

database	N	events	HR (95%CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1,13)
Germany	2,900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



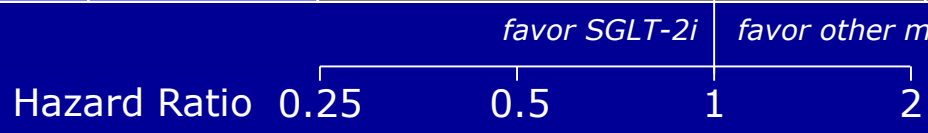
Heterogeneity p-value: 0.169

CVDREAL

Kosiborod M. et al.: Circulation 18:249, 2017

all cause death primary analysis
(N=215,622)

database	N	events	HR (95%CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1,15)
Total	215,622	1334	0.49 (0.41, 0.57)



CVDREAL

Kosiborod M. et al.: Circulation 18:249, 2017

CVD Real Nordic
data sources and Inclusion criteria

Data sources

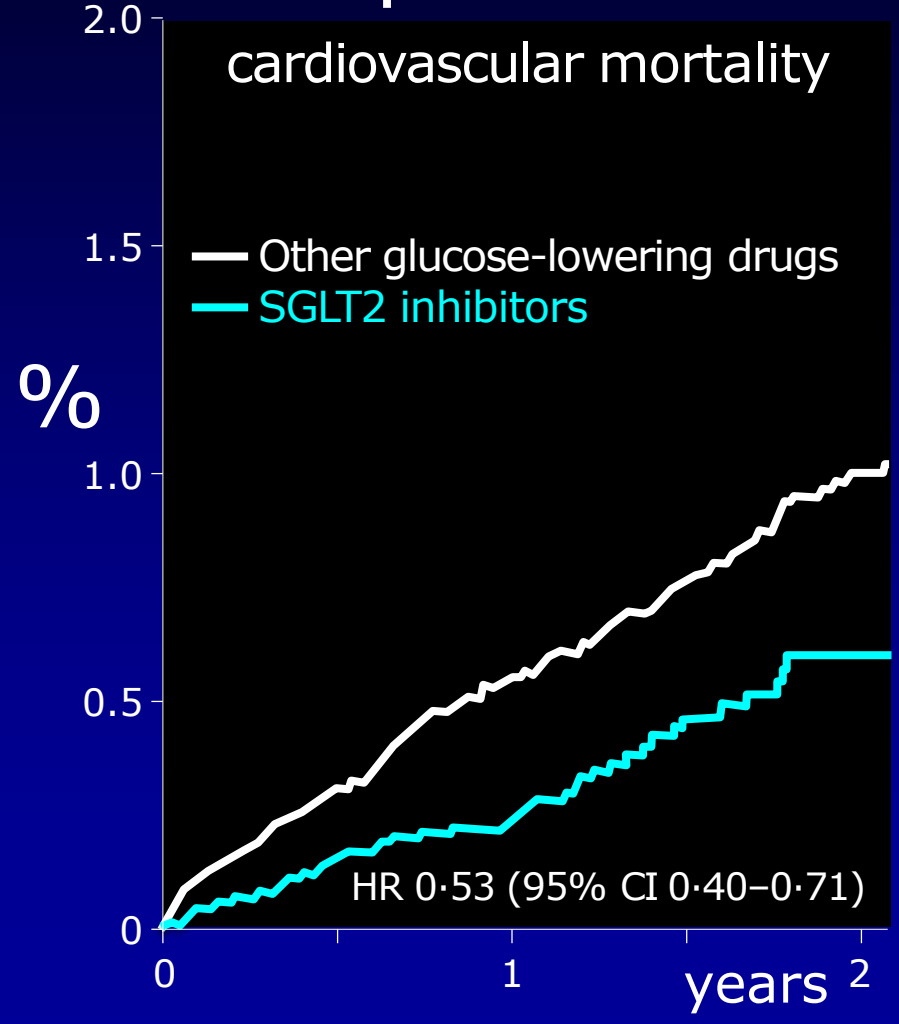
Inclusion criteria

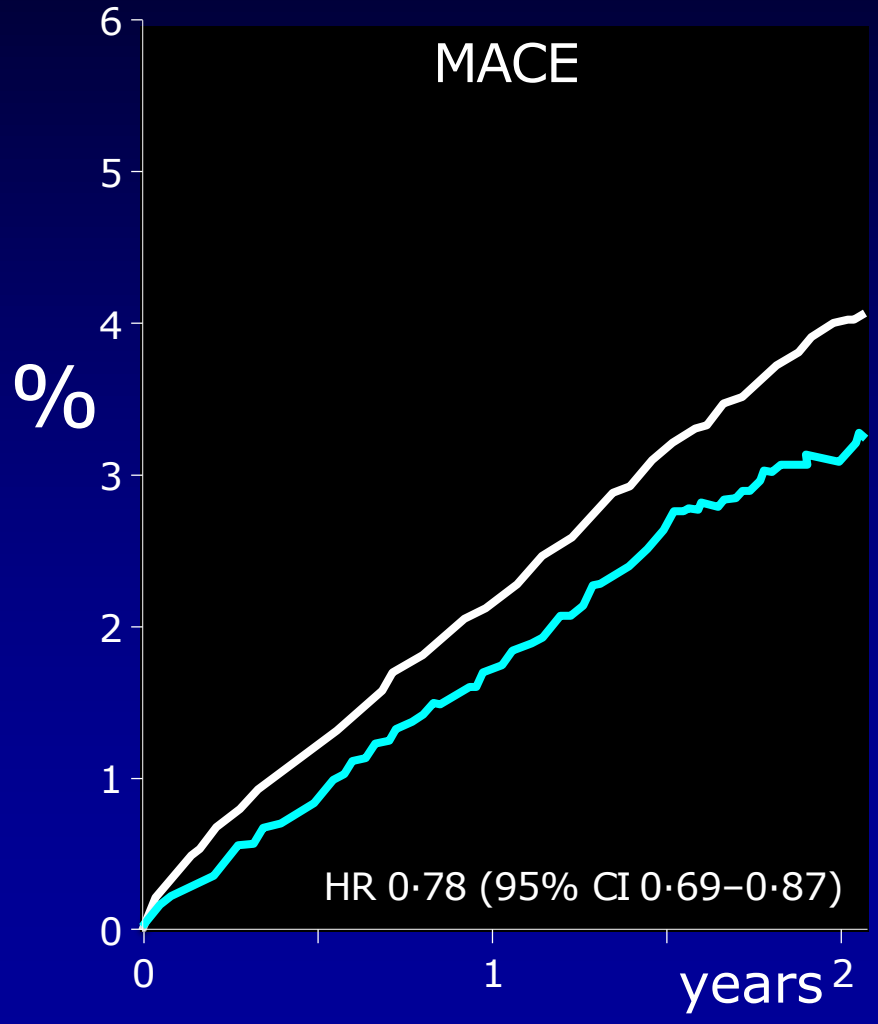
- All patients with T2D dispensed with glucose-lowering drugs between 2012–2015

Exclusion criteria

- T1D or gestational diabetes

CVD Real Nordic: SGLT-2i vs. others
CV mortality and MACE
Kaplan–Meier cumulative curves

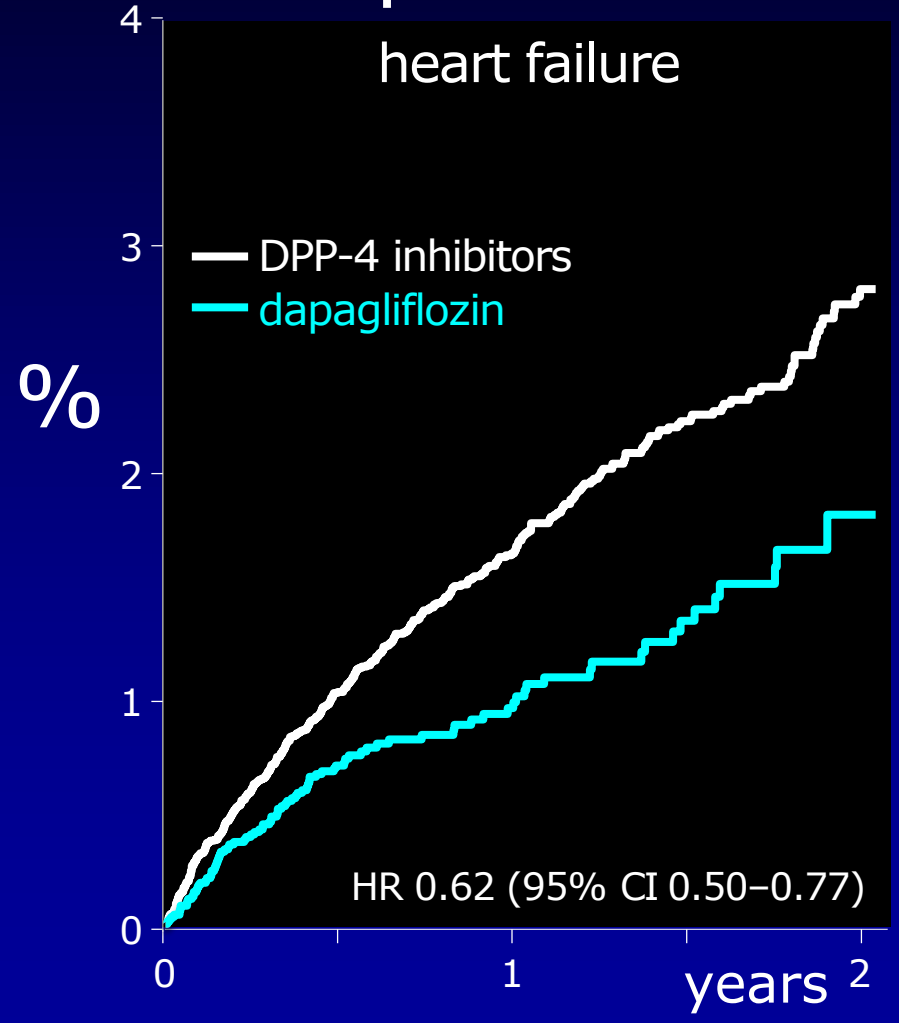


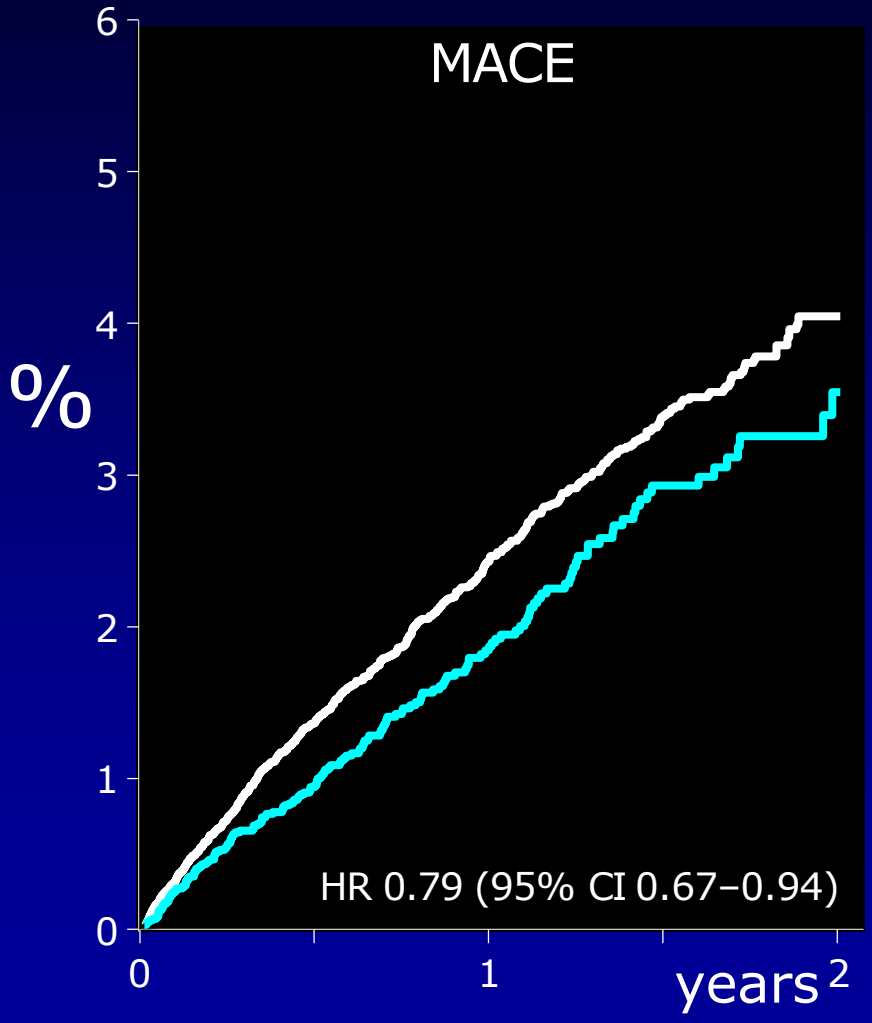


Birkeland KI et al.: Lancet DE 5:709 2017

CVD Real Nordic: dapa vs. DPP-4i
CV mortality and MACE

Kaplan–Meier cumulative curves





Persson F et al.: DOM 20:344, 2018

the burdening clinical point

le gliflozine prevengono CVD in prevenzione secondaria.

devono essere utilizzate

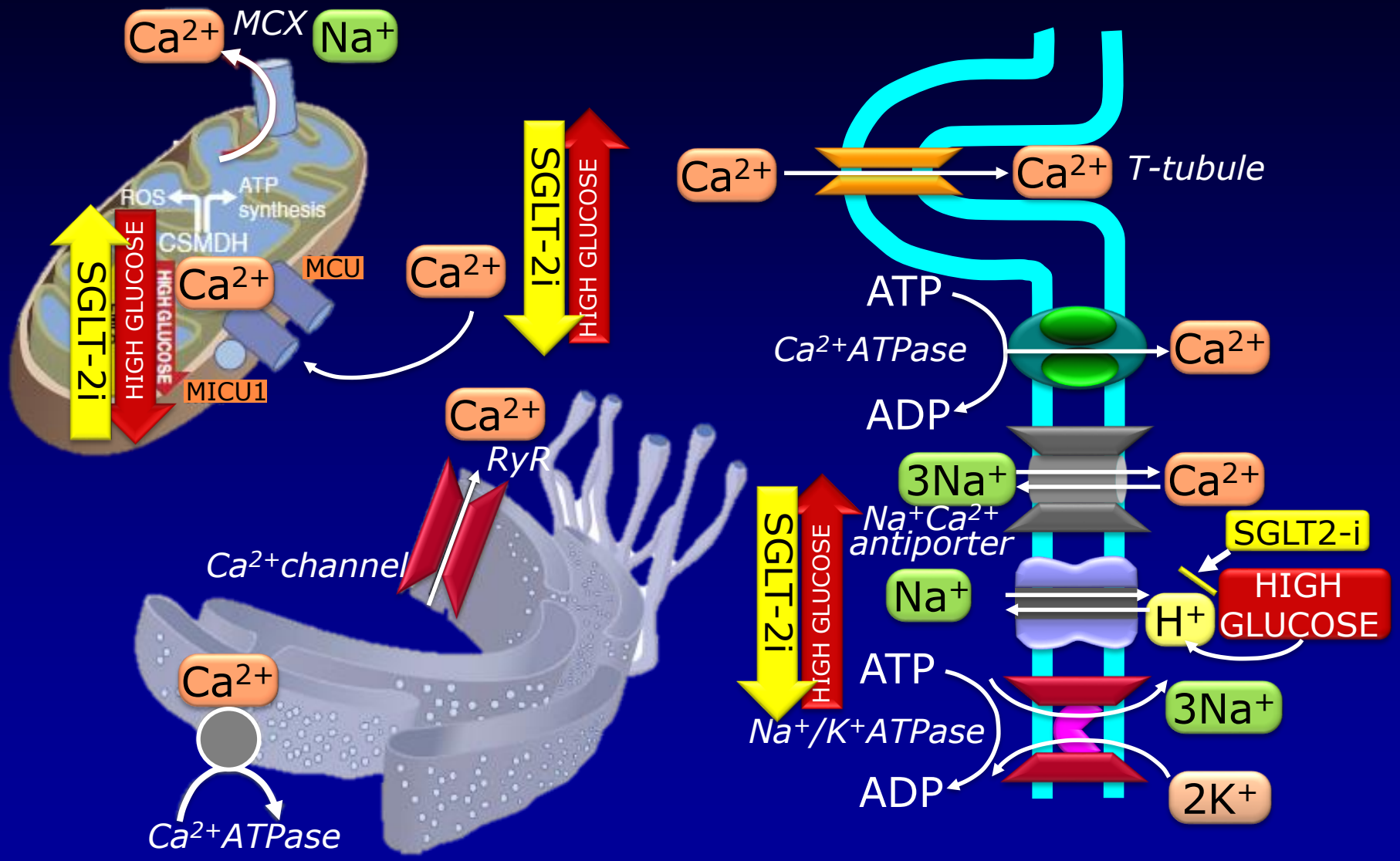
RWE (non trial) suggeriscono una attiva prevenzione nei **nostri** pazienti

con quali meccanismi?

possible mechanisms for CV protection

- vasoconstriction glomerular afferent arteriole
- other transporters
- hemoglobin
- hematocrit increase / fluid loss
- increased β OH oxidation
- increased glucose oxidation
- many others!

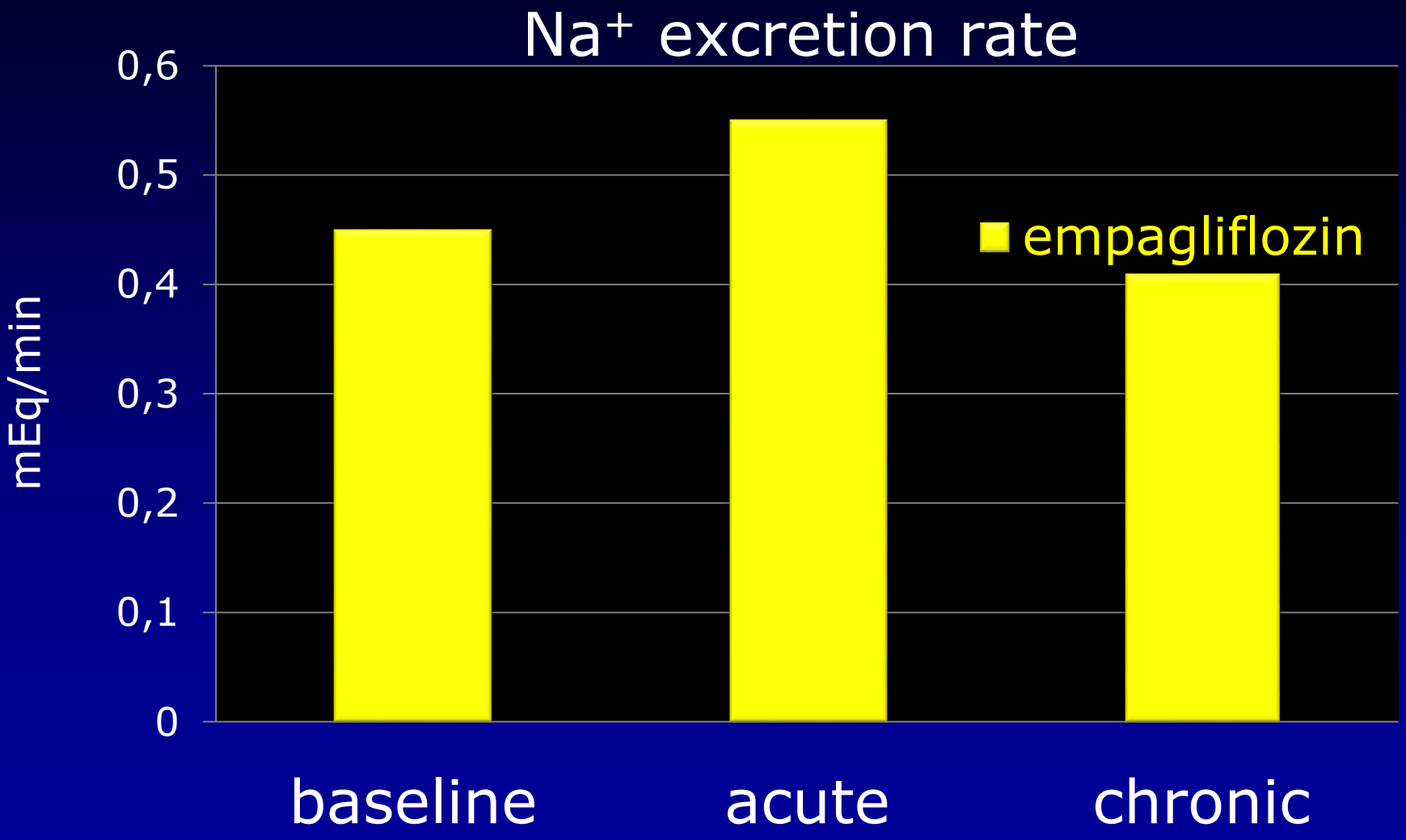
the electrolyte hypothesis



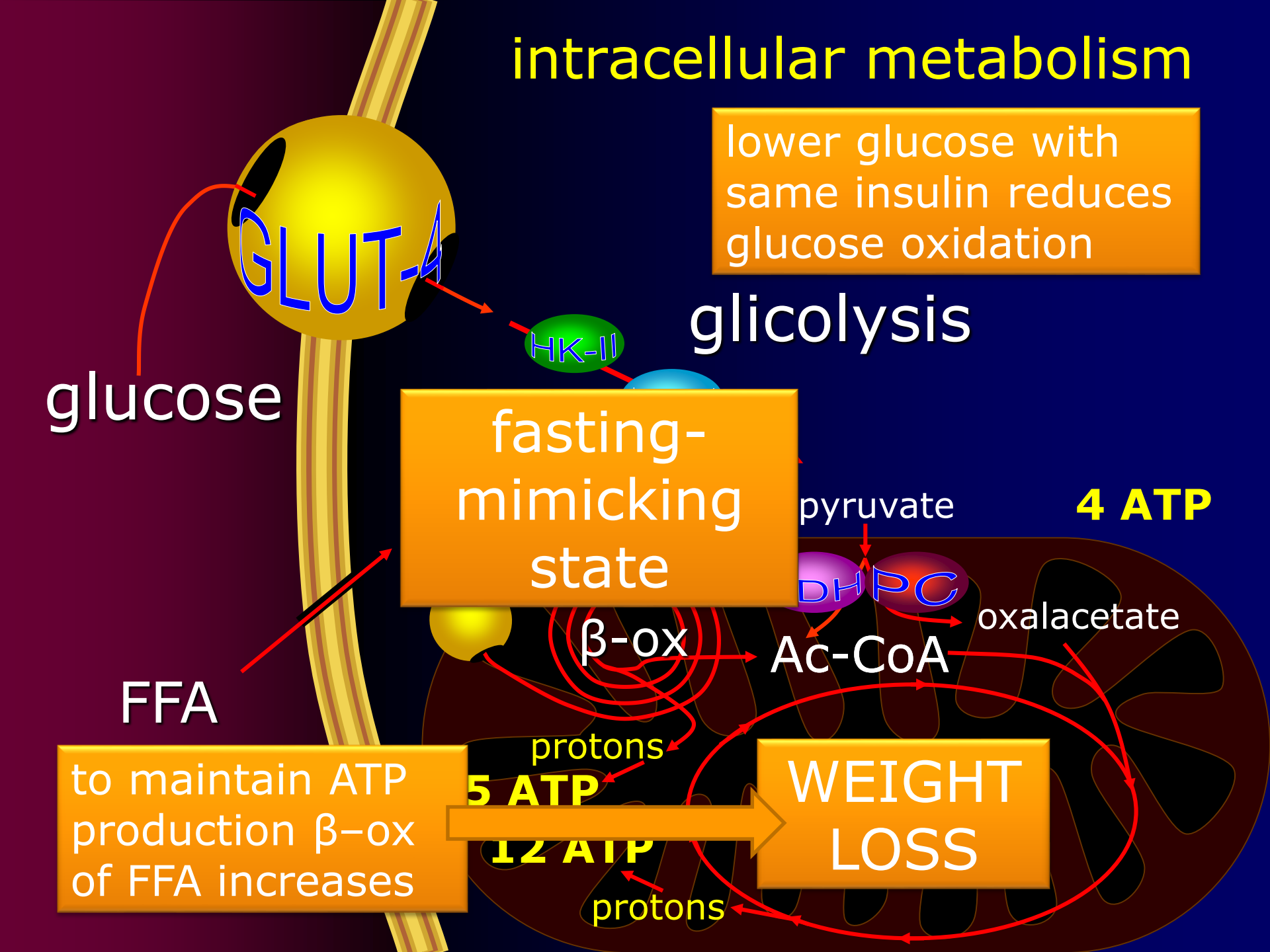
Vettor R, Inzucchi S and Fioretto P: Diabetologia 60:395, 2017

effect of gliflozins on renal sodium handling

in patients with T2D



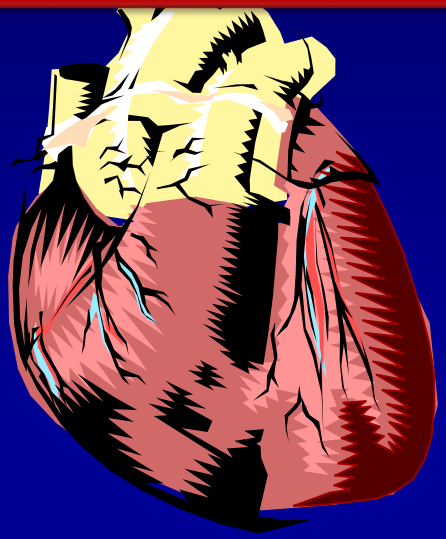
Ferrannini E. et al.:, Diabetes Care, in press 2017


intracellular metabolism
lower glucose with same insulin reduces glucose oxidation
GLUT-4
glucose
HK-II
glicolysis
fasting-mimicking state
pyruvate
4 ATP
DHPC
oxalacetate
β-ox
Ac-CoA
FFA
protons
5 ATP
12 ATP
protons
to maintain ATP production β–ox of FFA increases
WEIGHT LOSS

Shift in Fuel Energetics

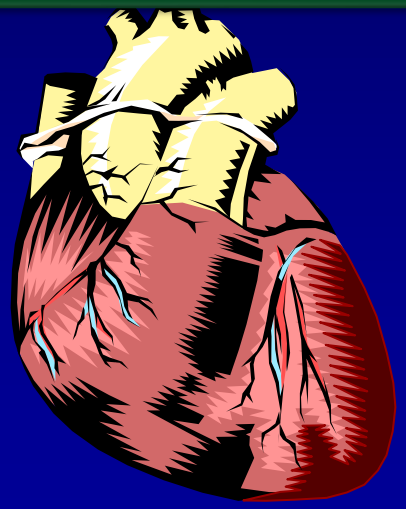
diabetic heart

- ↑ fat oxidation
- ↓ glucose uptake and oxidation
- ↓ P/O ratio
- ↓ cardiac work efficiency



SGLT-2i effect

- ↓ fat oxidation
- ↑ glucose uptake and oxidation
- ↑ P/O ratio
- ↑ cardiac work efficiency



Mudaliar S et al.: Diabetes Care 39:1115, 2016

the βOHB hypotheses compared

Author	glucose oxidation	FFA oxidation	βOHB oxidation
Mudaliar	↑	↓	↑
Ferrannini	↓	↓	↑↑
Lopaschuk	↑↑	↑	=

Mudaliar S et al.: Diabetes Care 39:1115, 2016 doi: 10.2337/dc16-0542
Ferrannini E et al.: Diabetes Care 39:1108, 2016 doi: 10.2337/dc16-0330
Lopaschuk GD and Verma S: Cell Metab 24:200, 2016 10.1016/j.cmet.2016.07.018

DapaHeart

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ClinicalTrials.gov

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Trial record **1 of 4** for: giaccari

Previous Study | Return to List | Next Study

Effects of SGLT2 Inhibition on Myocardial Insulin Sensitivity (DapaHeart)

ClinicalTrials.gov Identifier: NCT03313752

Recruitment Status : Recruiting
First Posted : October 18, 2017
Last Update Posted : January 24, 2018

See **Contacts and Locations**

Sponsor:
Andrea **Giaccari**

Information provided by (Responsible Party):
Andrea **Giaccari**, Catholic University of the Sacred Heart

Study Details | **Tabular View** | **No Results Posted** | Disclaimer | How to Read a Study Record

Study Description

Brief Summary:

A Phase III, single-centre, randomized, 2-arm, parallel-group, double blind, placebo-controlled study, consisting of a screening phase (Days -14 to -1), a 4-week double-blind, placebo-controlled treatment phas

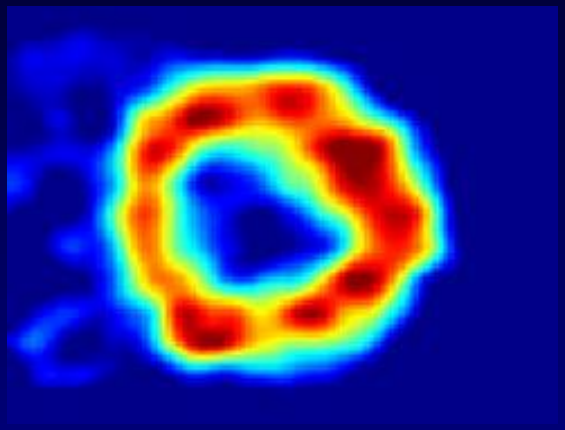
Subjects: Type 2 diabetic patients with coronary artery disease (CAD) not requiring revascularization, with sub-optimal glycemic control (HbA1c 7.5-8.5%) on their current anti-hyperglycemic regimen

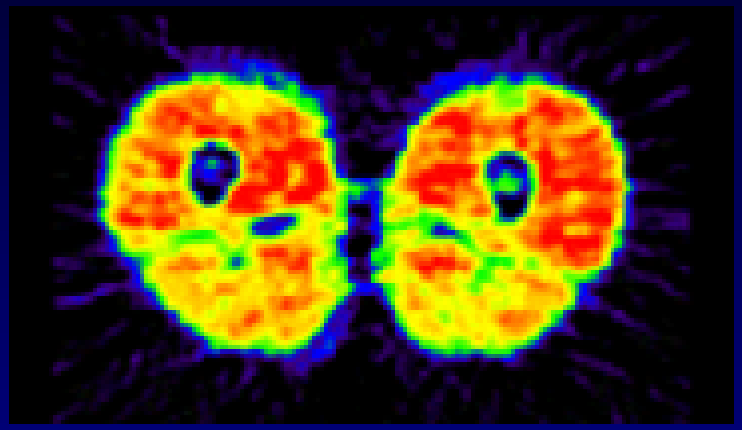
Subjects will be randomized in a 1:1 ratio to dapagliflozin or placebo.

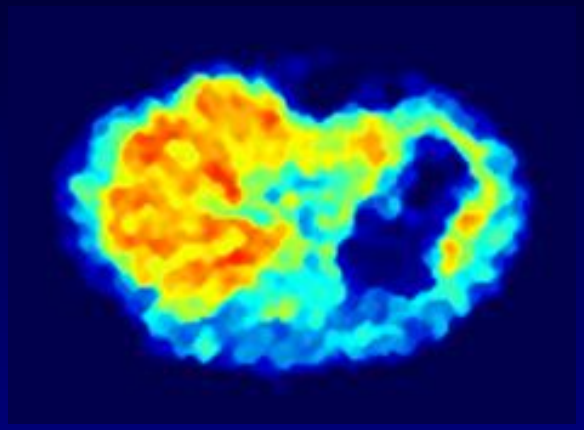
Subjects will undergo screening assessment in the 14-day period preceding administration of the first dose of study drug on Day 1.

organ specific insulin-resistance

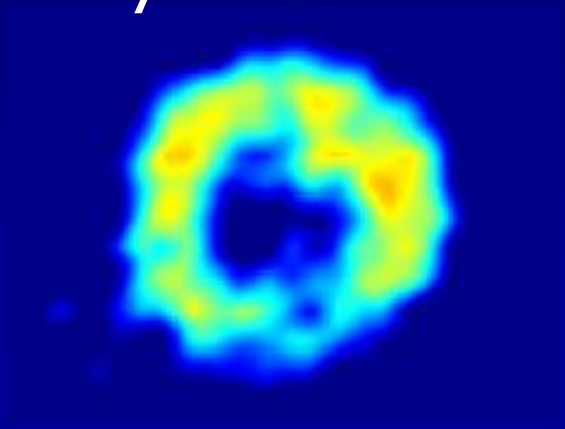
sensitive

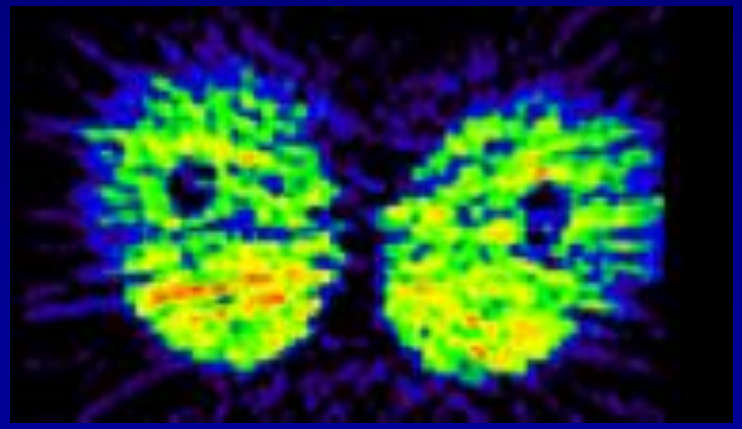


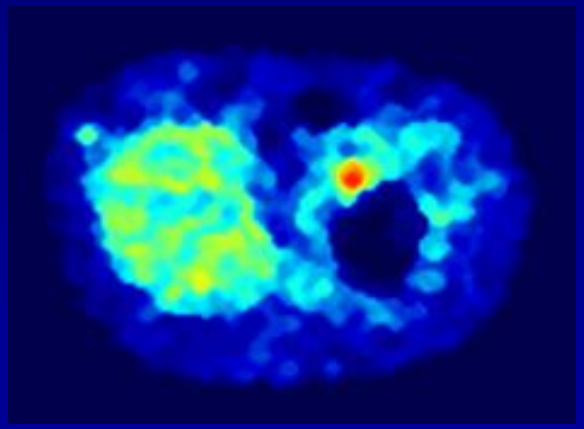




myocardium skeletal muscle liver-abdom







resistant

Iozzo P et al.: Diabetologia 45:1404, 2002

EMPAREG: % mediation analysis

of risk of CV death adjusted for the change from baseline

	HR for CV death	%
HbA1c	0.624 (0.496, 0.785)	3.0
FPG	0.665 (0.529, 0.837)	16.1
SBP	0.593 (0.473, 0.743)	-7,5
DBP	0.614 (0.490, 0.769)	-0,3
Heart rate	0.621 (0.495, 0.780)	2.0
LDL-C	0.596 (0.475, 0.748)	-6,5
HDL-C	0.636 (0.506, 0.799)	6.9
logTG	0.604 (0.482, 0.758)	-3,7
logUACR	0.649 (0.518, 0.815)	11.1
eGFR (CKD-EPI)	0.632 (0.505, 0.791)	5.6
BMI	0.578 (0.460, 0.726)	-12,8
WC	0.598 (0.477, 0.750)	-5,8
Hematocrit	0.791 (0.626, 1.000)	51.8
Hemoglobin	0.780 (0.619, 0.983)	48.9
Albumin	0.696 (0.555, 0.873)	25.5
Uric acid	0.693 (0.553, 0.869)	24.6

Inzucchi SE et al.: Diabetes Care 41:356, 2018

the burdening clinical point

le gliflozine prevengono CVD in prevenzione secondaria.

devono essere utilizzate

RWE (non trial) suggeriscono una attiva prevenzione nei nostri pazienti

con quali meccanismi?

vedremo. **Intanto usiamoli !**


Gian Pio
Francesca
Flavia
Ilaria
Teresa
Alice
Simona
Serena
Rachele
TEAM diabete
Centro per le malattie
Endocrine e Metaboliche
Gemelli