AMD ASSOCIAZIONE MEDICI DIABETOLOGI LAZIO

SID Società Italiana di Diabetologia

Evento intersocietario **AMD-SID Lazio**

NASH & NAFLD e farmaci per il diabete

DALLA MEDICINA DELLE PATOLOGIE ALLA SFIDA DELLE COMPLESSITÀ:

evoluzione e prospettive nella gestione della malattia diabetica

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TEAM DIABETE

Gemelli

SABATO 18 MAGGIO 2019

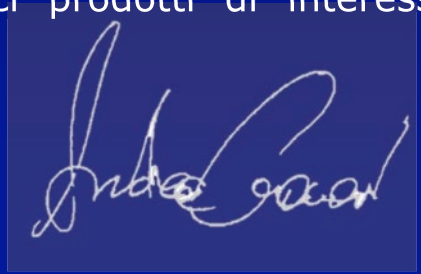
MONTE PORZIO CATONE || VILLA MONDRAGONE

disclosure

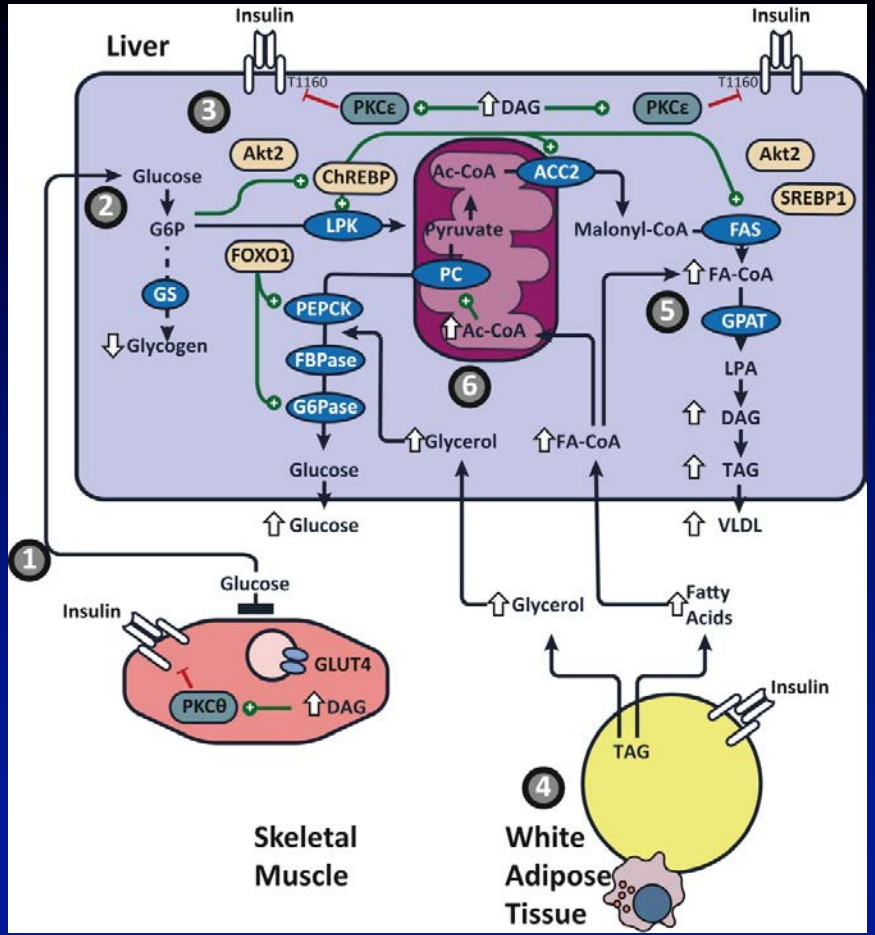
Il dr. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

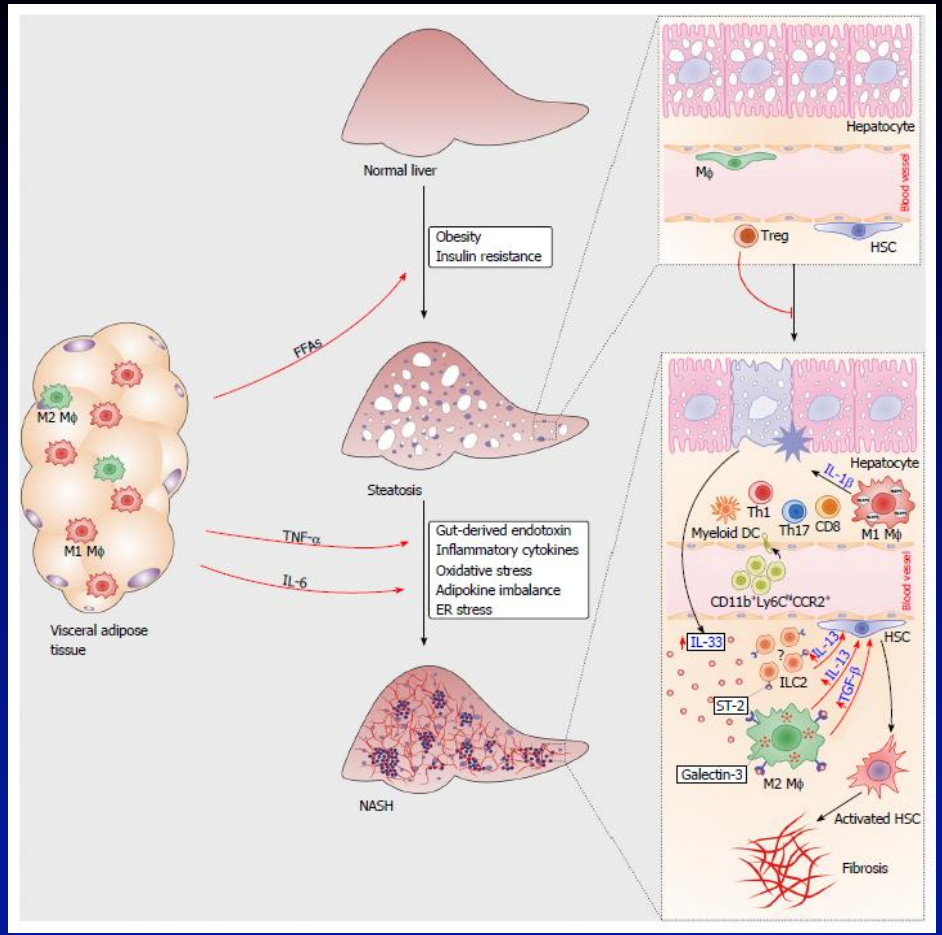
- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).



molecular mechanisms of NASH

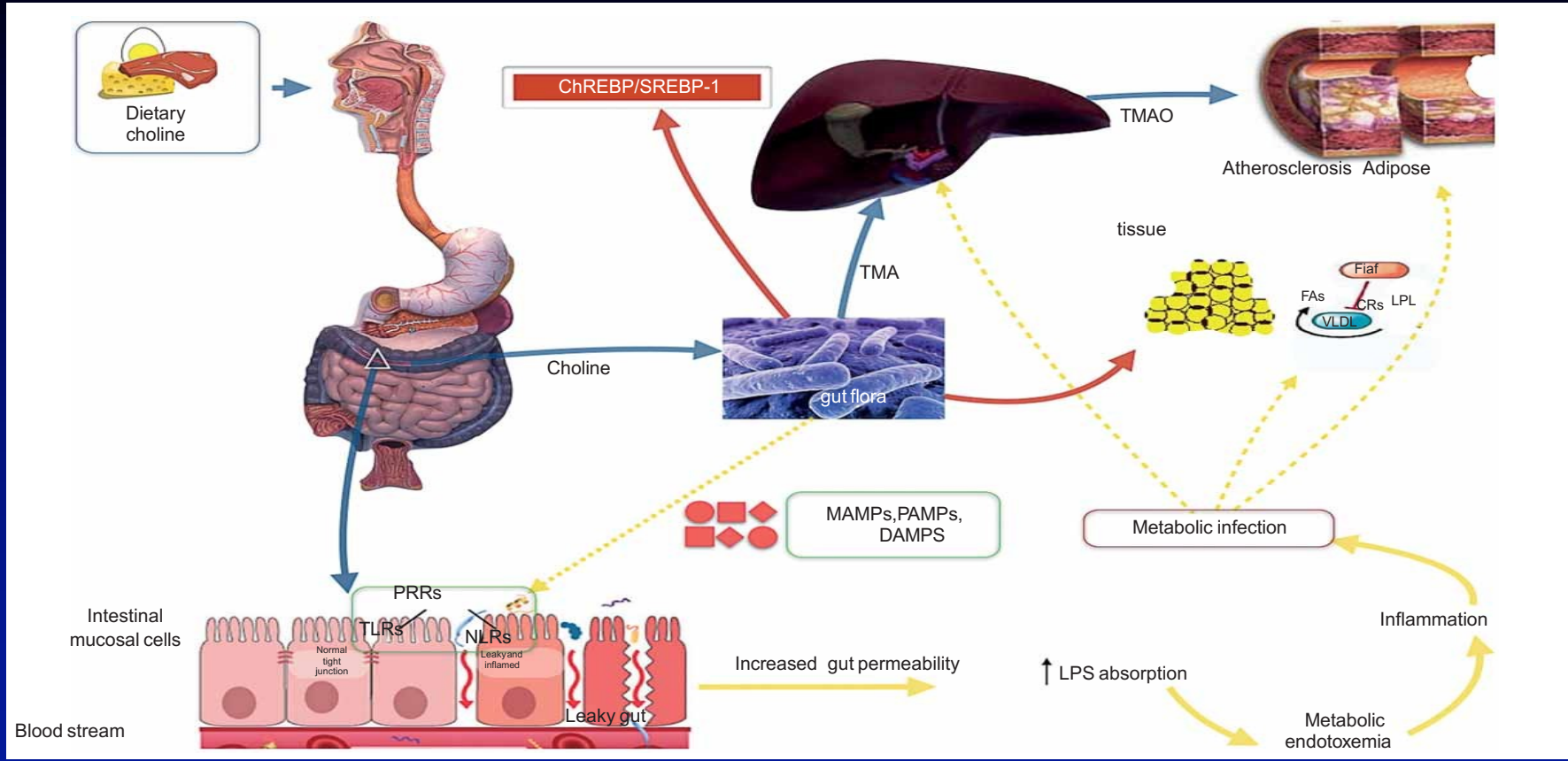




Samuel VT & Shulman GI Cell Metab 27:22, 2018

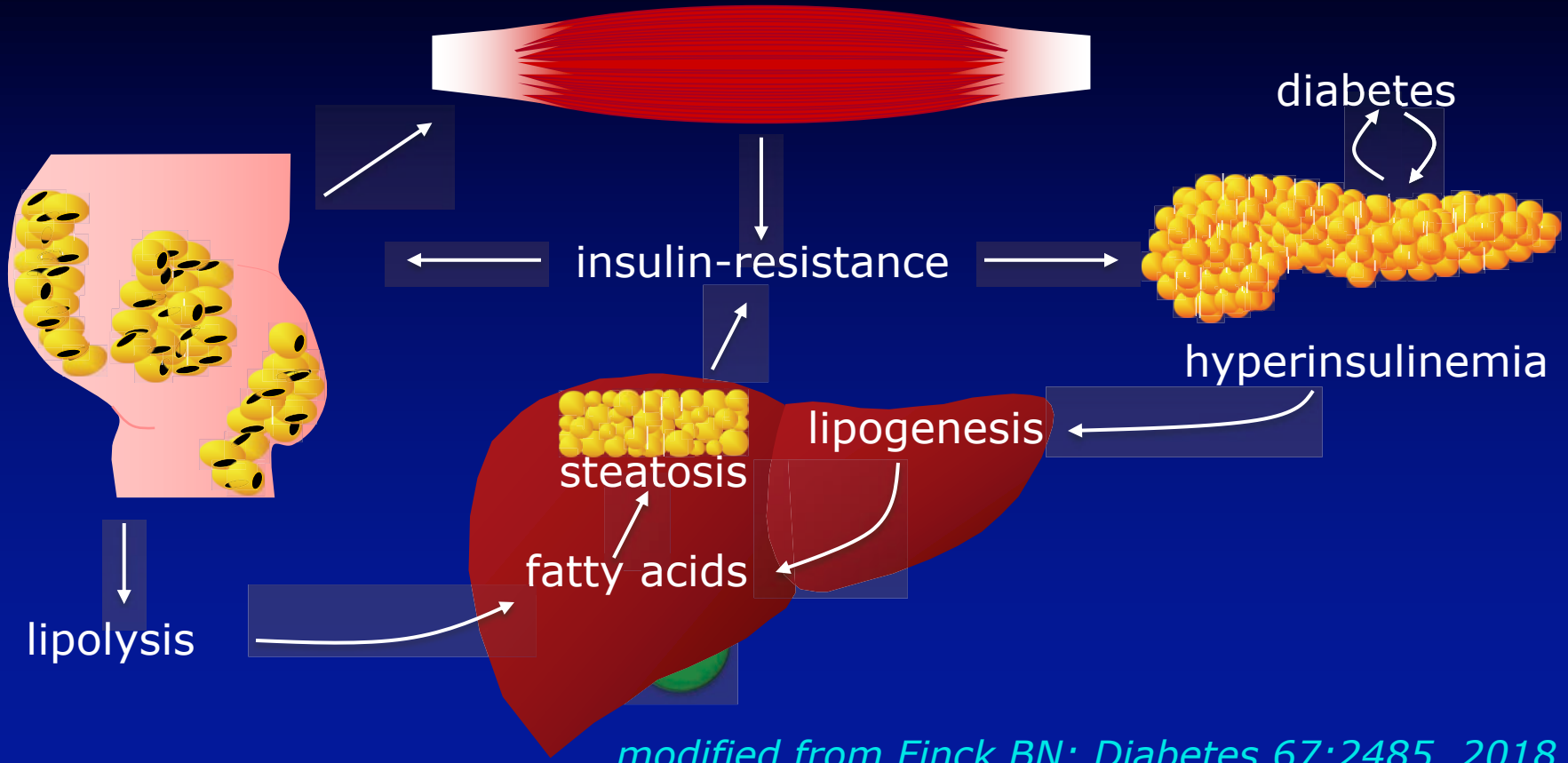
Pejnovic N et al.: W.J.Gastroenterol 22:9796, 2016

microbiota and NASH



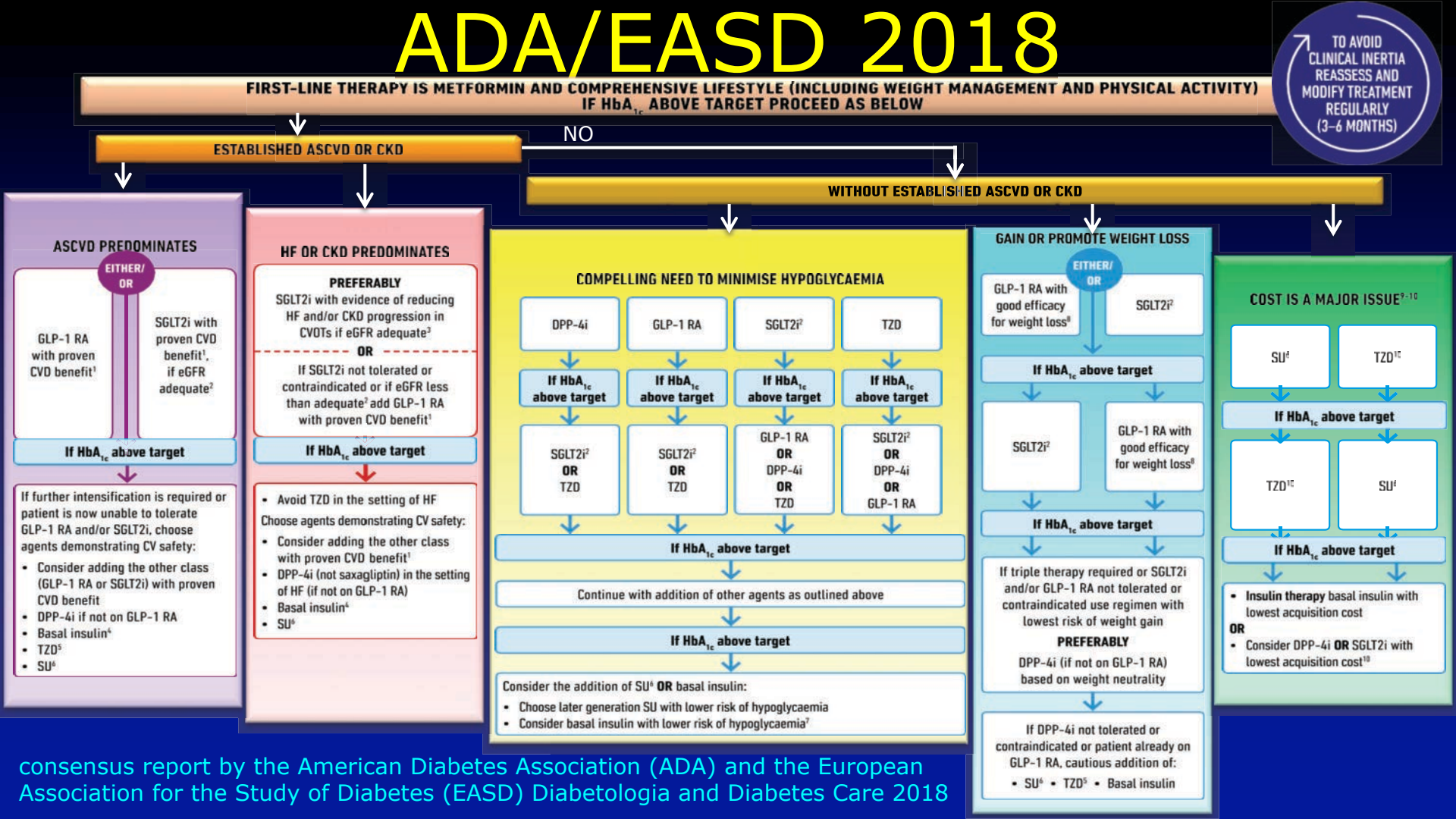
Ponziani FR et al.: Expert Rev Gastroenterol Hepatol 98:1055, 2016

from insulin-resistance to liver steatosis



modified from Finck BN: Diabetes 67:2485, 2018

ADA/EASD 2018

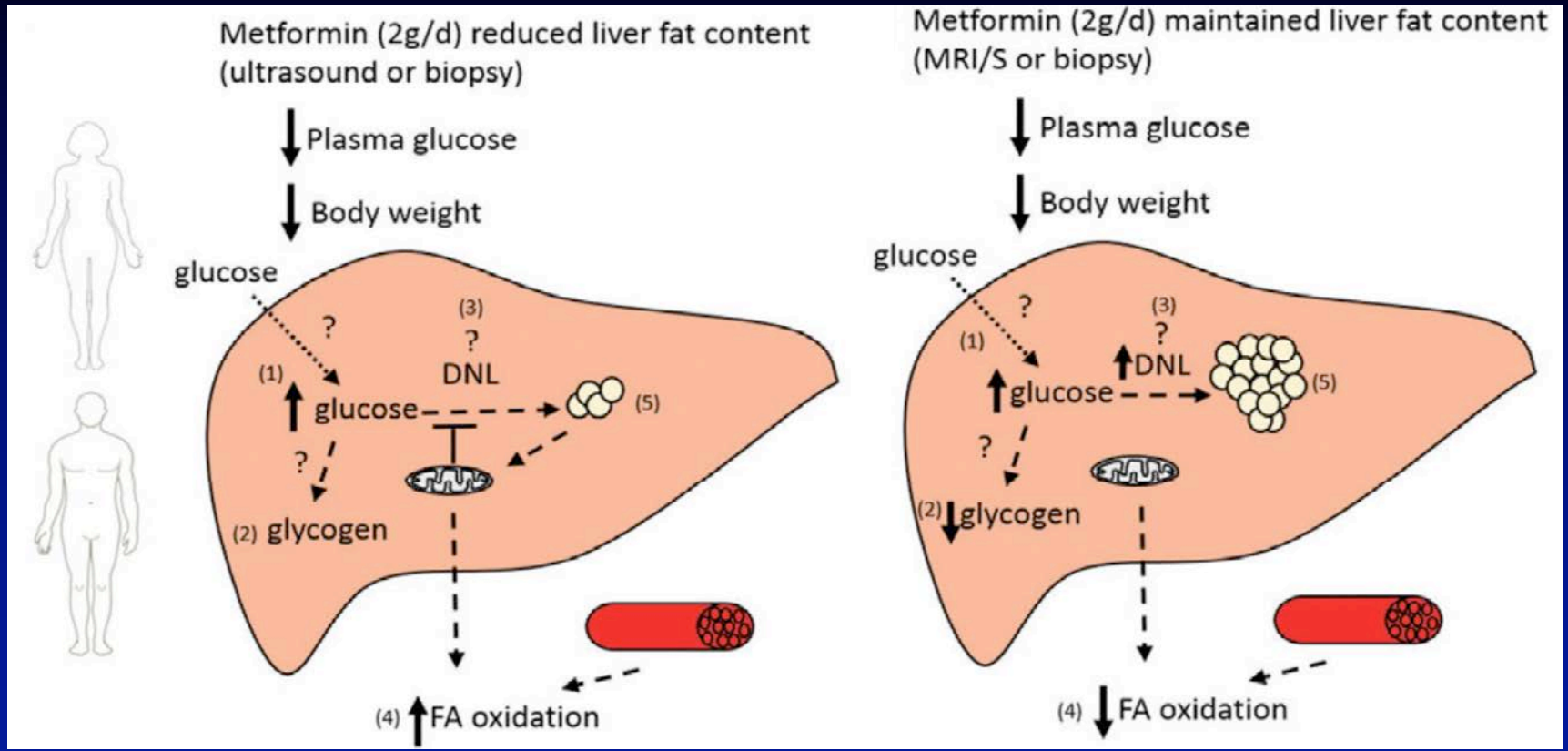


consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetologia and Diabetes Care 2018

insulin sensitizers

- metformin
- GLP-1 RA
- pioglitazone
- SGLT inhibitors

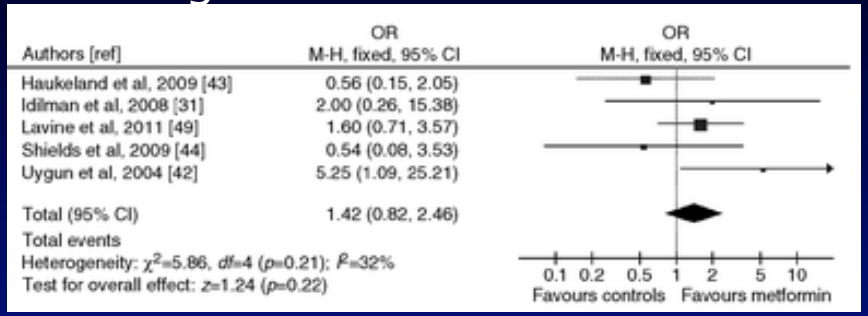
metformin and NASH



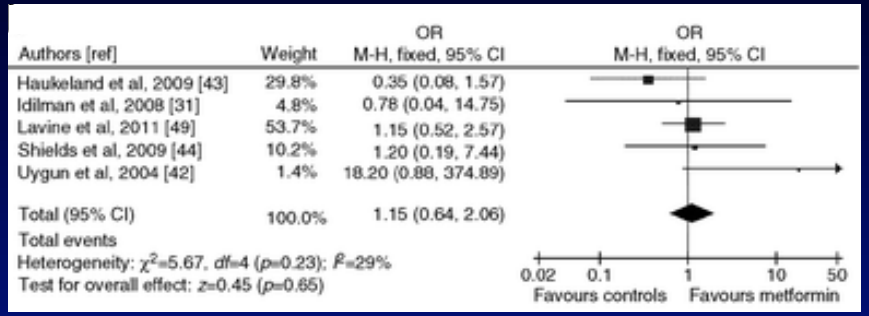
Green CJ et al.: DOM 21:749, 2019 doi: 10.1111/dom.13592

metformin and NASH

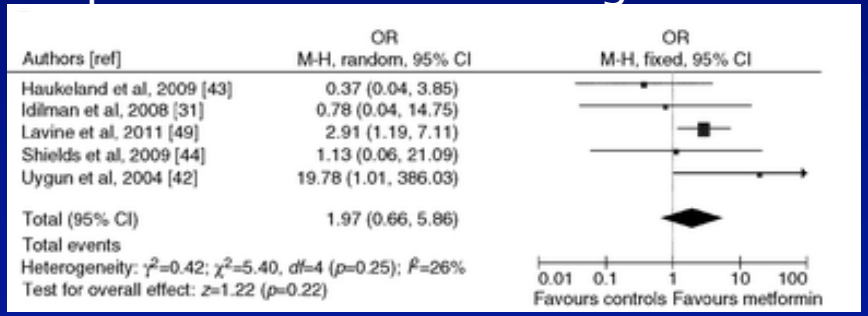
histological steatosis



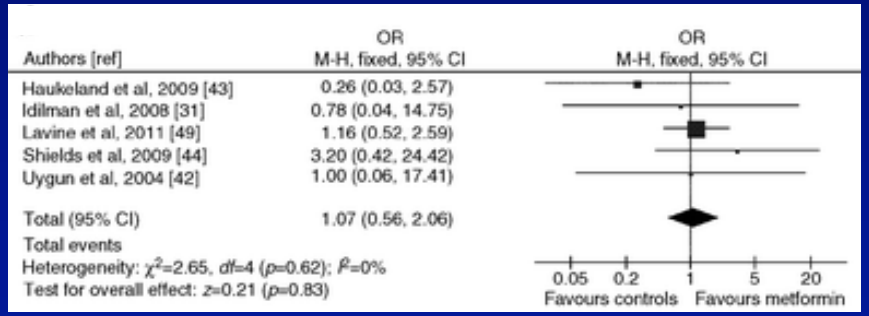
lobular inflammation



hepatocellular ballooning



fibrosis

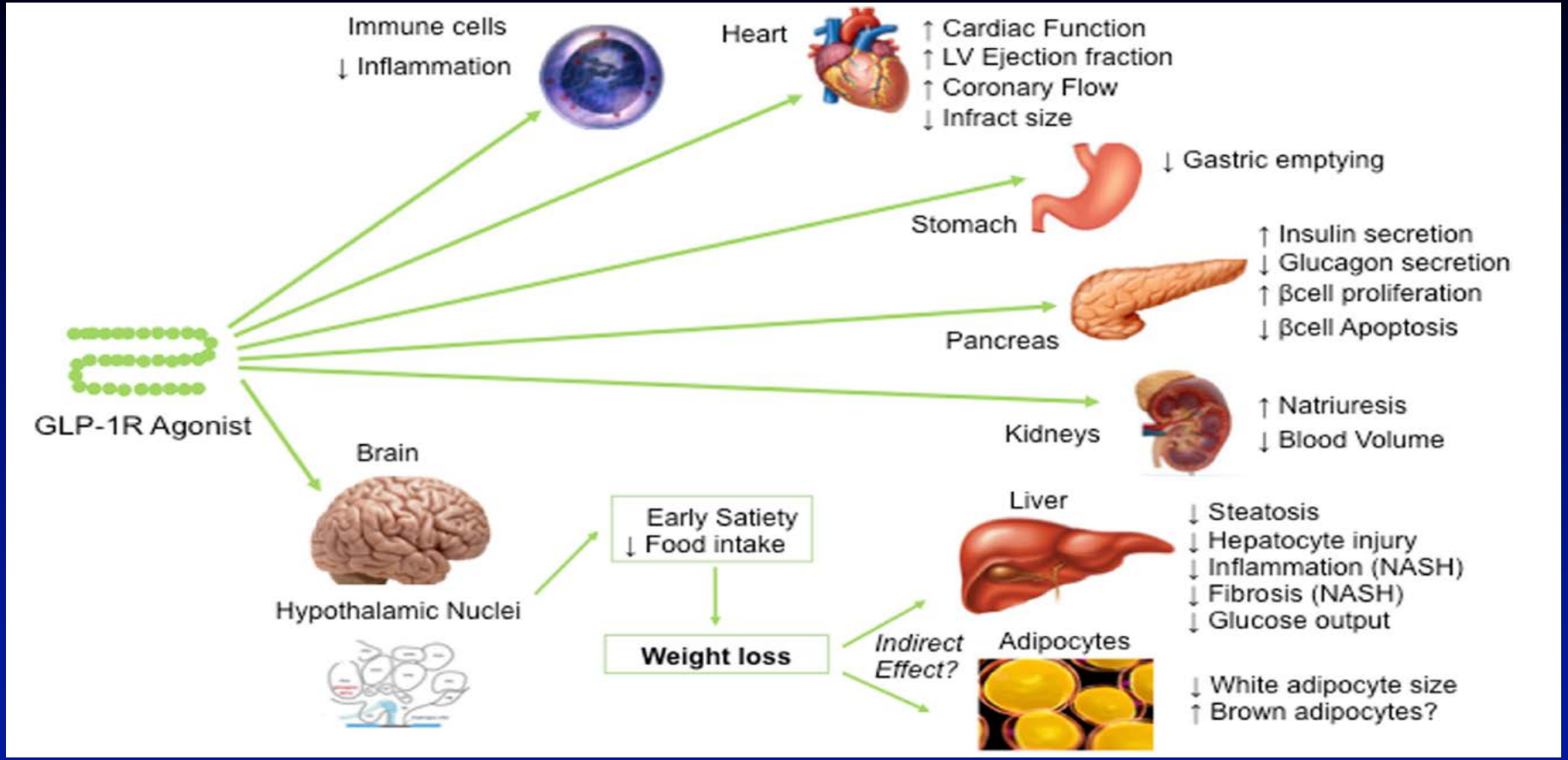


Musso G et al.: Diabetologia. 55:885, 2012 doi: 10.1007/s00125-011-2446-4

insulin sensitizers

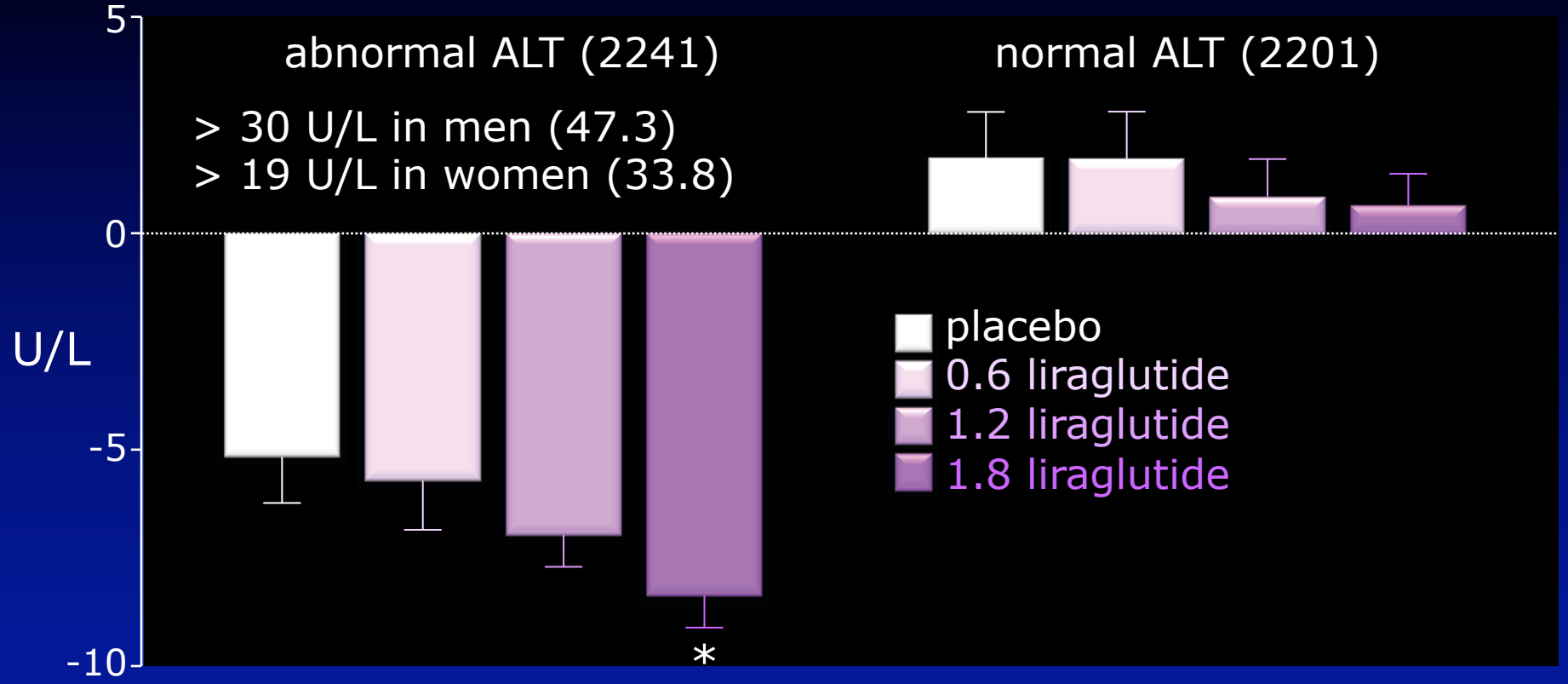
- metformin: no evidence
- GLP-1 RA
- pioglitazone
- SGLT inhibitors

GLP-1 RA and NASH



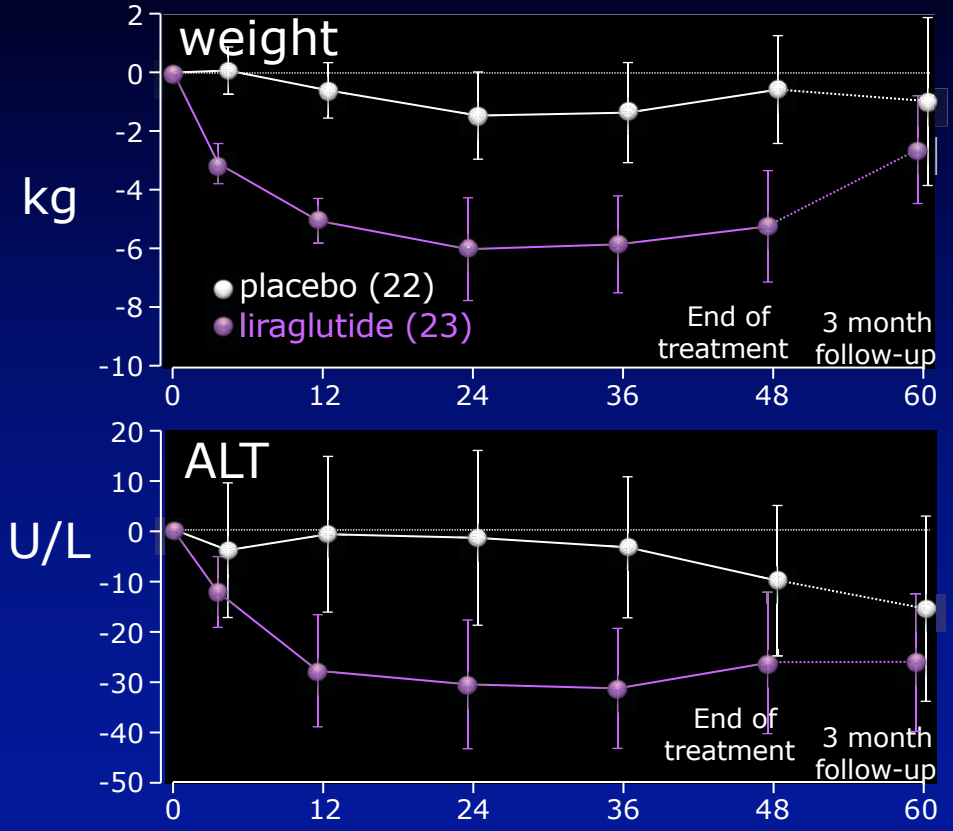
Dhir G and Cusi K.: J Investig Med. 66:7, 2018 doi: 10.1136/jim-2017-000554

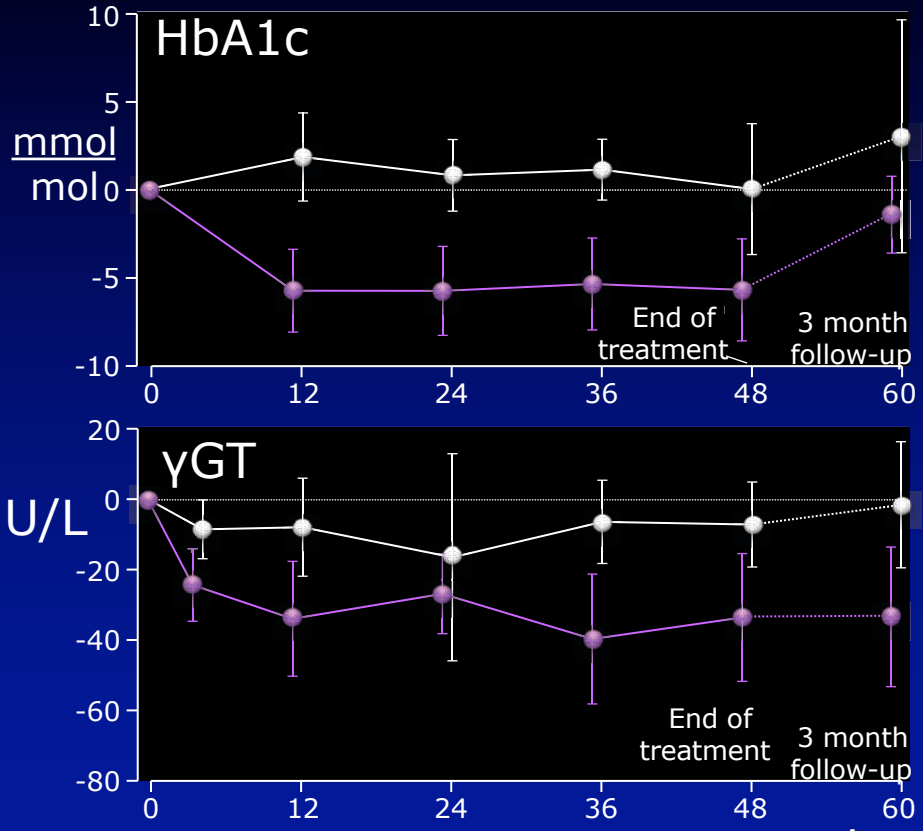
ALT in LEAD program



Armstrong MJ et al.: Aliment Pharmacol Ther 37:234, 2013 doi: 10.1111/apt.12149

LEAN: liraglutide in NASH





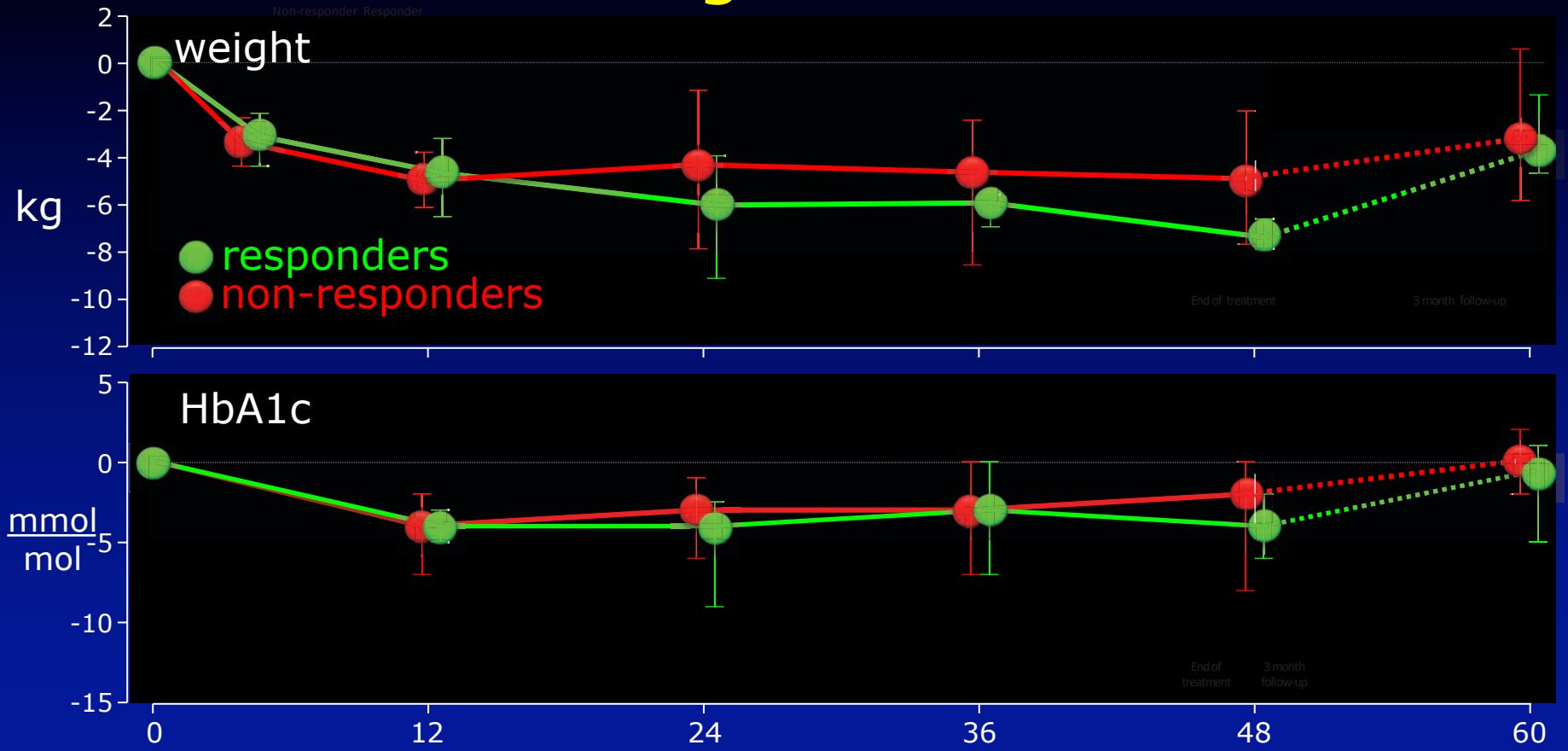
Armstrong MJ et al.: Lancet 387:679, 2016 doi: 10.1016/S0140-6736(15)00803-X.

LEAN: liraglutide in NASH

endpoint	liraglutide	placebo	Relative Risk	p value
Number of patients with paired liver biopsies	23	22		
Patients with resolution of NASH	9 (39%)	2 (9%)	4.3 (1.0 to 17.7)	**0.019**
Total NAFLD activity score				
Change in score	-1.3 (1.6)	-0.8 (1.2)	-0.5 (-1.3 to 0.3)	0.24
Patients with improvement	17 (74%)	14 (64%)	1.2 (0.8 to 1.7)	0.46
Hepatocyte ballooning score				
Mean change	-0.5 (0.7)	-0.2 (0.6)	-0.3 (-0.7 to 0.1)	0.15
Patients with improvement	14 (61%)	7 (32%)	1.9 (1.0 to 3.8)	**0.05**
Steatosis				
Change in score	-0.7 (0.8)	-0.4 (0.8)	-0.2 (-0.6 to 0.2)	0.32
Patients with improvement	19 (83%)	10 (45%)	1.8 (1.1 to 3.0)	**0.009**
Lobular inflammation				
Change in score	-0.2 (0.6)	-0.2 (0.5)	-0.01 (-0.3 to 0.3)	0.97
Patients with improvement	11 (48%)	12 (55%)	0.9 (0.5 to 1.6)	0.65

Armstrong MJ et al.: Lancet 387:679, 2016 doi: 10.1016/S0140-6736(15)00803-X.

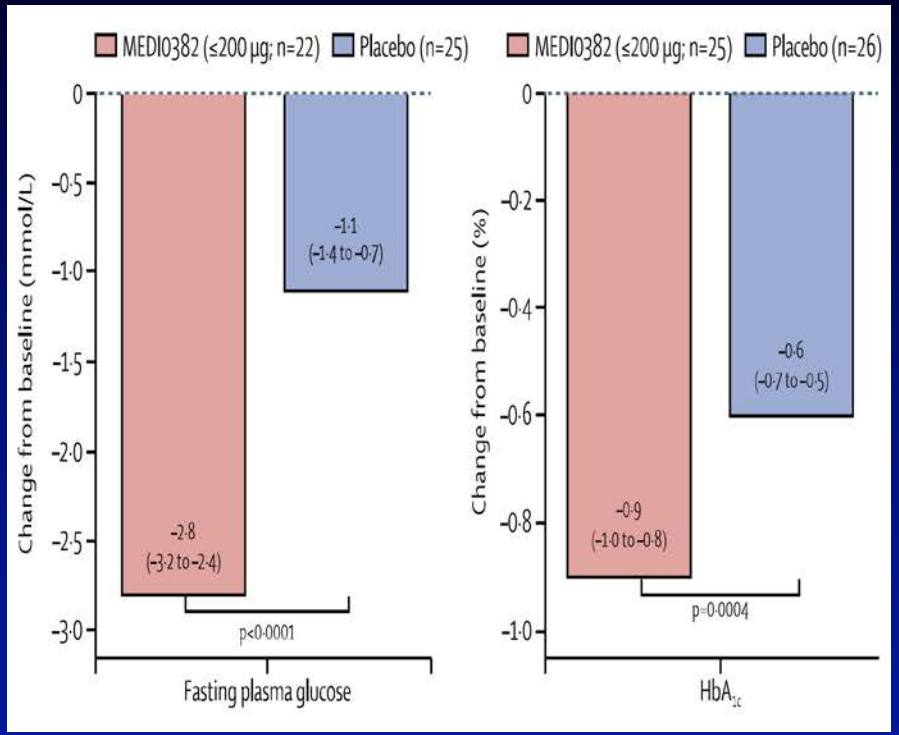
LEAN: liraglutide in NASH

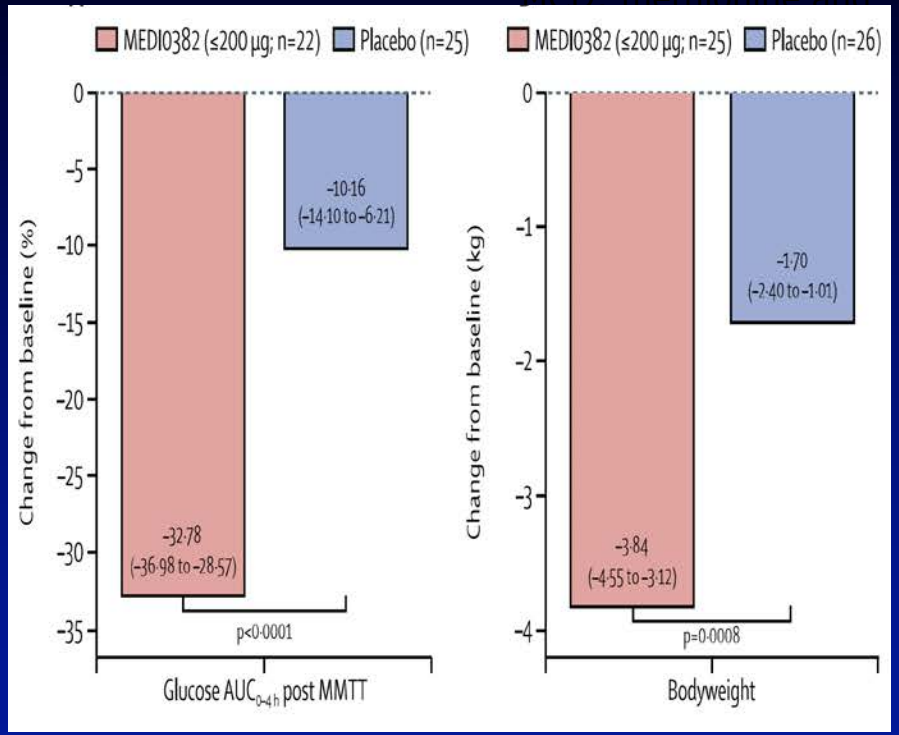


Armstrong MJ et al.: Lancet 387:679, 2016 doi: 10.1016/S0140-6736(15)00803-X.

GLP-1/Glucagon dual agonist

a phase 2 study

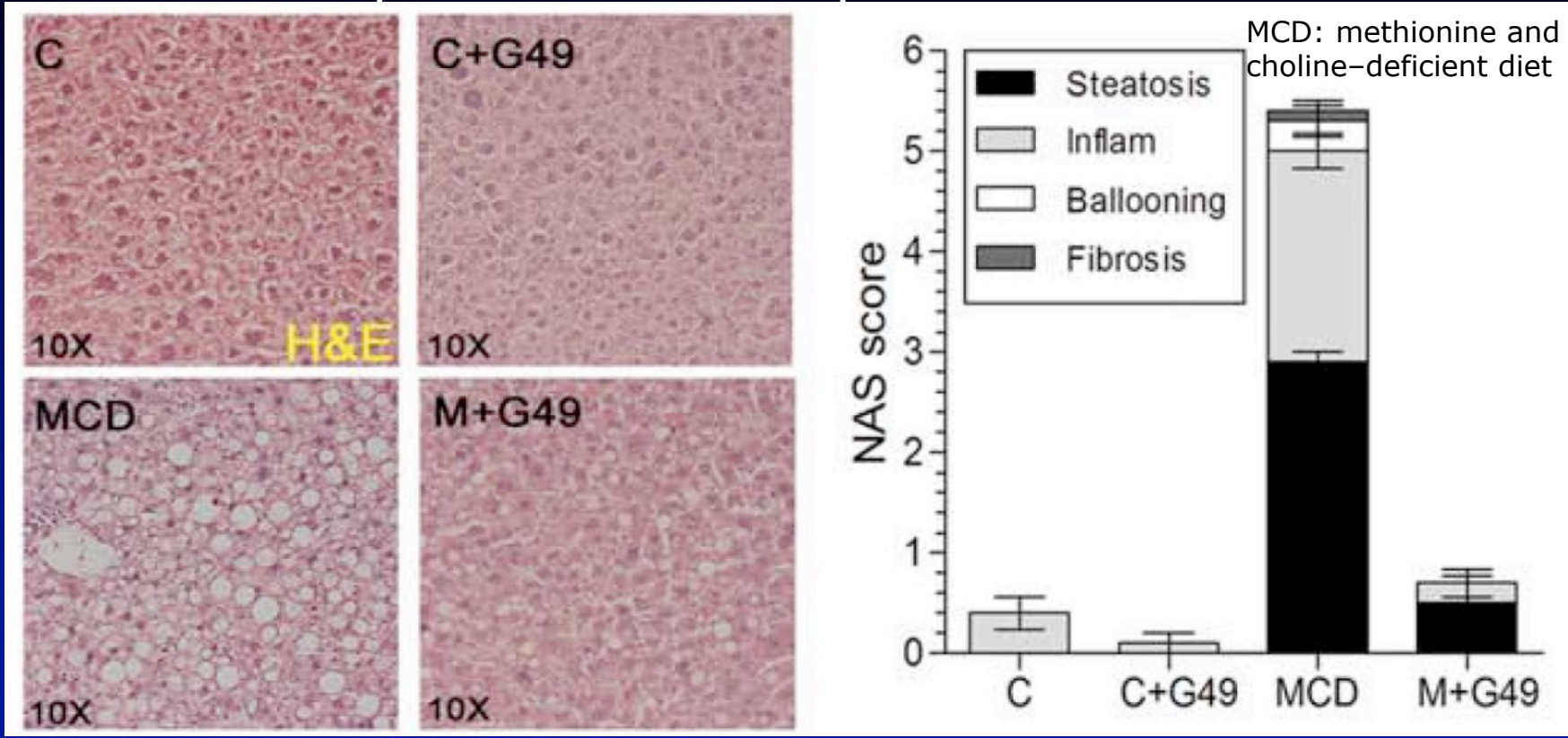




Ambery P. et al.: Lancet 391:2607, 2018 doi: 10.1016/S0140-6736(18)30726-8

GLP-1/Glucagon dual agonist

improves steatohepatitis in mice



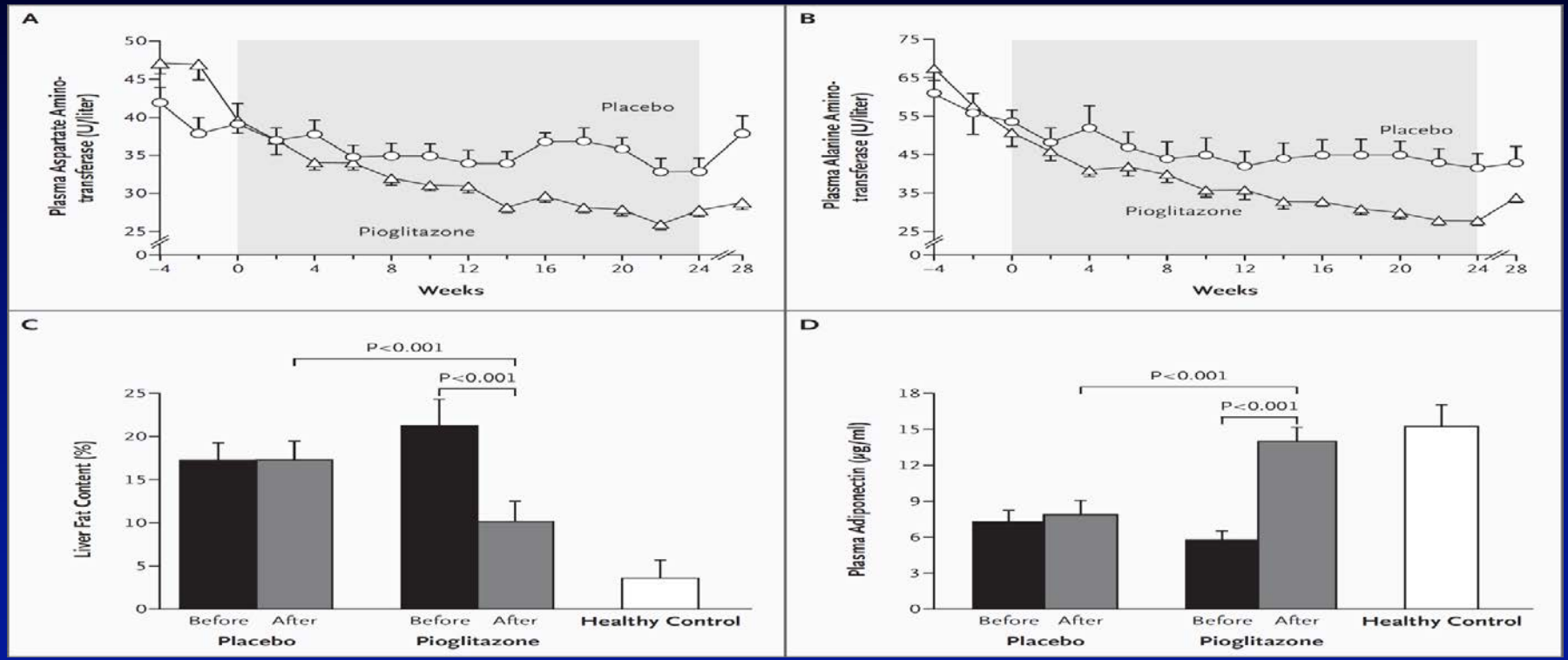
Valdecantos MP et al.: Hepatology. 65:950, 2017 doi: 10.1002/hep.28962

insulin sensitizers

- metformin: no evidence
- GLP-1 RA: works; weight loss?
- pioglitazone
- SGLT inhibitors

pioglitazone in NASH

(55; biopsy proven, IGT or T2DM)



Belfort R. et al.: NEJM 355:2297, 2006

pioglitazone in NASH

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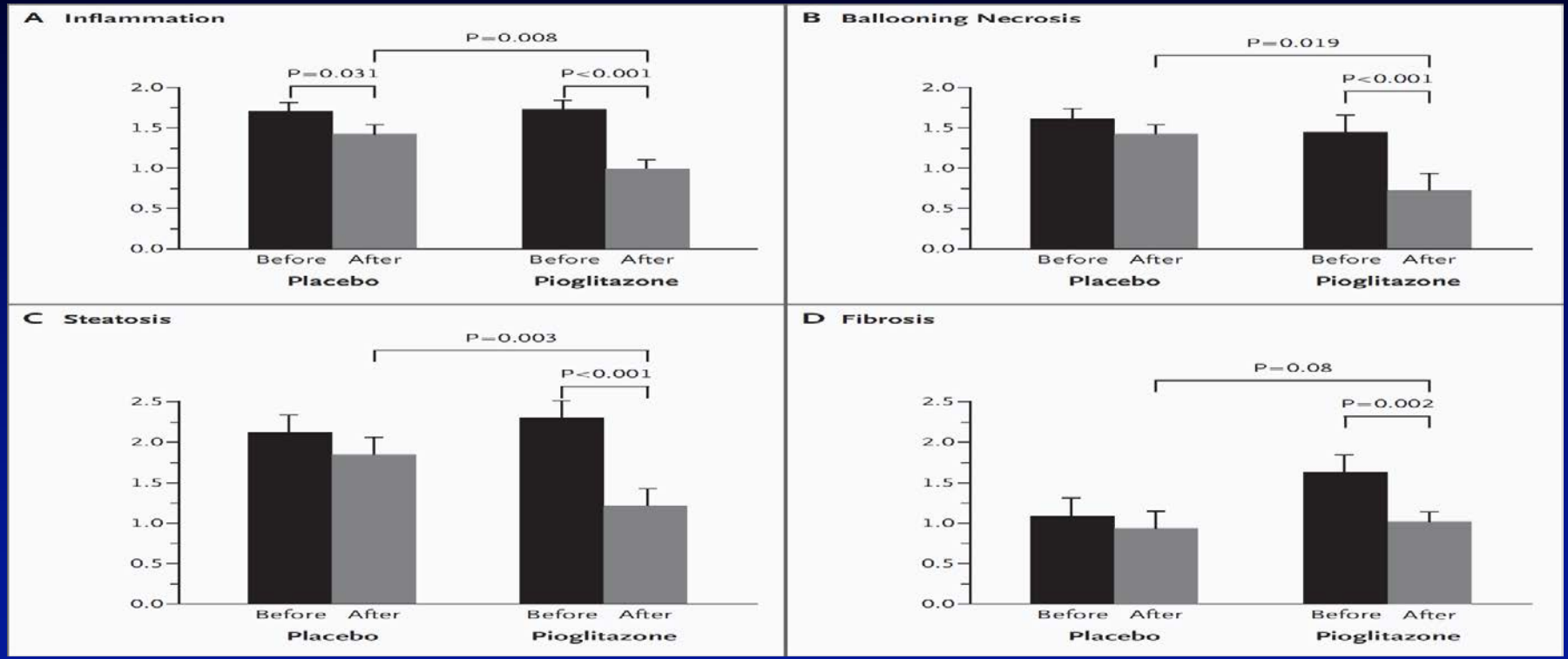


Belfort R. et al.: NEJM 355:2297, 2006

pioglitazone in NASH

18 months follow-up in IGT and T2DM

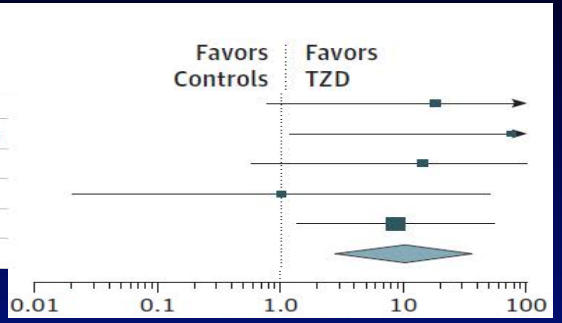
body weight	before	after	Treatment Diff.	p value
pioglitazone	98.2 (16)	99.4 (17)		
placebo	99.2 (17)	99.5 (17)	2.5 (0.4 to 4.5)	0.02
BMI				
pioglitazone	34.3 (4.8)	34.6 (4.8)		
placebo	34.5 (4.8)	34.6 (5.0)	0.9 (0.1 to 1.6)	0.019
fat mass (DEXA)				
pioglitazone	33 (7)	36 (7)		
placebo	34 (8)	36 (8)	2 (1 to 3)	<0.001
HbA1c (%, only T2DM)				
pioglitazone	7.1 (0.9)	6.2 (0.7)		
placebo	6.8 (1.0)	6.5 (0.7)	-0.6 (-1.1 to -0.2)	0.009
fasting insulin (µ/U/ml)				
pioglitazone	15 (11)	8 (15)		
placebo	16 (12)	17 (16)	-6 (-12 to 0)	0.041

Cusi K et al.: Ann Intern Med 165:305, 2016 doi:10.7326/M15-1774

meta-analysis of pioglitazone in NASH

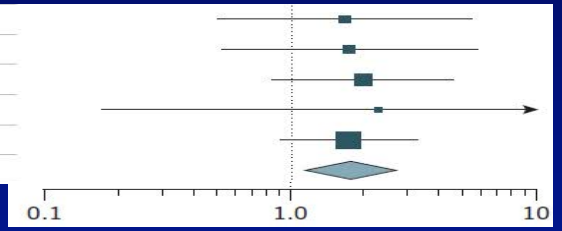
Patients with NASH with advanced fibrosis at baseline

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)
Aithal et al,[17] 2008	3	7	0	11	17.89 (0.76-420.49)
Belfort et al,[16] 2006	7	7	0	2	75.00 (1.16-4868.64)
Cusi et al,[12] 2016	4	7	0	5	14.14 (0.57-352.00)
Sanyal et al,[15] 2004	1	2	1	2	1.00 (0.02-50.40)
Sanyal et al,[20] 2010	6	12	2	19	8.50 (1.33-54.13)
Total (95% CI)	21	35	3	39	10.17 (2.83-36.54)



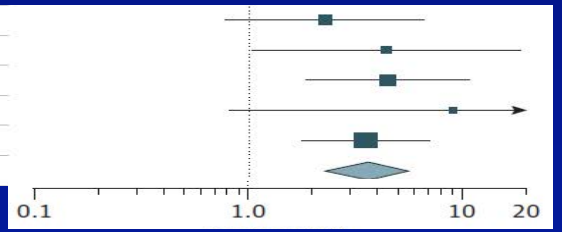
Improvement in fibrosis of any stage

Aithal et al,[17] 2008	9	31	6	30	1.64 (0.50--5.35)
Belfort et al,[16] 2006	12	26	7	21	1.71 (0.52-5.64)
Cusi et al,[12] 2016	20	50	13	51	1.95 (0.84-4.54)
Sanyal et al,[15] 2004	2	10	1	10	2.25 (0.17-29.77)
Sanyal et al,[20] 2010	35	80	26	83	1.71 (0.90-3.24)
Total (95% CI)	78	197	53	195	1.77 (1.15-2.72)



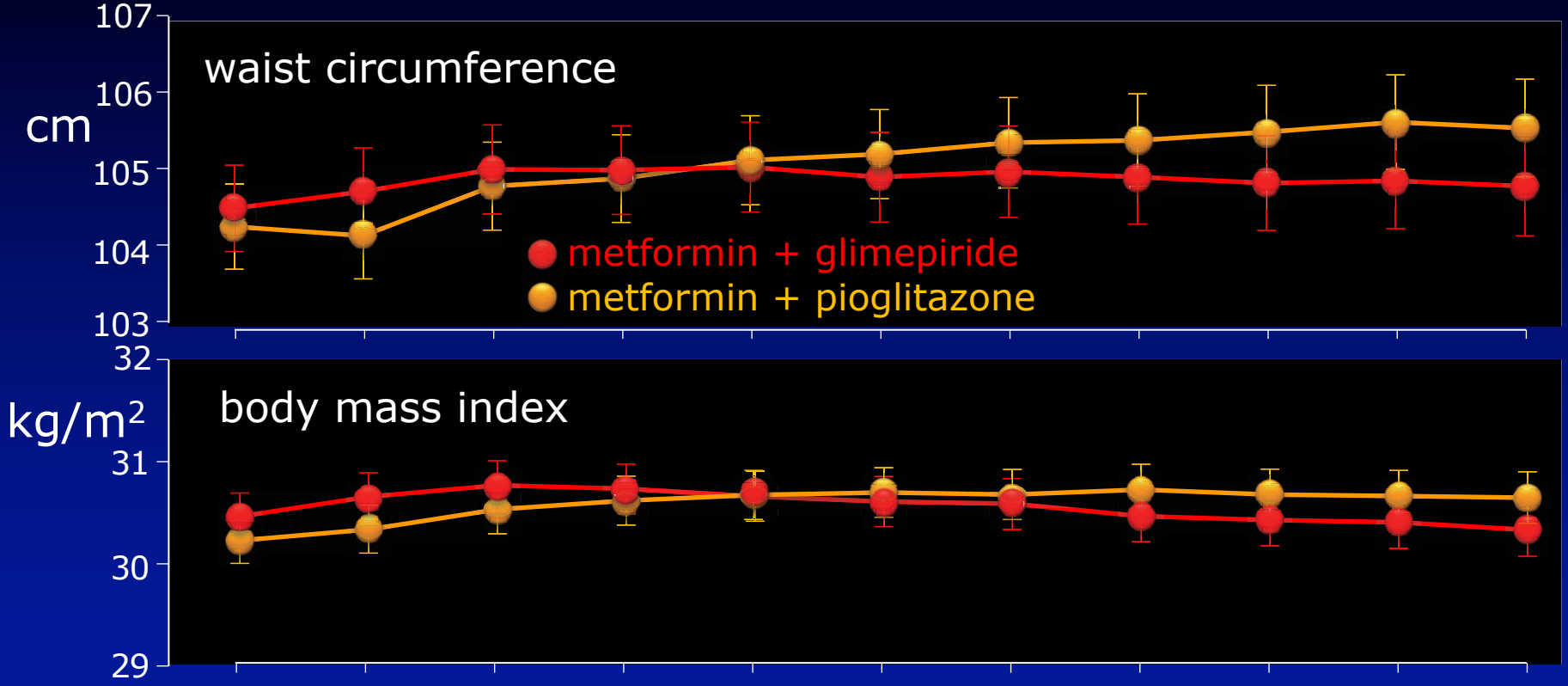
Induction of NASH resolution

Aithal et al,[17] 2008	14	31	8	30	2.26 (0.77-6.63)
Belfort et al,[16] 2006	11	26	3	21	4.40 (1.03-18.74)
Cusi et al,[12] 2016	26	50	10	51	4.44 (1.83-10.78)
Sanyal et al,[15] 2004	5	10	1	10	9.00 (0.81-100.14)
Sanyal et al,[20] 2010	38	80	17	83	3.51 (1.76-7.01)
Total (95% CI)	94	197	39	195	3.65 (2.32-5.74)



Musso G. et al.: JAMA Intern Med 177:633, 2017 doi:10.1001/jamainternmed.2016.9607

TOSCA.IT pioglitazone increases body weight



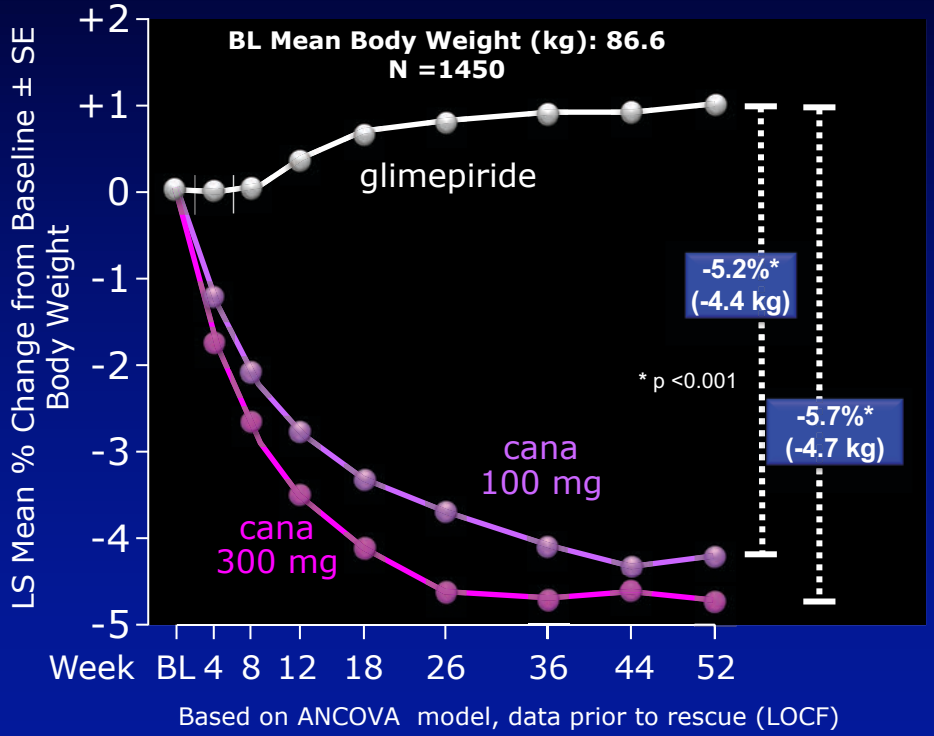
Vaccaro O. et al for the Italian Diabetes Society: Lancet DE 5:887, 2017 doi: 10.1016/S2213-8587(17)30317-0

insulin sensitizers

- metformin: no evidence
- GLP-1 RA: works; weight loss?
- pioglitazone: works; weight gain!
- SGLT inhibitors

gliflozins mostly reduce fat mass

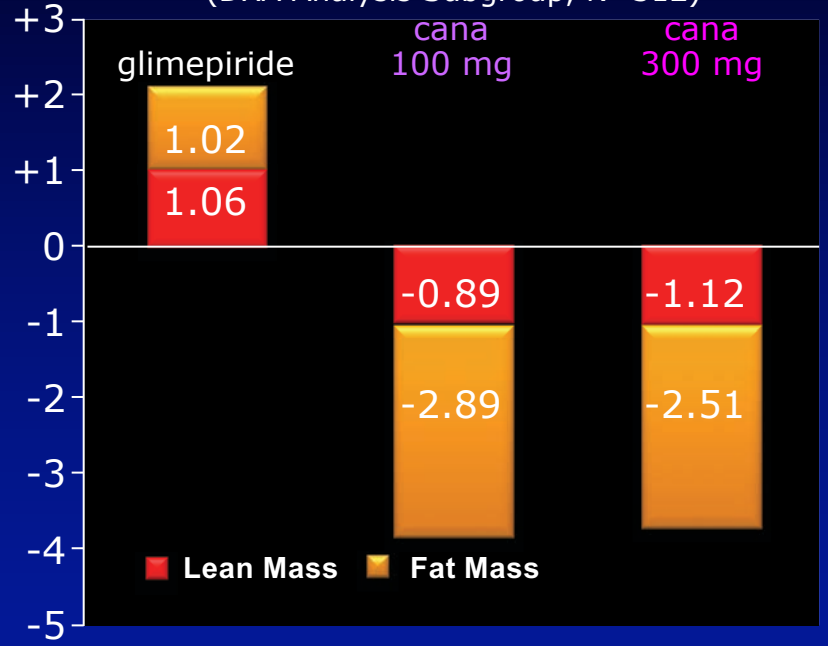
Weight Loss Over Time



Based on ANCOVA model, data prior to rescue (LOCF)

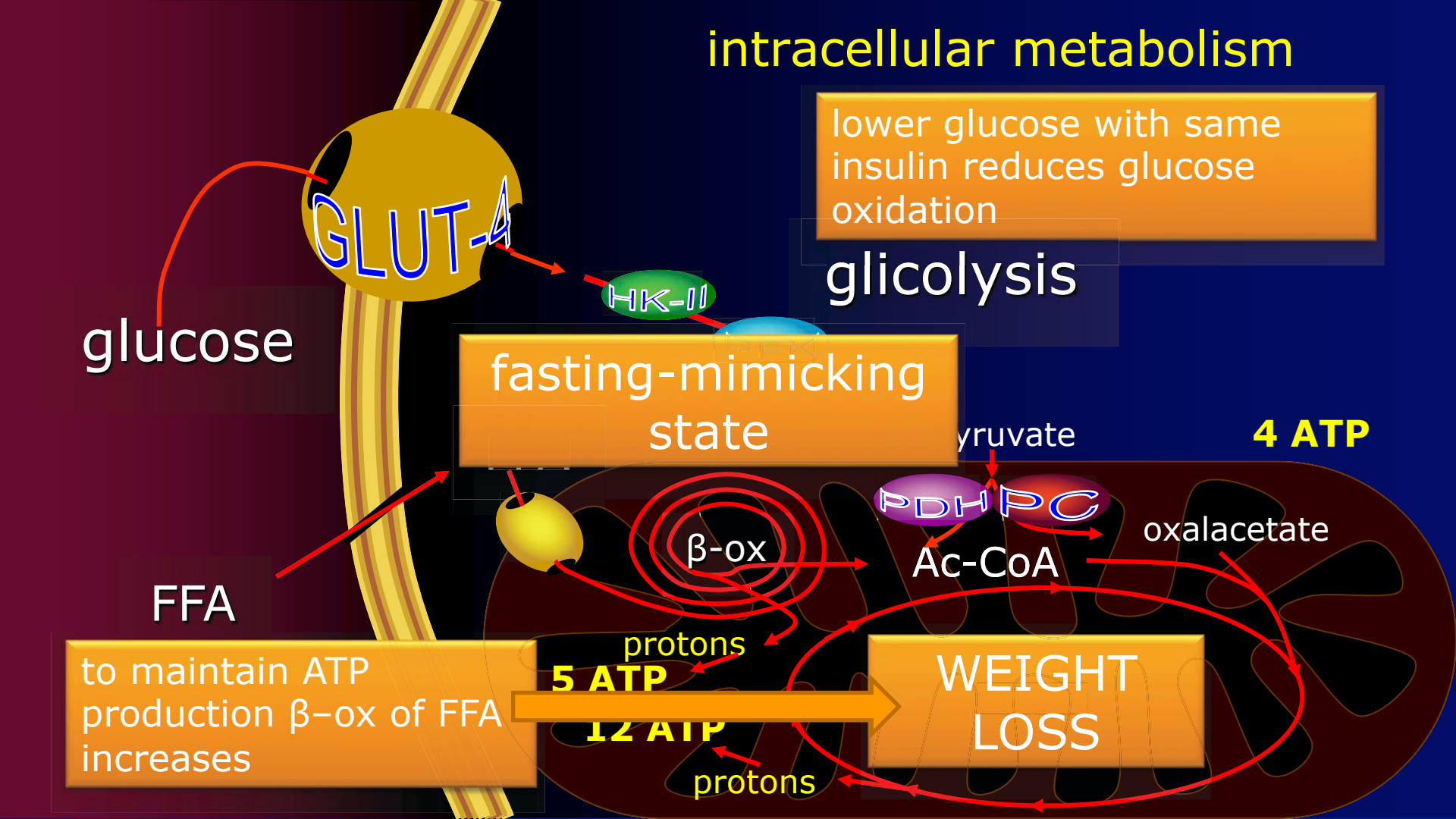
Change in Body Composition

(DXA Analysis Subgroup, N=312)



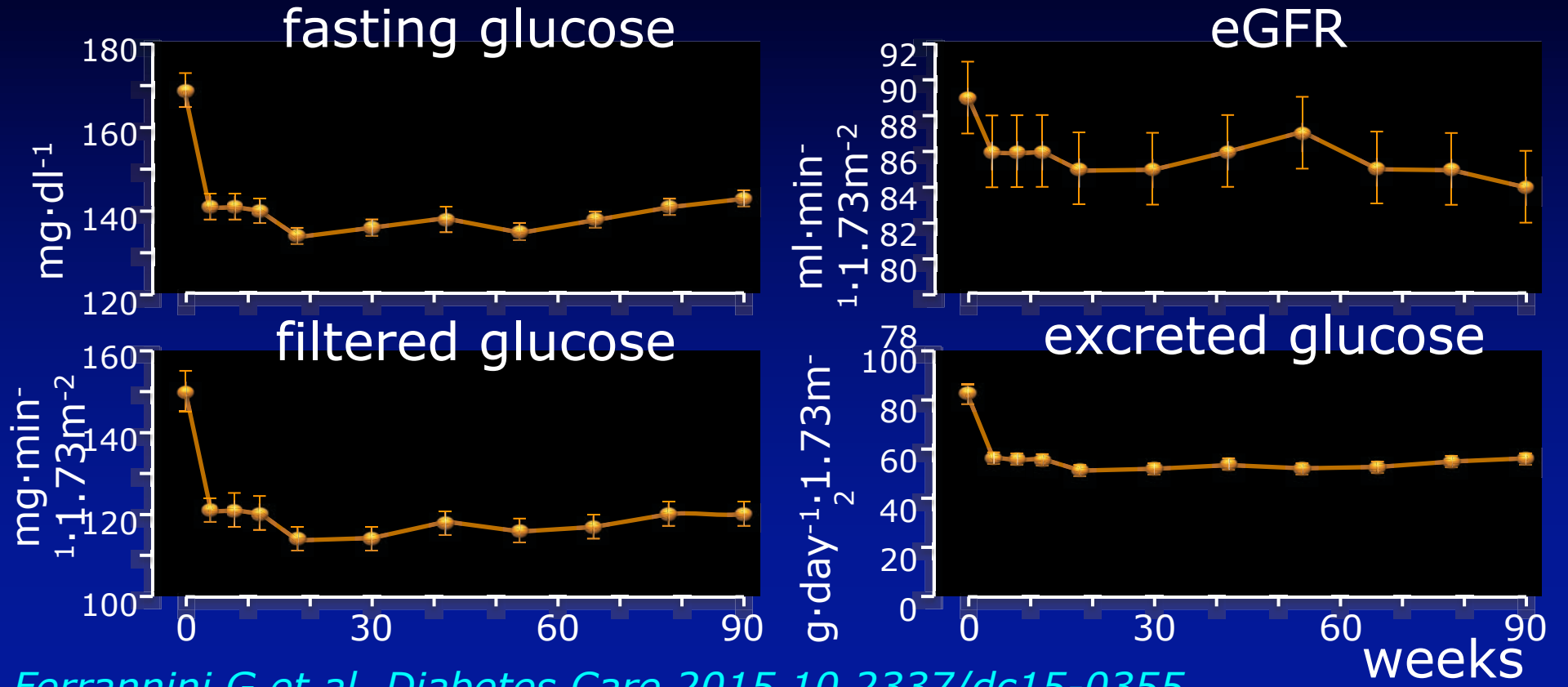
Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

Cefalu WT et al. Lancet 382:941, 2013


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

estimated glucose loss with SGLT2i

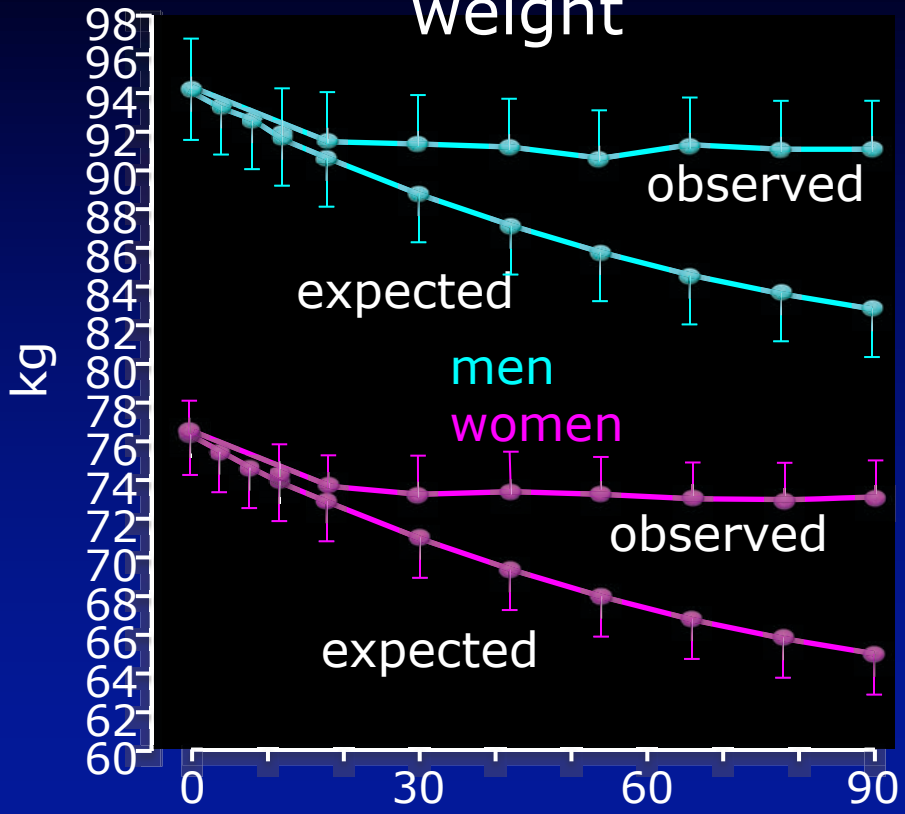
empa 25, ext. of 2 12-w trials; HbA1c: 7.8 BMI: 29.8

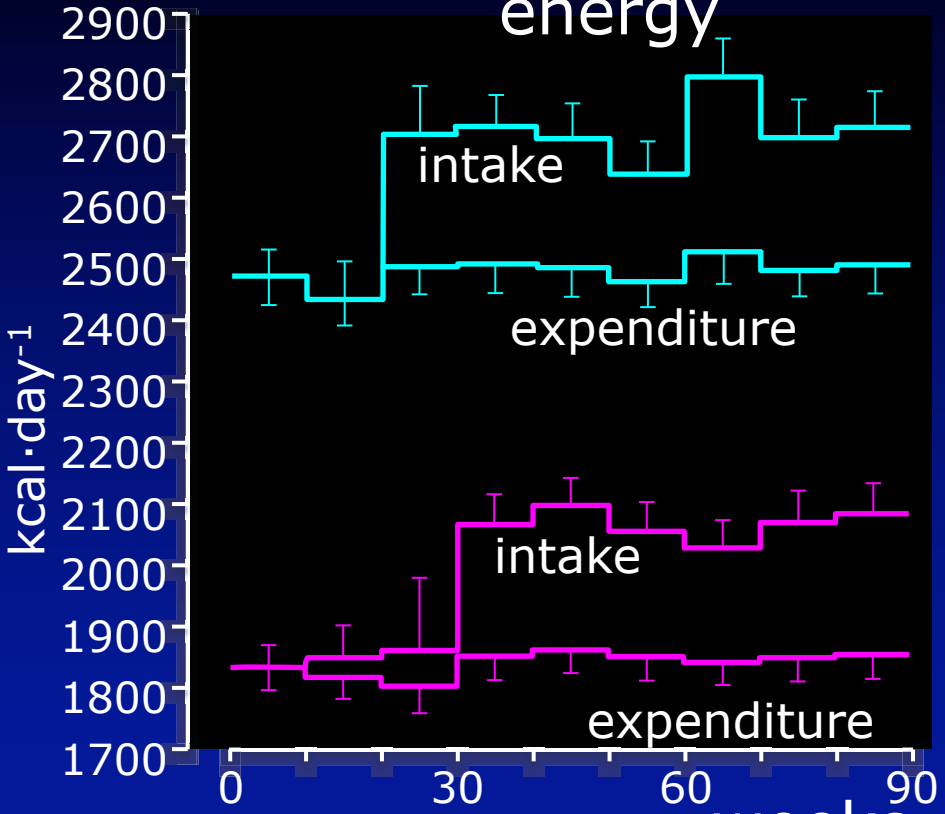


Ferrannini G et al, Diabetes Care 2015 10.2337/dc15-0355

energy balance with SGLT2i

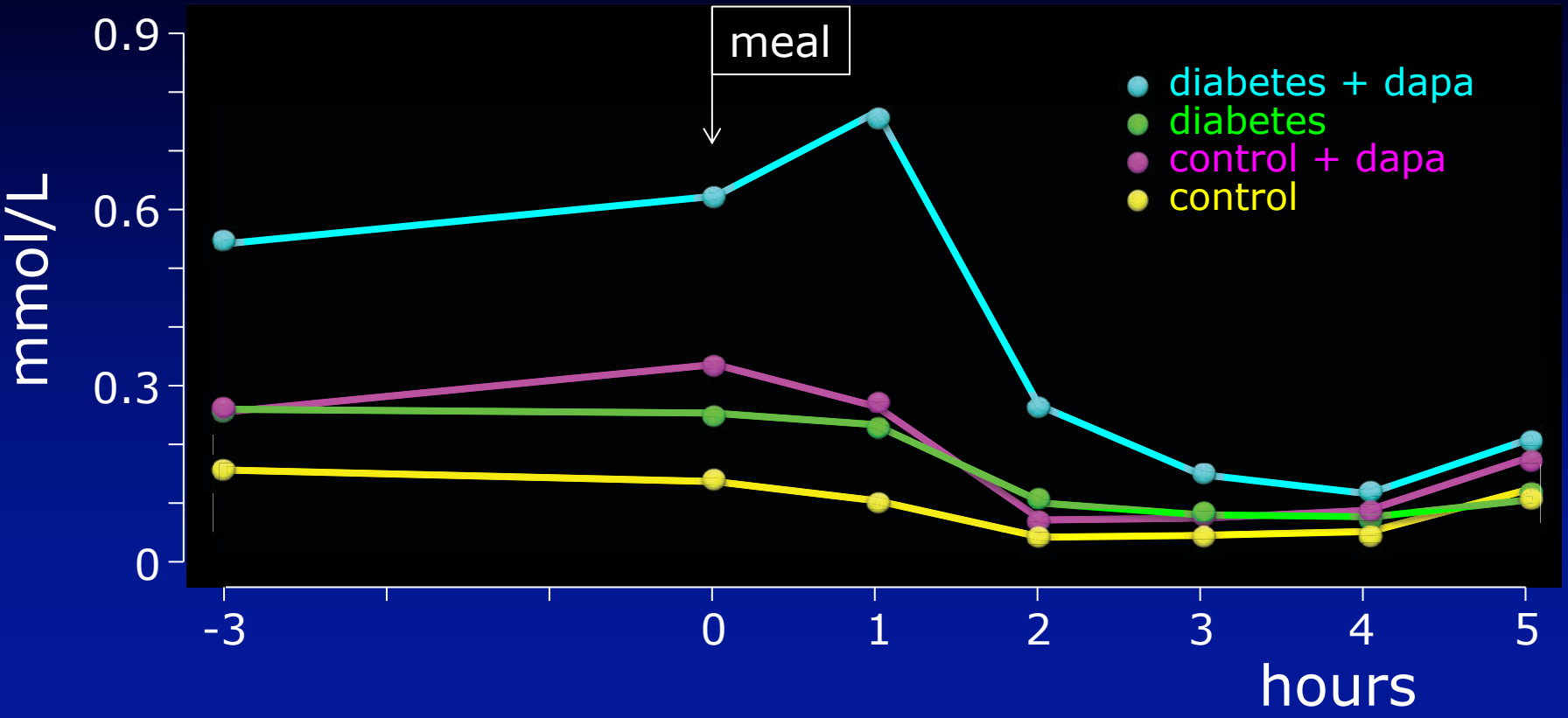
empa 25, ext. of 2 12-w trials; HbA1c: 7.8 BMI: 29.8





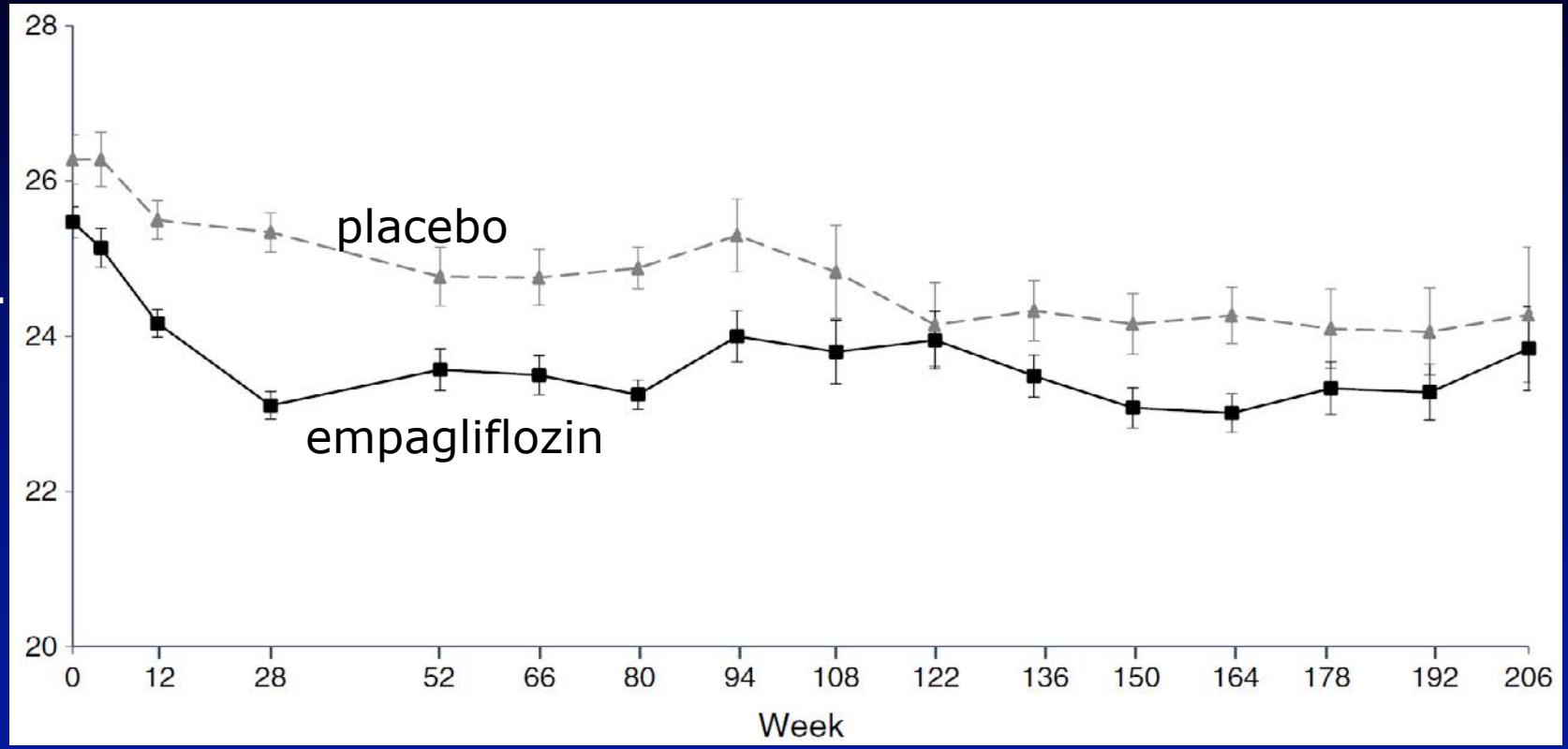
Ferrannini G et al, Diabetes Care 2015 10.2337/dc15-0355

SGLT-2is increase ß-OH-butyrate



Ferrannini E et al.: Diabetes 65:1190, 2016 doi: 10.2337/db15-1356

EMPAREG: ALT with empagliflozin



Sattar N et al.: Diabetologia 61:2155, 2018 doi: 10.1007/s00125-018-4702-3

SGLT2-is reduce NASH

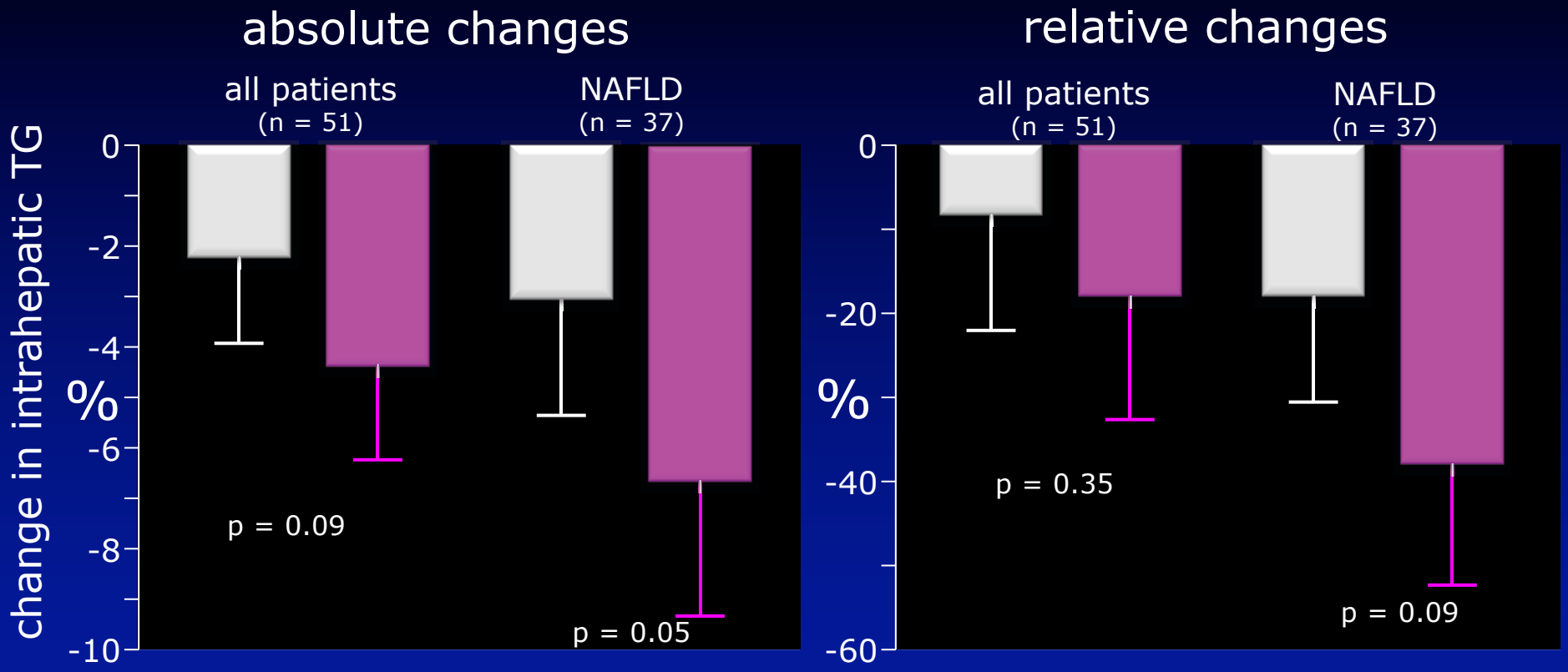
liver-to-spleen attenuation ratio

	Luseogliflozin			Metformin		
	Baseline	At 6 months	*P* value	Baseline	At 6 months	*P* value
L/S	0.907 (0.637, 1.036)	1.033 (0.798, 1.199)	.0008	0.991 (0.813, 1.118)	0.851 (0.675, 1 0.001)	.017
ALT	49.5 (31, 70)	31 (26, 55)	.057	39 (23,56)	39 (27, 51)	.518
Glu (mg/dL)	127 (116, 136)	125 (113, 138)	.87	147 (126–161)	134 (122, 145)	.32
HbA1c	7.8 (7.2, 7.9)	6.5 (6.4, 7.0)	.002	7.4 (6.9, 7.7)	7.3 (6.7, 7.6)	.362
CPR	2.05 (1.8, 3.3)	2.3 (1.9, 3.5)	.397	2.9 (1.8, 3.3)	2.7 (1.9, 3.5)	.756
CPR index	1.30 (1.25-1.65)	1.57 (1.48-1.84)	.041	1.86 (1.13, 2.14)	2.08 (1.10, 2.31)	.247
VFA	158.3 (104.1, 177.2)	137.6 (99.6, 156.8)	.009	142.3 (116.1, 189.3)	153 (103.5, 196.5)	.426
BMI	27.9 (26.2, 28.7)	27.0 (25.6, 28.3)	.002	27.2 (24.8, 32.1)	27.3 (24.3, 31.6)	.646
	Luseogliflozin			Metformin		*P* value
ΔL/S	0.176 (0.088, 0.191)			−0.116 (-0.217, 0.013)		.00002
ΔALT	9 (−20, 1)			4.5 (−5, 9)		.064
ΔGlu	−6.5 (−15, 11)			−4.5 (−25, 5)		.583
ΔHbA1c	−0.8 (− 1.3, −0.1)			−0.1 (0.5, 0.2)		.023
ΔCPR	0.1 (−0.325–0.64)			−0.1 (−0.2–0.35)		.642
ΔCPR index	0.155 (−0.005, 0.279)			0.079 (−0.007, 0.407)		.666
ΔVFA	−11.9 (−31.3, −4.4)			6.7 (−7, 12.8)		.015
ΔBMI	−0.61 (−0.86, −0.24)			0.038 (−0.41, 0.23)		.031

L/S, liver-to-spleen attenuation ratio; Alt, alanine aminotransferase; Glu, fasting glucose; CPR, C-peptide immunoreactivity; VFA, visceral fat mass area

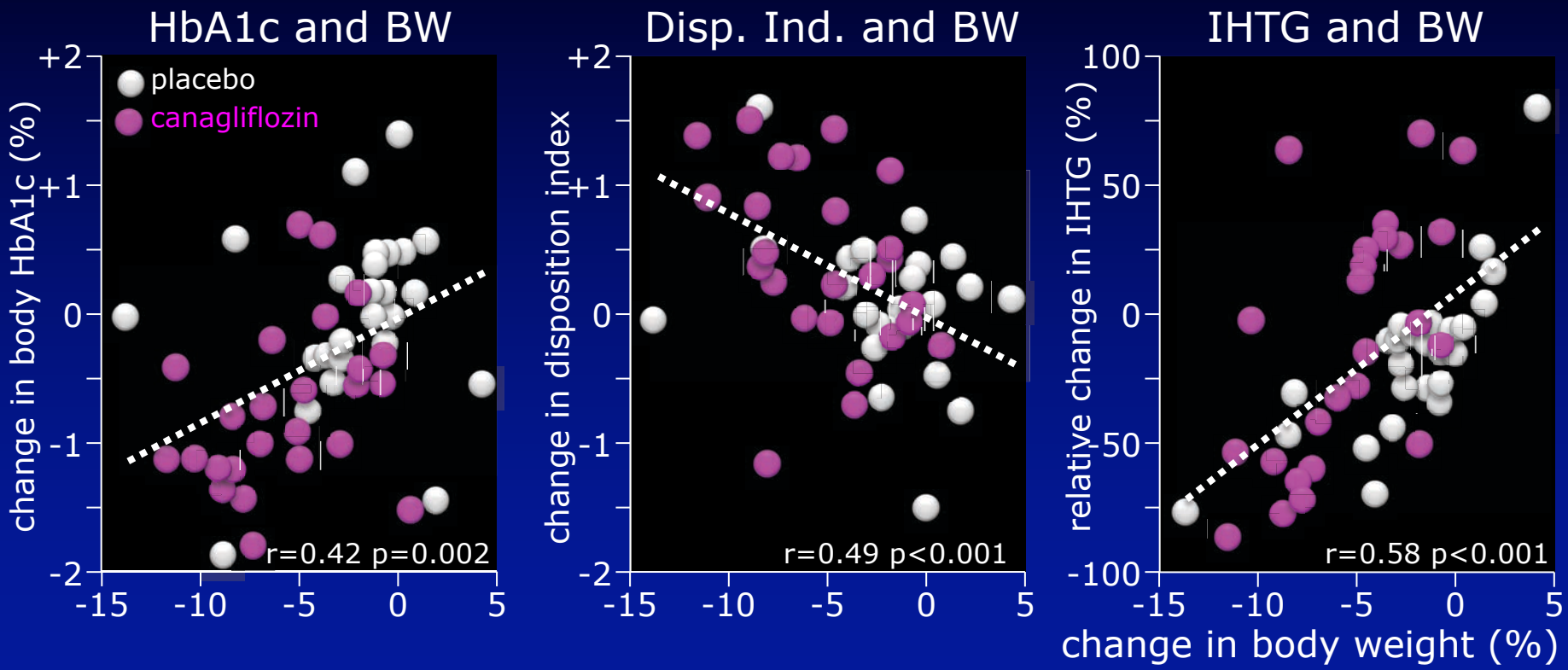
Shibuja T et al.: DOM 20:438, 2018 doi: 10.1111/dom.13061

effect of cana on intrahepatic TG content (NMR)



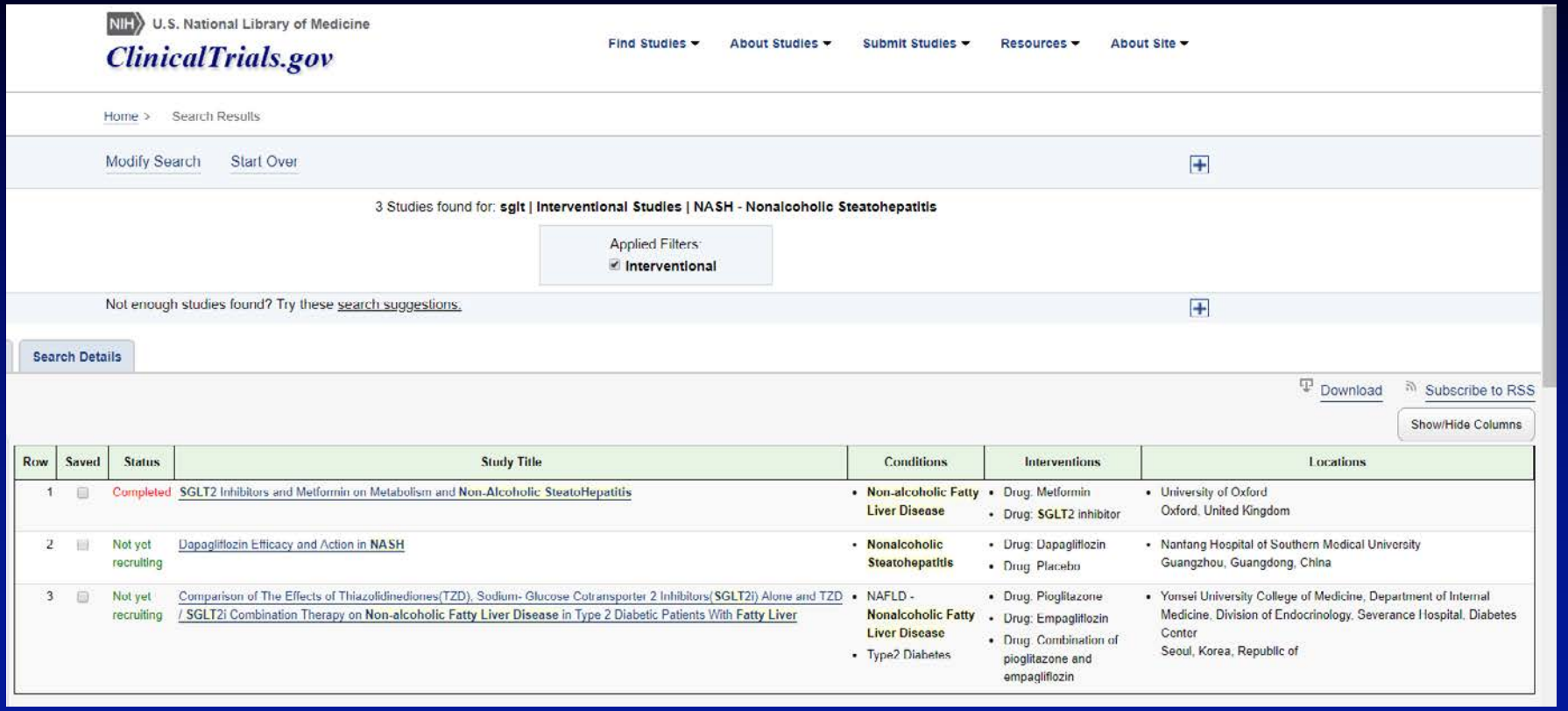
Cusi K et al.: DOM in press doi: 10.1111/dom.13584

effect of cana on intrahepatic TG content (NMR)



Cusi K et al.: DOM in press doi: 10.1111/dom.13584

SGLTi in NASH: ongoing studies



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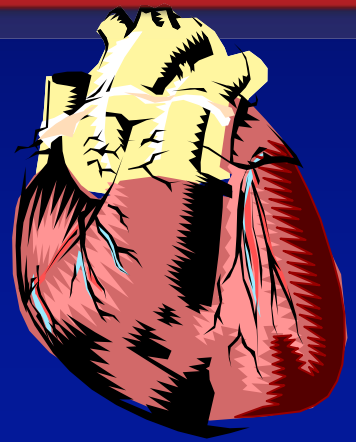
Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	SGLT2 Inhibitors and Metformin on Metabolism and Non-Alcoholic SteatoHepatitis	• Non-alcoholic Fatty Liver Disease	• Drug: Metformin • Drug: SGLT2 inhibitor	• University of Oxford Oxford, United Kingdom
2	☐	Not yet recruiting	Dapagliflozin Efficacy and Action in NASH	• Nonalcoholic Steatohepatitis	• Drug: Dapagliflozin • Drug: Placebo	• Nantang Hospital of Southern Medical University Guangzhou, Guangdong, China
3	☐	Not yet recruiting	Comparison of The Effects of Thiazolidinediones(TZD), Sodium- Glucose Cotransporter 2 Inhibitors(SGLT2i) Alone and TZD / SGLT2i Combination Therapy on Non-alcoholic Fatty Liver Disease in Type 2 Diabetic Patients With Fatty Liver	• NAFLD - Nonalcoholic Fatty Liver Disease • Type2 Diabetes	• Drug: Pioglitazone • Drug: Empagliflozin • Drug: Combination of pioglitazone and empagliflozin	• Yonsei University College of Medicine, Department of Internal Medicine, Division of Endocrinology, Severance Hospital, Diabetes Center Seoul, Korea, Republic of

Shift in Fuel Energetics

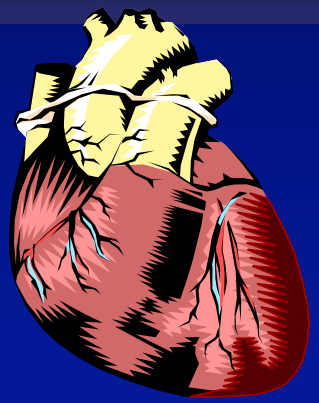
diabetic heart

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



SGLT-2i effect

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



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

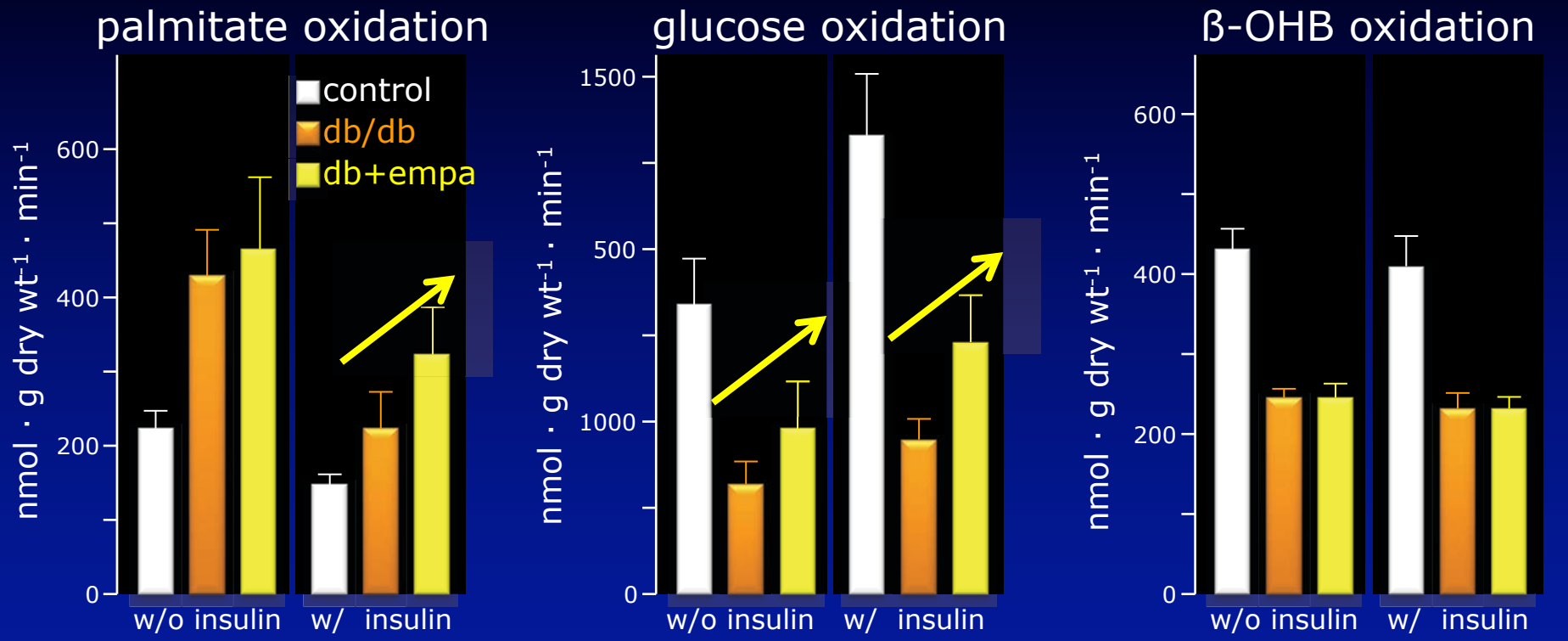
the βOHB hypotheses compared

Author	glucose oxidation	FFA oxidation	βOHB oxidation
Mudaliar [1]	↑	↓	↑
Ferrannini [2]	↓	↓	↑↑
Lopaschuk [3]	↑↑	↑	=

1. Diabetes Care 39:1108, 2016. doi: 10.2337/dc16-0330.
2. Diabetes Care 39:1115, 2016. doi: 10.2337/dc16-0542.
3. Cell Metab. 24:200, 2016. doi: 10.1016/j.cmet.2016.07.018

empagliflozin increases glucose oxidation

(in isolated hearts)

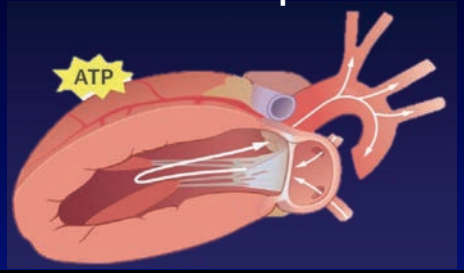


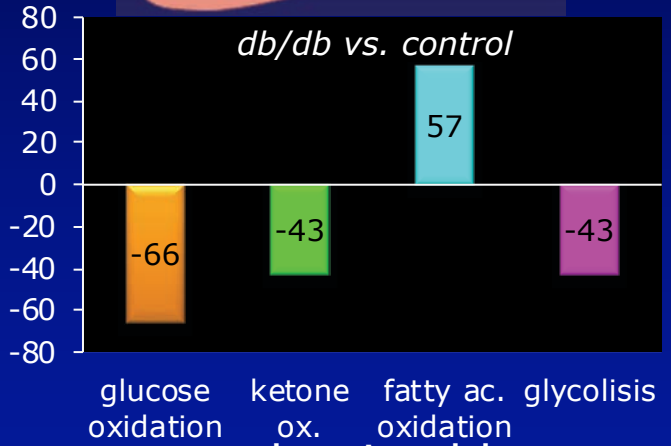
Verma S. et al.: JACC Basic Transl Sci 3:575, 2018; doi: 10.1016/j.jacbts.2018.07.006

empagliflozin improves metabolic efficacy

(in isolated hearts)

reduced ATP production

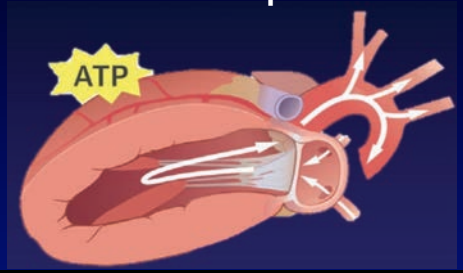


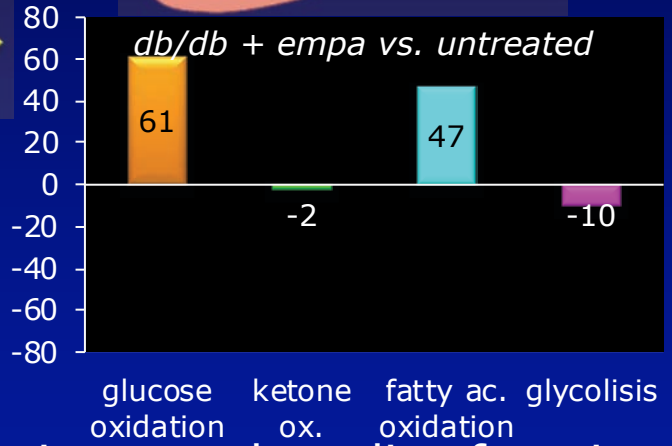


energy deprived heart

SGLT-2 i

improved ATP production





improved cardiac function

Verma S. et al.: JACC Basic Transl Sci 3:575, 2018; doi: 10.1016/j.jacbts.2018.07.006

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:

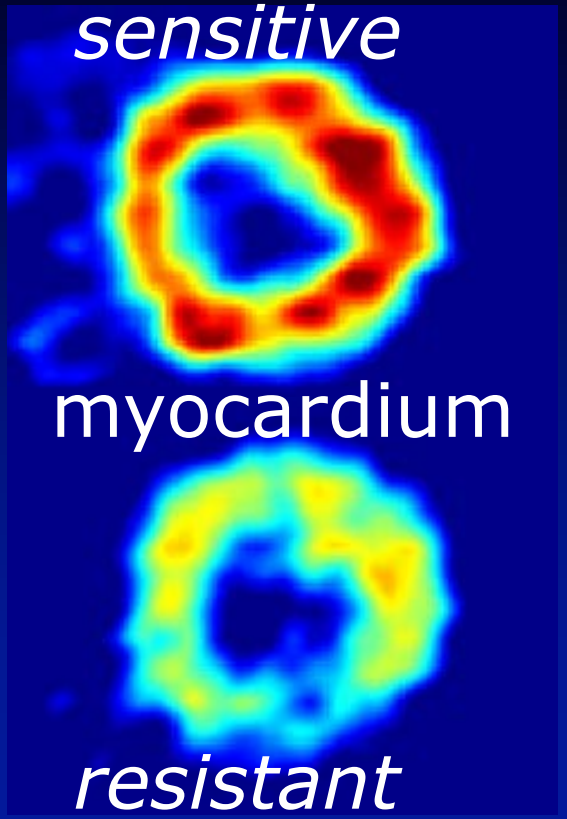
A Phase III, single-centre, randomized, 2-arm, parallel-group, double blind, placebo-controlled study, consisting of a screening phase (Days -14 to -1), a 4-week double-blind, placebo-controlled treatment phase

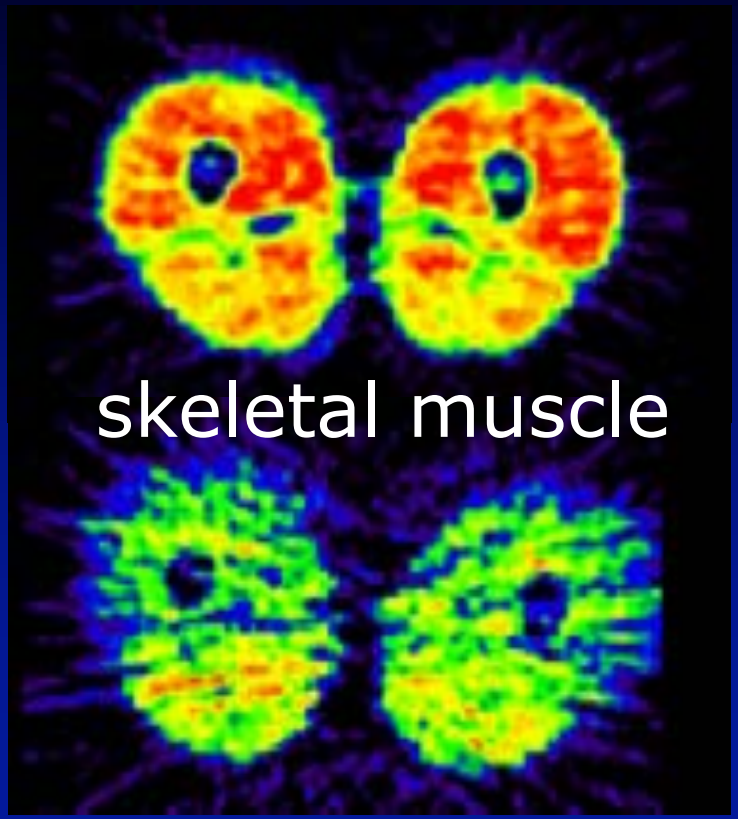
Subjects: Type 2 diabetic patients with coronary artery disease (CAD) not requiring revascularization, with sub-optimal glycemic control (HbA1c 7.5-8.5%) on their current anti-hyperglycemic regimen

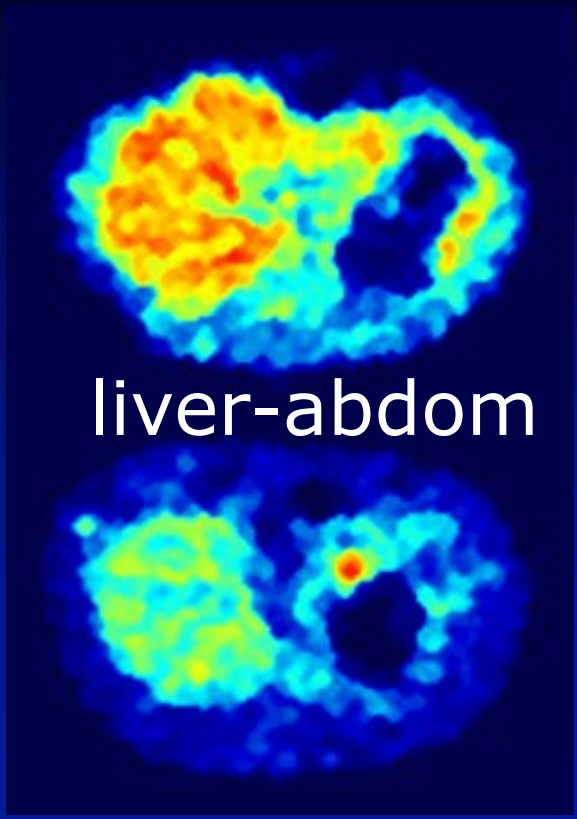
Subjects will be randomized in a 1:1 ratio to dapagliflozin or placebo.

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

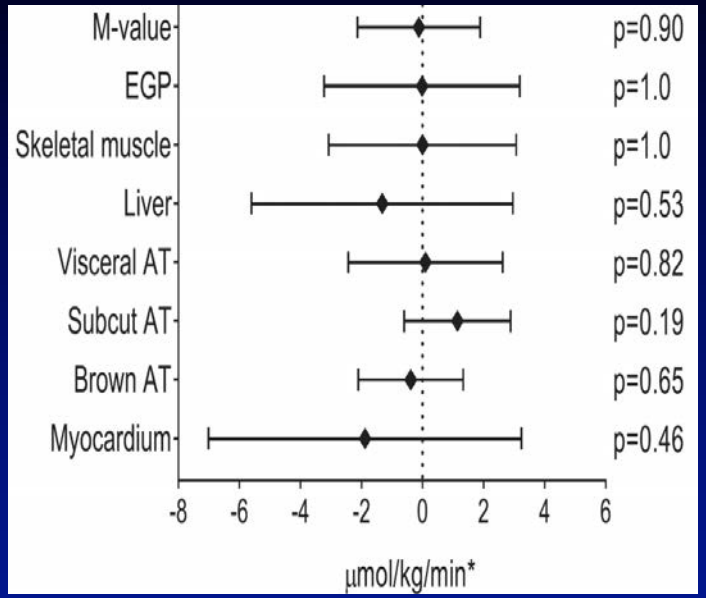
organ specific insulin-resistance

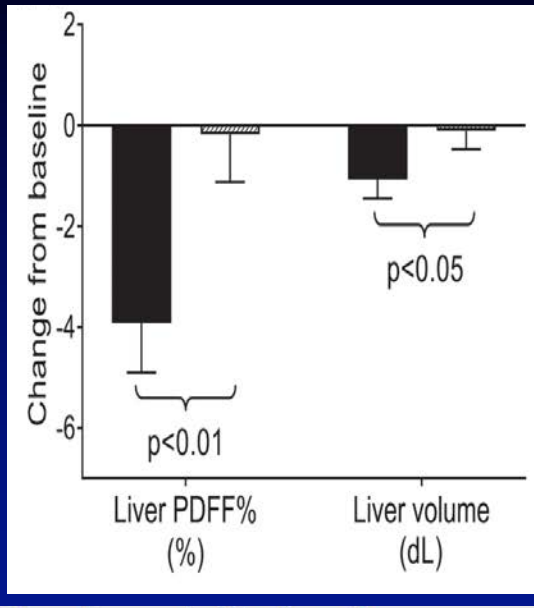






SGLT-2i: no effects on glucose uptake?





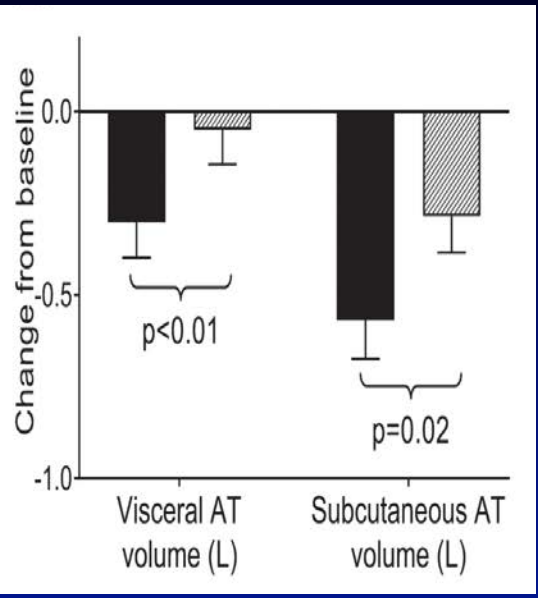


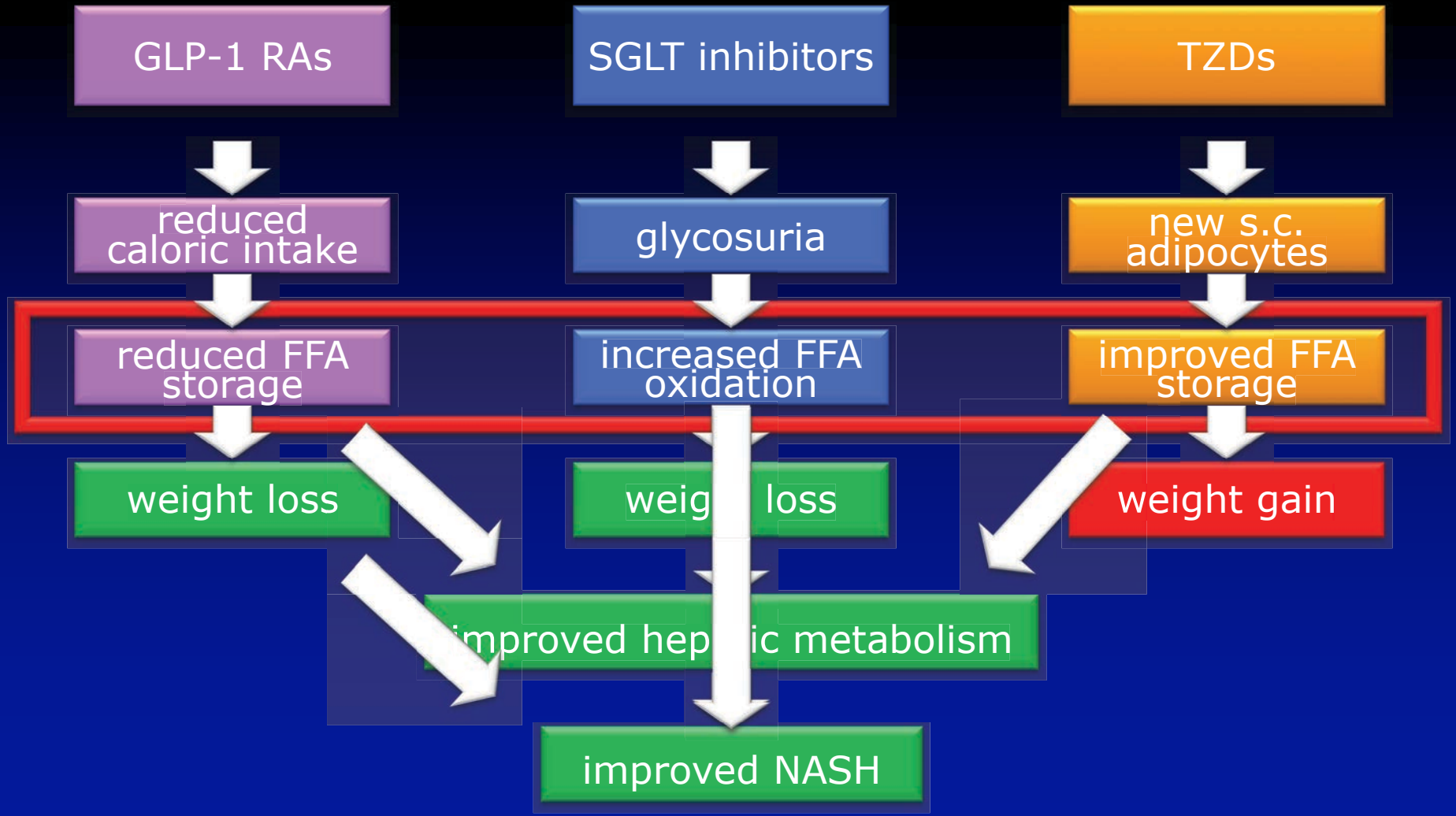
Table 1—Characteristics of the treatment arms at baseline and after 8 weeks

Variable	Placebo		Dapagliflozin 10 mg		*P* value
	Baseline (*n* = 16)	At 8 weeks (*n* = 16)	Baseline (*n* = 15)	At 8 weeks (*n* = 15)	
HbA_{1c} (%)	6.8 ± 0.5	6.8 ± 0.4	7.0 ± 0.6	6.6 ± 0.6	<0.01

Latva-Rasku A. et al.: Diabetes Care 2019 doi: 10.2337/dc18-1569. [Epub ahead of print]

insulin sensitizers

- metformin: no evidence
- GLP-1 RA: works; weight loss?
- pioglitazone: works; weight gain!
- SGLT inhibitors: works?
  increased FFA oxidation?


GLP-1 RAs
SGLT inhibitors
TZDs
reduced caloric intake
glycosuria
new s.c. adipocytes
reduced FFA storage
increased FFA oxidation
improved FFA storage
weight loss
weig loss
weight gain
improved hep ic metabolism
improved NASH


Gian Pio
Francesca
Flavia
Ilaria
Teresa
Chiara
Simona
Serena
Rachele
TEAM DIABETE
Gemelli