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Current Pharmacological Treatment for Nonalcoholic Steatohepatitis (NASH): A Deeper Dive

Kenneth Cusi, MD, FACP, FACE,
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida,
Gainesville, United States

Disclosures

Research support to the University of Florida:

National Institute of Health and industry as follows: Echosens, Inventiva, Janssen, Nordic, Novo Nordisk, Poxel, Target-NASH, Zydus.

Consultant:

Amgen, AstraZeneca, 89Bio, BMS, Boehringer-Ingelheim, Coherus, Esperion, Ionis, Janssen, Genentech, Gilead, Madrigal, Merck, Novo Nordisk, Pfizer, Poxel, Terns Pharma.

Stock/Shareholder: None

Other: None

Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease

Fasiha Kanwal,[1,2] Jay H. Shubrook,[3] Leon A. Adams,[4] Kim Pfotenhauer,[5] Vincent Wai-Sun Wong,[6] Eugene Wright,[7] Manal F. Abdelmalek,[7] Stephen A. Harrison,[8] Rohit Loomba,[9] Christos S. Mantzoros,[10] Elisabetta Bugianesi,[11] Robert H. Eckel,[12] Lee M. Kaplan,[10,13] Hashem B. El-Serag,[1,2] and Kenneth Cusi[14,15]

NAFLD Treatment

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal, Shubrook/Cusi et al, Gastroenterology, September 2021 (online)

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Role of Lifestyle Modifications in NASH Resolution

Kenneth Cusi, MD, FACP, FACE,
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida,
Gainesville, United States

Lifestyle modification leads to improvement in histology in patients with NASH – but results are variable

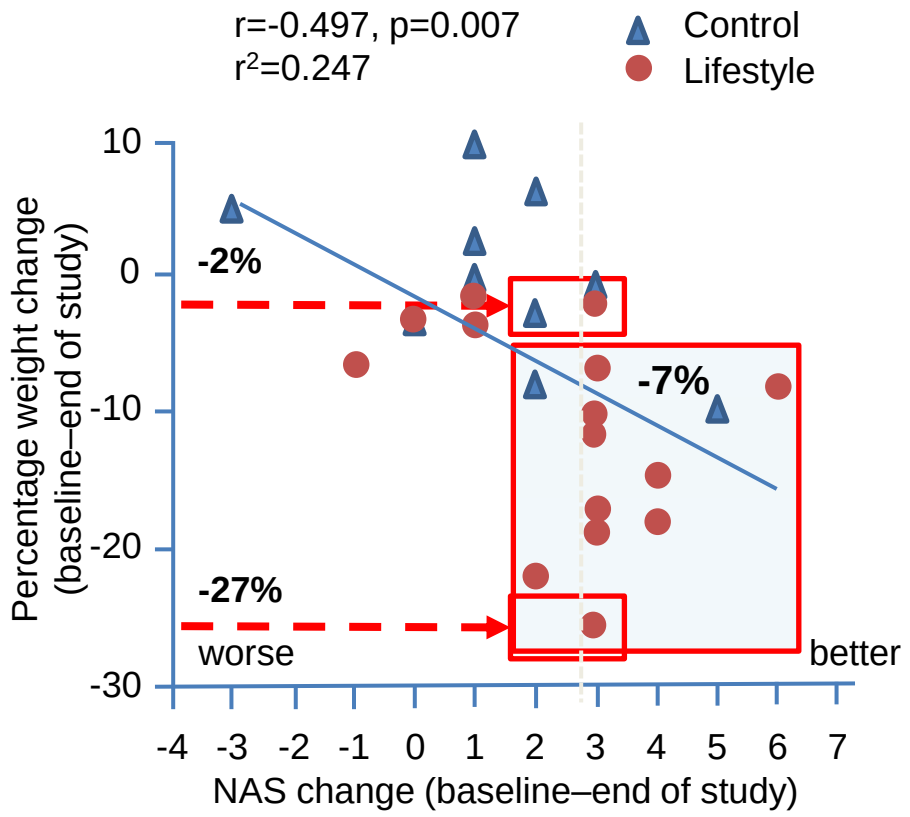
Interventions

Control group: education on NASH, healthy eating, physical activity and weight control

Lifestyle intervention: intensive weight loss intervention focussed on changing both eating and exercise habit with a goal of 7–10% weight loss within 6 months followed by maintenance

Main results

- Mean weight reduction in the lifestyle group was 9.3% versus 0.2% in the control group (P=0.003) at Week 48
- 40% of the lifestyle group achieved ≥10% weight loss (none of the control group)



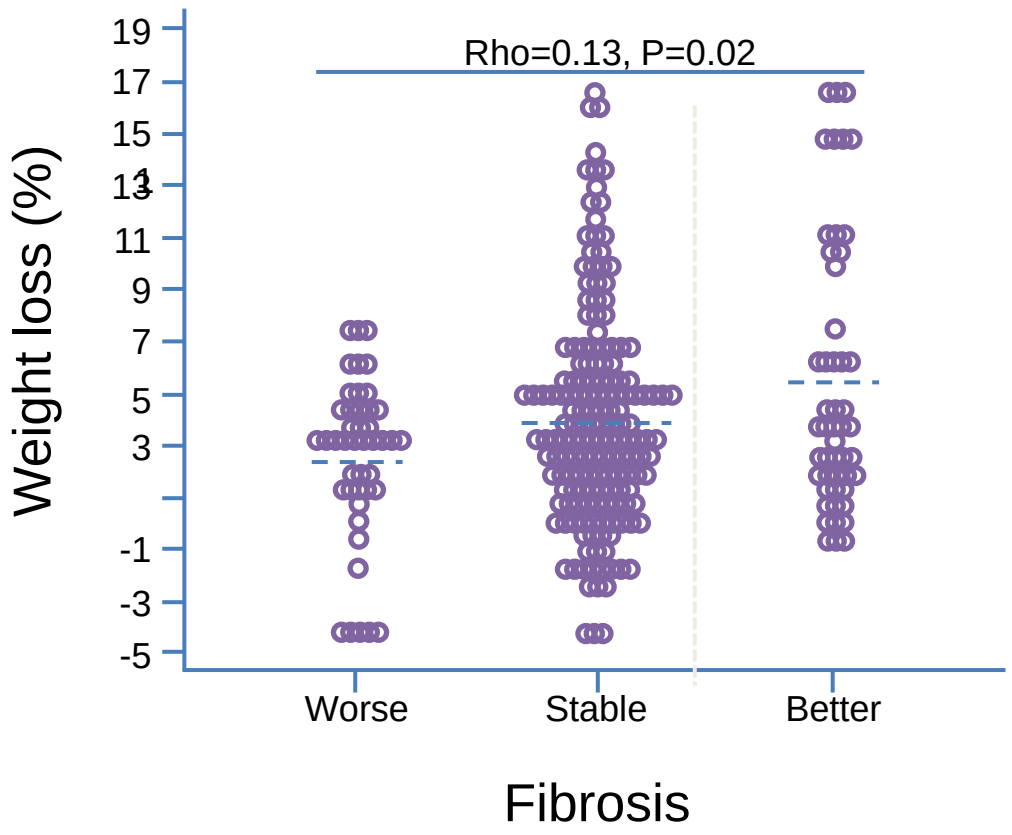
NAS: NASH histological activity score

Promrat K, et al. Hepatology 2010;51:121–9

Significant Variability in the Response of Fibrosis to Weight Loss

More weight loss

Less weight loss

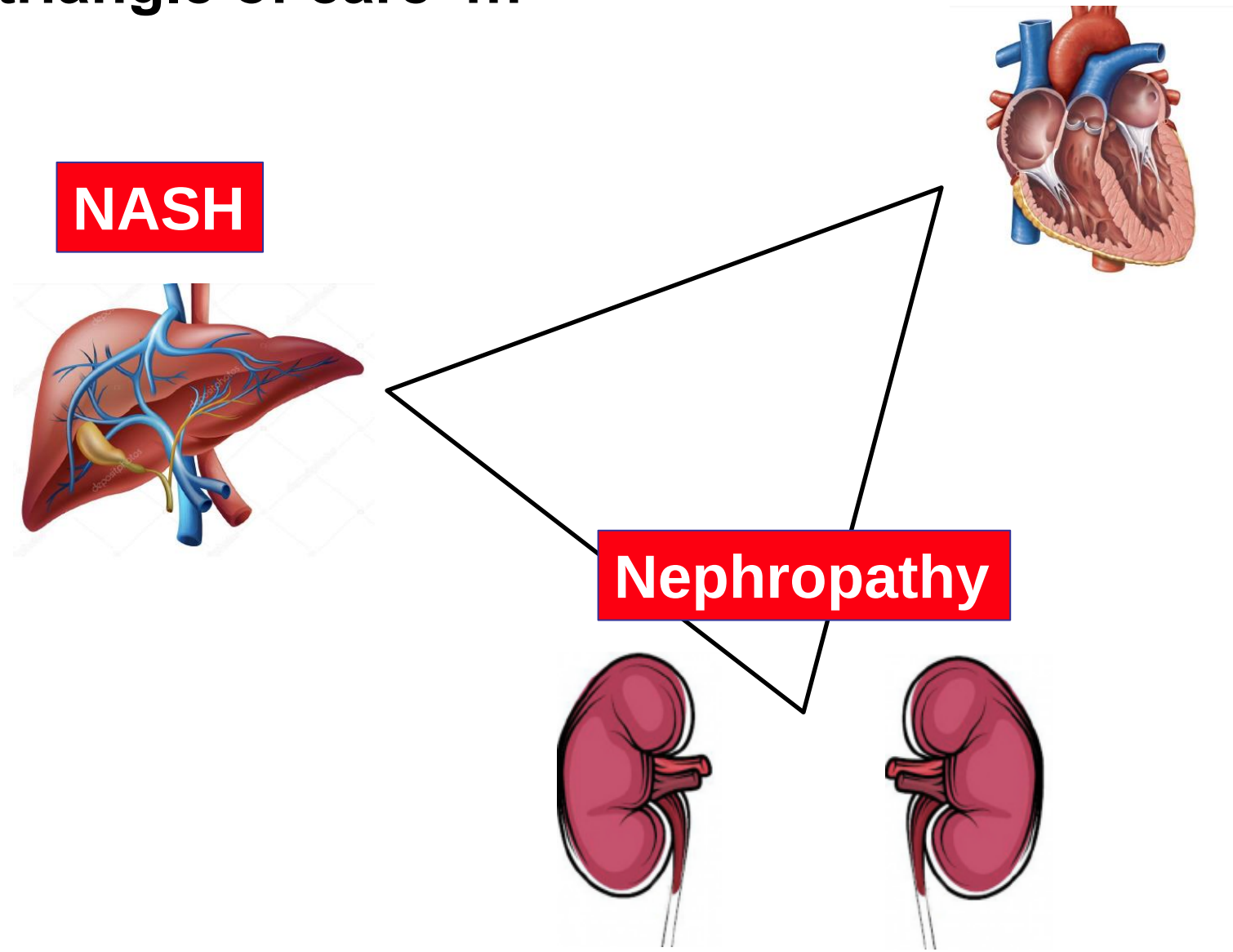


Great variability of fibrosis improvement

Romero-Gomez M, et al. J Hepatology 2017; 67:829–46
(Adapted from Vilar-Gomez E et al. Gastroenterology 2015;149:367–78)

Cardiometabolic Risk Reduction in obesity T2DM:

A “triangle of care”…

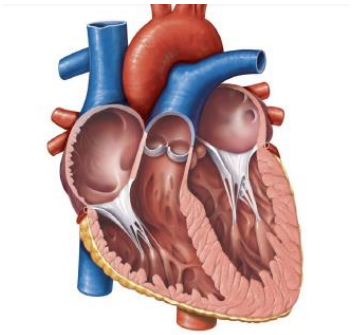


Cusi K (unpublished 2021)

Cardiometabolic Risk Reduction in obesity T2DM:

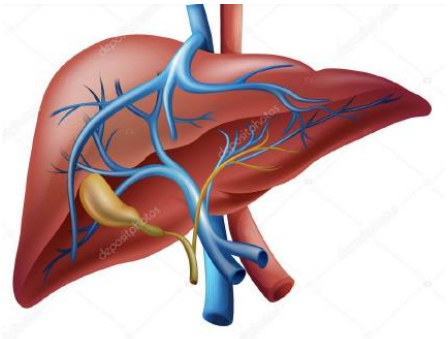
A “triangle of care”…

CVD



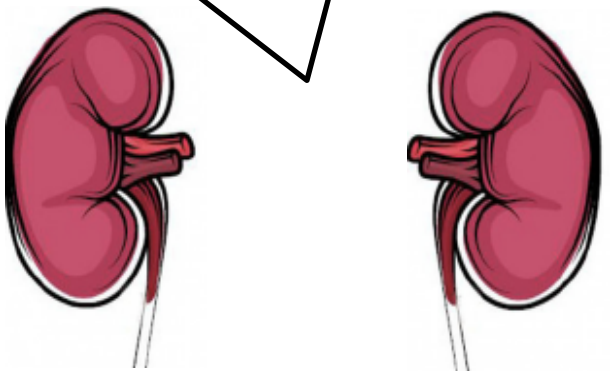
- ✓GLP-1RAs
- ✓SGLT2i
- ✓Pioglitazone

NASH



- ✓ Pioglitazone
- ✓ GLP-1RAs
- ✓ SGLT2i (?)

Nephropathy



- ✓ SGLT2i
- ✓ GLP-1RAs

Cusi K (unpublished 2021)

Clinical Care Pathways for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease

NAFLD Treatment

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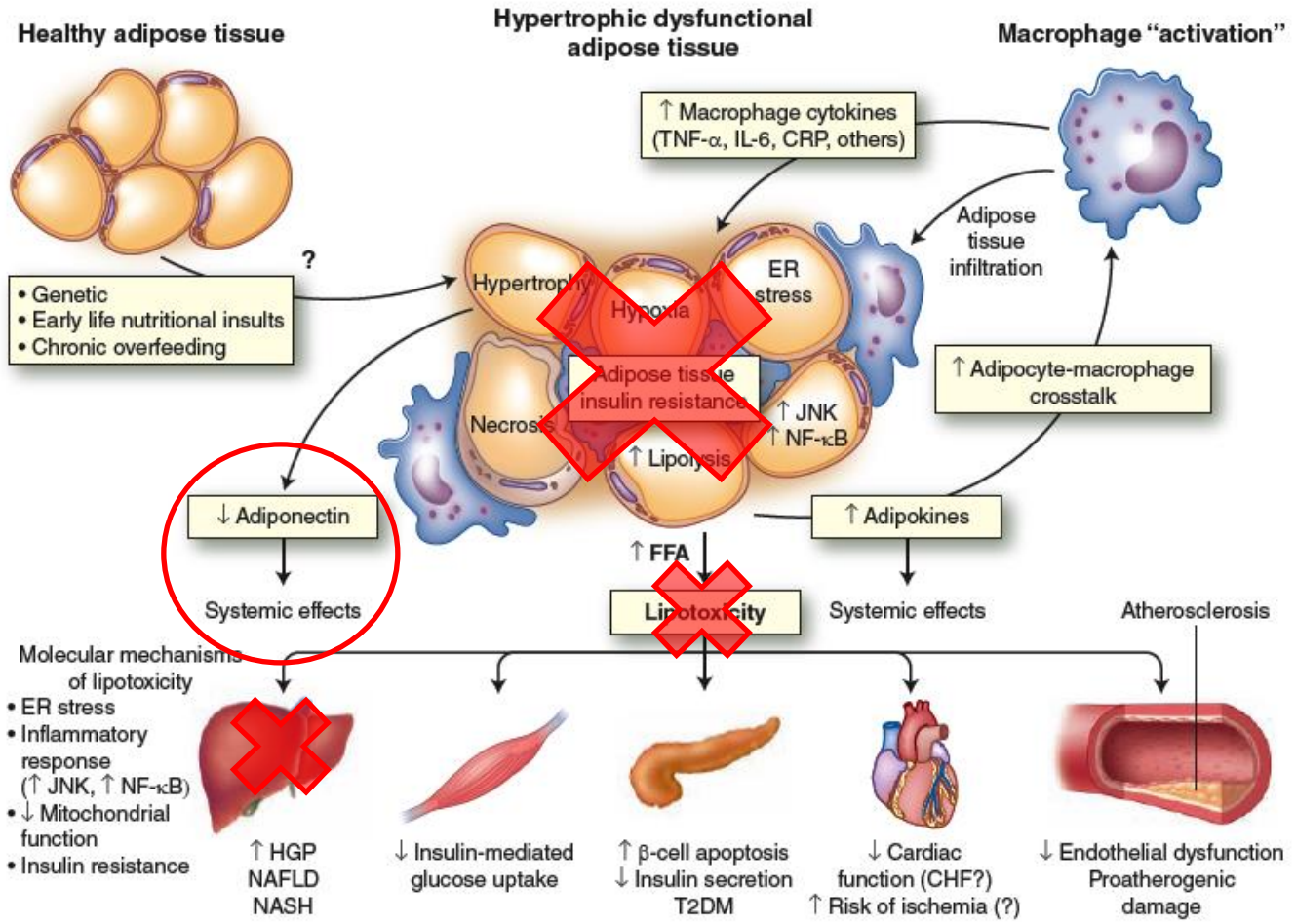
Kanwal, Shubrook/Cusi et al, Gastroenterology, September 2021 (online)

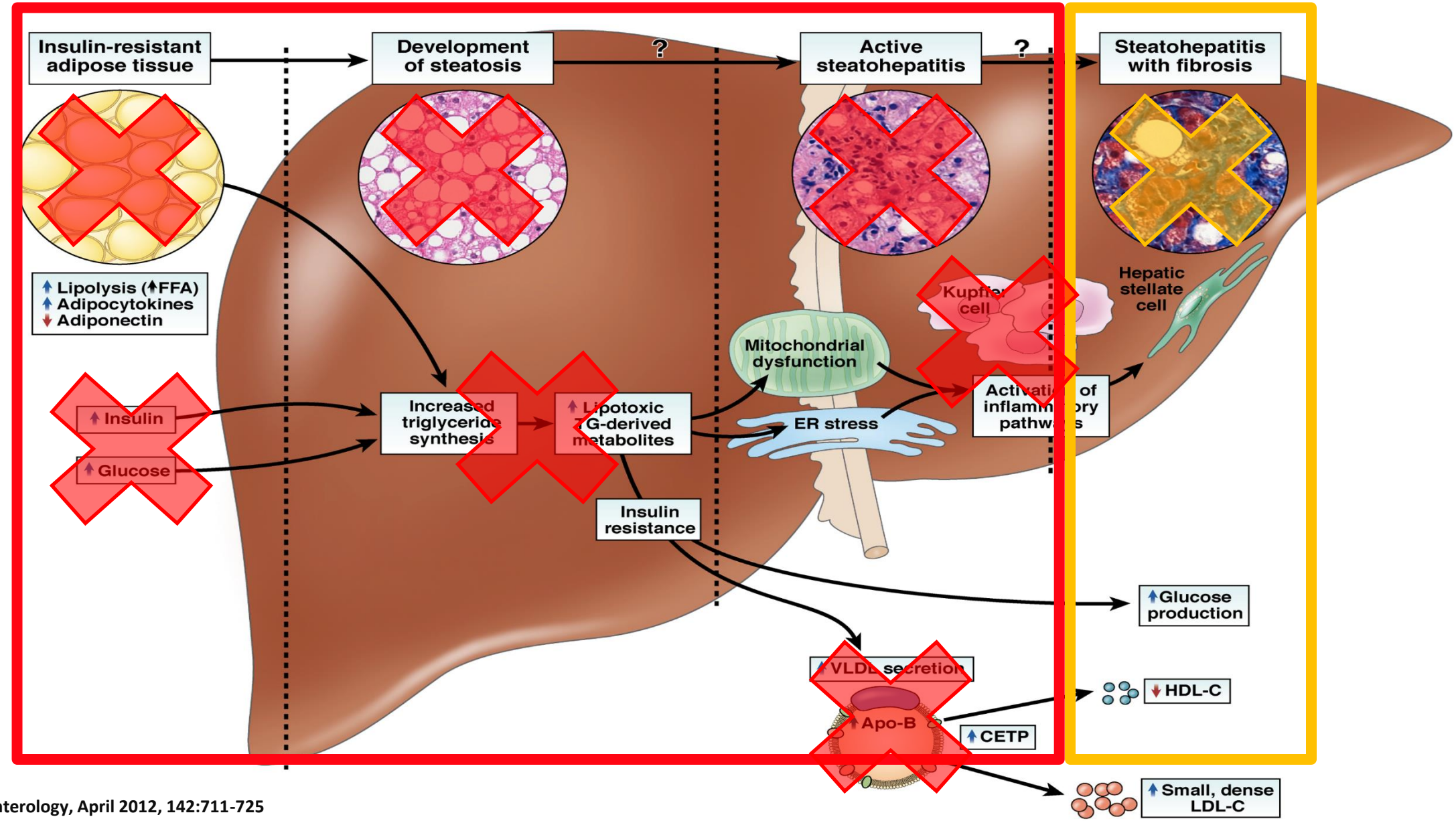
Treatment of Patients with NASH and T2DM 2021

a) Reduce adipose tissue "mass" (weight loss by any means, GLP-1RA)
b) Reverse adipose tissue dysfunction (pioglitazone)



K Cusi. Current Diabetes Reports. 2010 10:306-315.

Targeting steatohepatitis AND fibrosis in NASH



Cusi K, Gastroenterology, April 2012, 142:711-725

Impact of Weight Gain from Excess Caloric Intake

	Weight gain from overnutrition (i.e., in obesity)
Insulin resistance ○ Liver fat content ○ Visceral fat mass ○ Adipocyte function (insulin sensitivity, FFA, adiponectin secretion)	**Worse**
Type 2 diabetes ○ Glycemia ○ Atherogenic dyslipidemia	**Worse**
Cardiometabolic risk ○ Cardiovascular disease ○ Endothelial dysfunction ○ Subclinical inflammation	**Worse**

Cusi K, in press (2021)

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Role of GLP-1RA and SGLT-2 Inhibitors in NASH Resolution

Kenneth Cusi, MD, FACP, FACE,
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida,
Gainesville, United States

Impact of Weight Gain from Excess Caloric Intake vs. Weight Loss

	Weight gain from overnutrition (i.e., in obesity)	Weight loss by different methods (lifestyle, medications, bariatric surgery)
Insulin resistance ○ Liver fat content ○ Visceral fat mass ○ Adipocyte function (insulin sensitivity, FFA, adiponectin secretion)	**Worse**	**Better**
Type 2 diabetes ○ Glycemia ○ Atherogenic dyslipidemia	**Worse**	**Better**
Cardiometabolic risk ○ Cardiovascular disease ○ Endothelial dysfunction ○ Subclinical inflammation	**Worse**	**Better**

Cusi K, in press (2021)

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. XX, No. XX, 1–10
https://doi.org/10.1210/clinem/dgab578
Mini-Review

Mini-Review

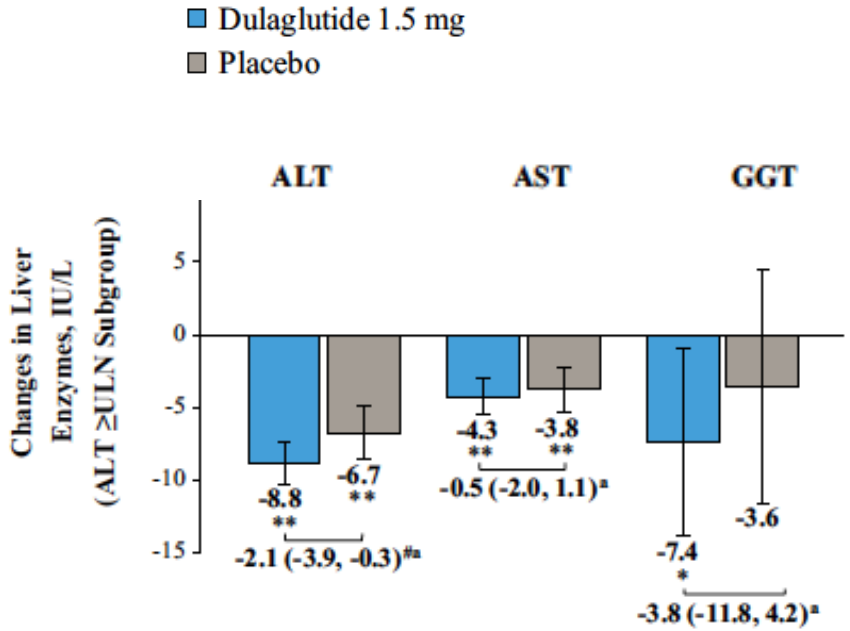
The Emerging Role of Glucagon-like Peptide-1 Receptor Agonists for the Management of NAFLD

Chandani Patel Chavez,[1] Kenneth Cusi,[1,2] and Sushma Kadiyala[1,2]

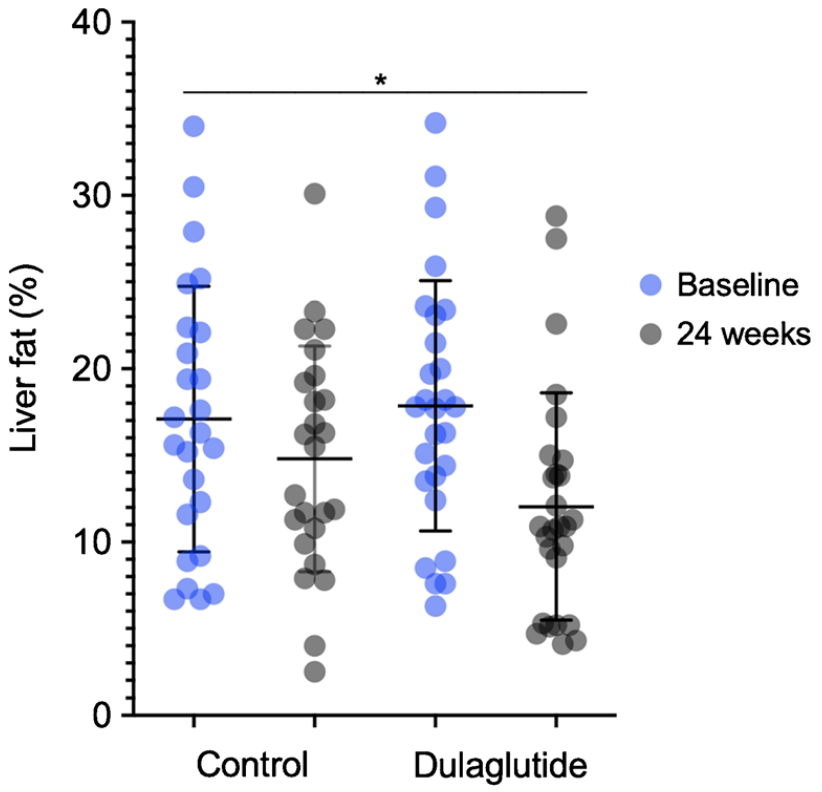
[1]Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL 32610, USA; and [2]Malcom Randall Veteran Administration Medical Center at Gainesville, FL 32610, USA

Effect of Dulaglutide in Patients with T2DM: Changes in Plasma ALT, AST and GGT at 24 weeks

Patients with T2DM and NAFLD



*p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. placebo.
Treatment difference [LSM difference (SE)].
Note: Integrated data from AWARD-1, AWARD-5, AWARD-8 and AWARD-9.



Kuchay et al. Diabetologia 2020; 63:2434–2445.

Cusi et al. Diabetic Medicine. 2018;35:1434.1439.

GLP-1RAs in NAFLD

Table 1. Summary of studies on the effect of GLP-1RA on hepatic steatosis by imaging or liver histology in patients with NAFLD

Primary outcome: relative reduction in liver fat on imaging[a]

Author	GLP1-RA	n	Study design	Weight change[b]	Reduction in liver fat content
Vanderheiden et al, 2016	Liraglutide	71	RCT	↓ 2.2%	↓ 31%
Feng et al, 2017	Liraglutide	87	Open label	↓ 6.4%	↓ 19%
Petit et al, 2017	Liraglutide	68	Open label	↓ 4.4%	↓ 19%
Frossing et al, 2018	Liraglutide	72	RCT	↓ 5.7%	↓ 32%
Kuchay et al, 2020	Dulaglutide	52	Open label	↓ 2.6%	↓ 20%

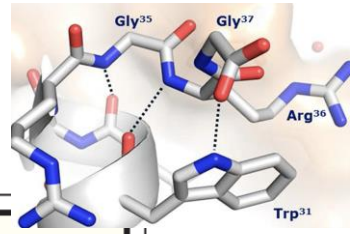
Primary outcome: percentage of patients with resolution of NASH (by liver histology)[c]

Author	GLP1-RA	n	Study design	Weight change[b]	NASH resolution
Armstrong et al, 2016	Liraglutide	52	RCT	↓ 4.8%	30%
Newsome et al, 2020	Semaglutide	320	RCT	↓ 4%-12%	19%-42%

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial.
[a] Placebo or comparator subtracted change in hepatic steatosis.
[b] Placebo or comparator subtracted weight loss.
[c] Placebo-subtracted change in number of patients with resolution of NASH.

Chandani, Cusi and Kadiyala; JCEM October 2021 (https://doi.org/10.1210/clinem/dgab578)

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

November 13, 2020

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

Population:

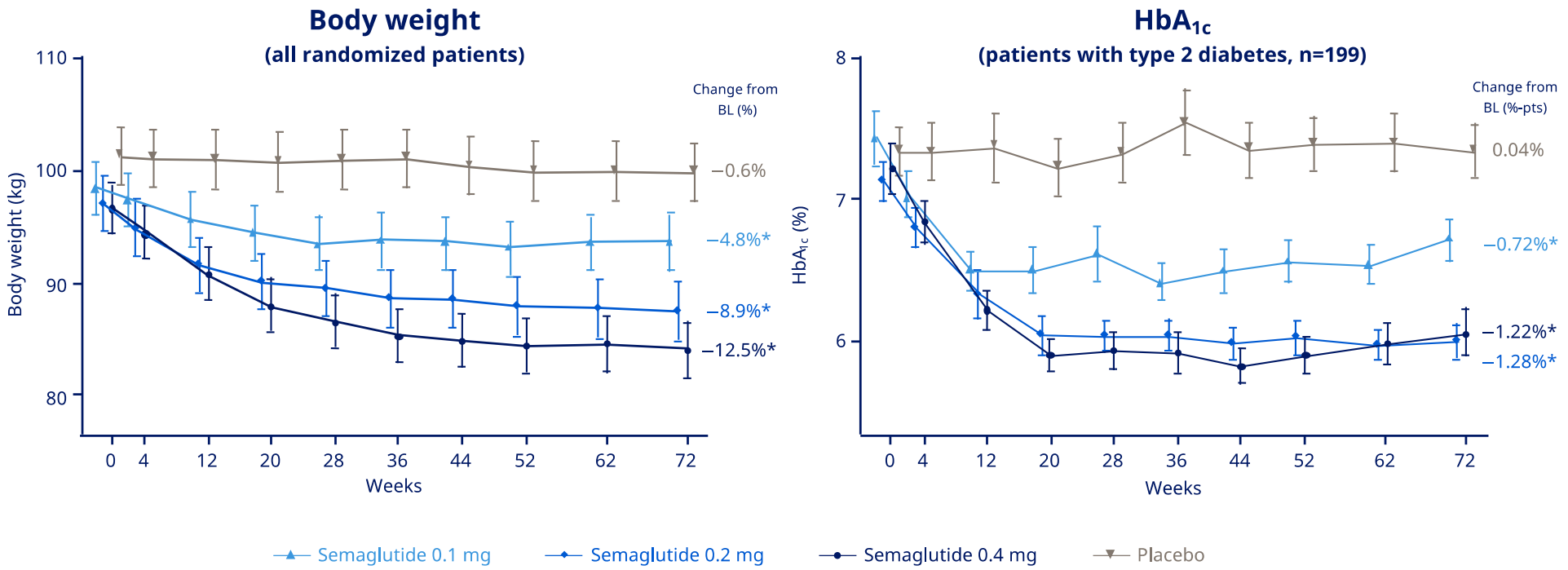
320 patients (62% T2DM) randomized to daily semaglutide 0.1, 0.2, and 0.4 mg.

(of whom 230 had stage F2 or F3 fibrosis).

Primary outcome:

NASH resolution without worsening of fibrosis after 72 weeks (yes/no).

Effects of Semaglutide in Patients with NASH

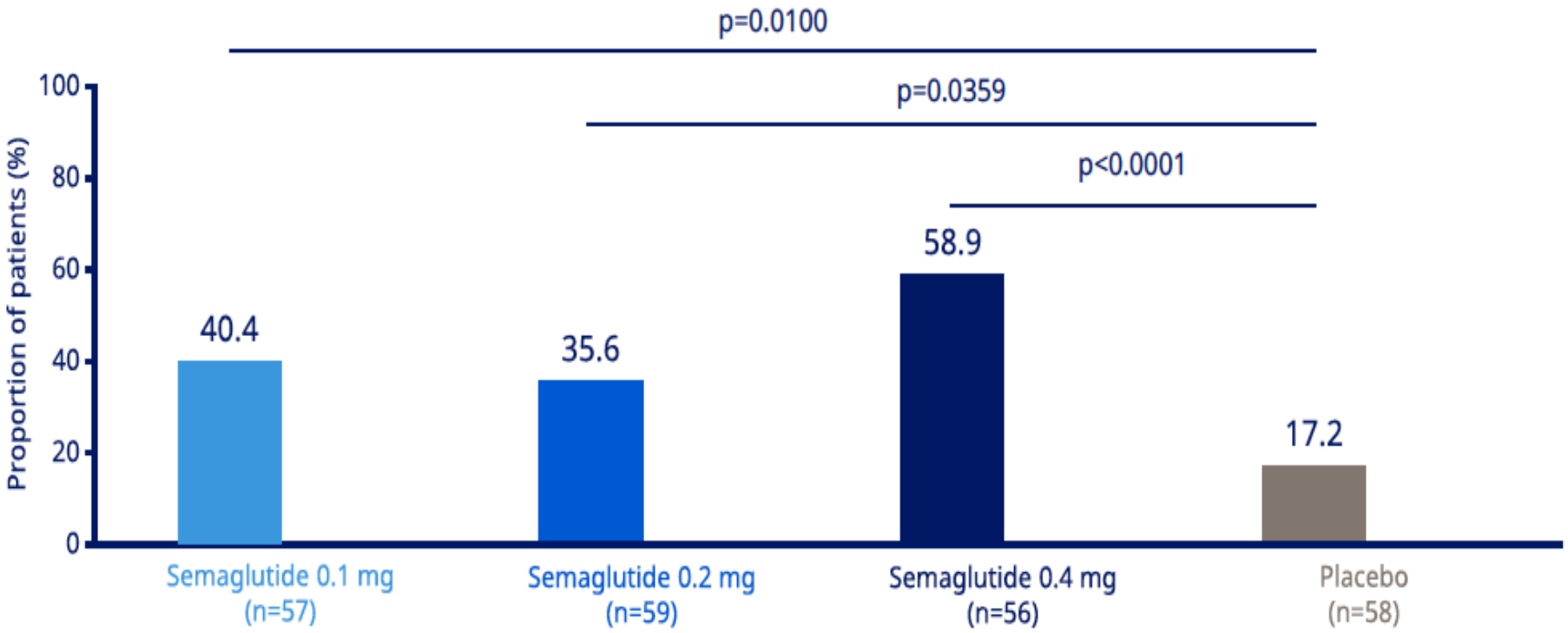


Newsome, Buchholz, Cusi et al. NEJM. November 13, 2020

Effect of Semaglutide in Patients with NASH

Resolution of steatohepatitis and no worsening in liver fibrosis

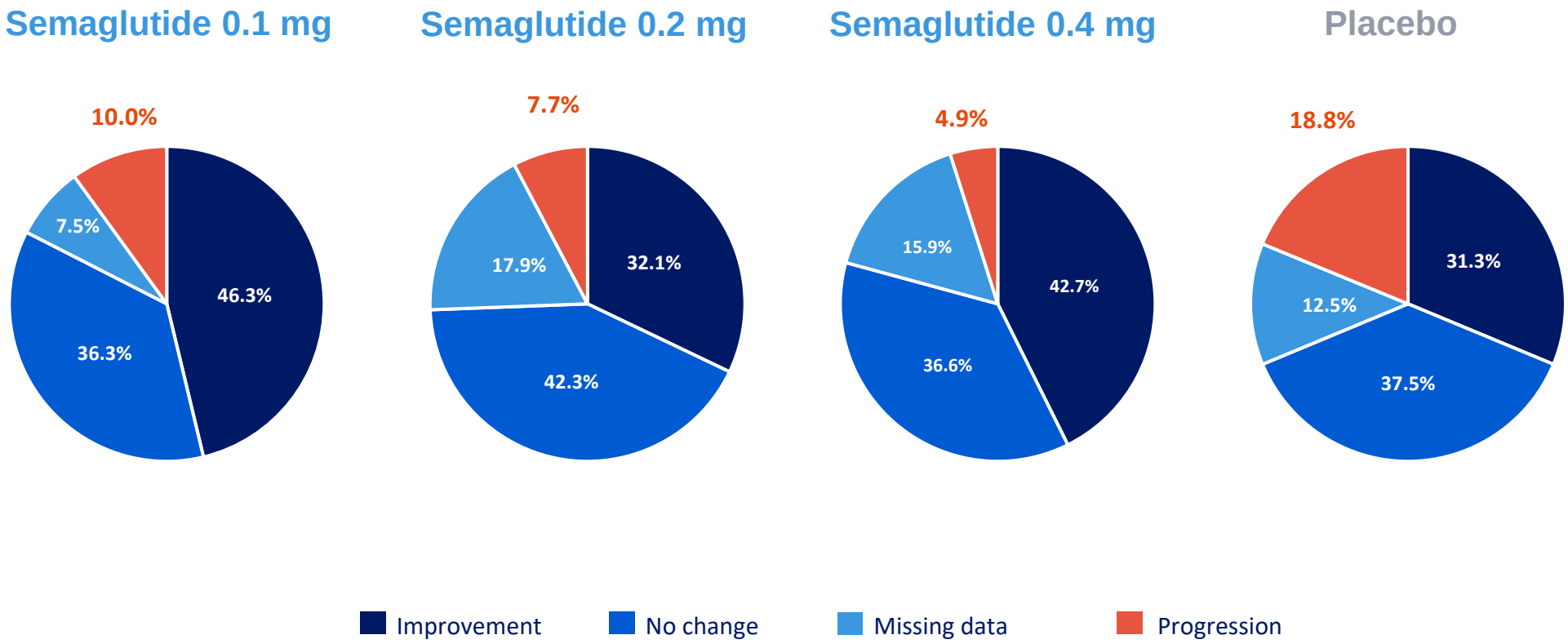
(Patients with fibrosis stage 2 or 3 at baseline)



Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

Newsome, Buchholz, Cusi et al. NEJM. November 13, 2020

Effect of Semaglutide in Patients with NASH



Newsome, Buchholz, Cusi et al. NEJM 2021; 384:1113-1124.

Effect of SGLT2 Inhibitors on Intrahepatic Triglycerides in Patients with T2DM and NAFLD

					Main study results		
Author	**Agent**	**n**	**Duration (weeks)**	**Comparator**	**Body weight***	**ALT**	**Liver fat***
Prospective open label studies							
Ito et al, 2017	Ipragliflozin	66	24	Pioglitazone	↓ 3.7%	↓ ¶	↓ ¶
Ohta et al, 2017	Ipragliflozin	20	24	Standard care	↓2.5%	↓	↓39%
Shibuya et al, 2017	Luseogliflozin	32	24	Standard care	↓ 3.2%	unchanged	↓ ¶
Kuchay et al, 2018	Empagliflozin	50	20	Standard care	↓ 1.1%	↓	↓ 26%
Shimizu et al, 2019	Dapagliflozin	57	24	Standard care	↓ 3.1%	↓	↓ †
Inohue et al, 2019	Canagliflozin	20	52	Standard care	↓ 3.4%	↓	↓ 31%
Randomized controlled trials							
Bolinder et al, 2012	Dapagliflozin	67	24	placebo	↓ 2.2%	-	unchanged
Eriksson et al, 2018	Dapagliflozin	84	12	placebo	↓ 2.2%	↓	↓ 10% §
Cusi et al, 2019	Canagliflozin	56	24	placebo	↓ 3.4%	unchanged	↓ 18% §
Latva-Rasku et al, 2019	Dapagliflozin	32	8	placebo	↓ 2.1%	unchanged	↓ 13%
Kahl et al, 2019	Empagliflozin	84	24	placebo	↓ 2.4%	unchanged	↓ 22%

Arrows indicate statistically significant changes vs. comparator

* Comparison-corrected (open-label) or placebo-corrected relative treatment difference in weight and liver fat measured with MRI-based imaging techniques.

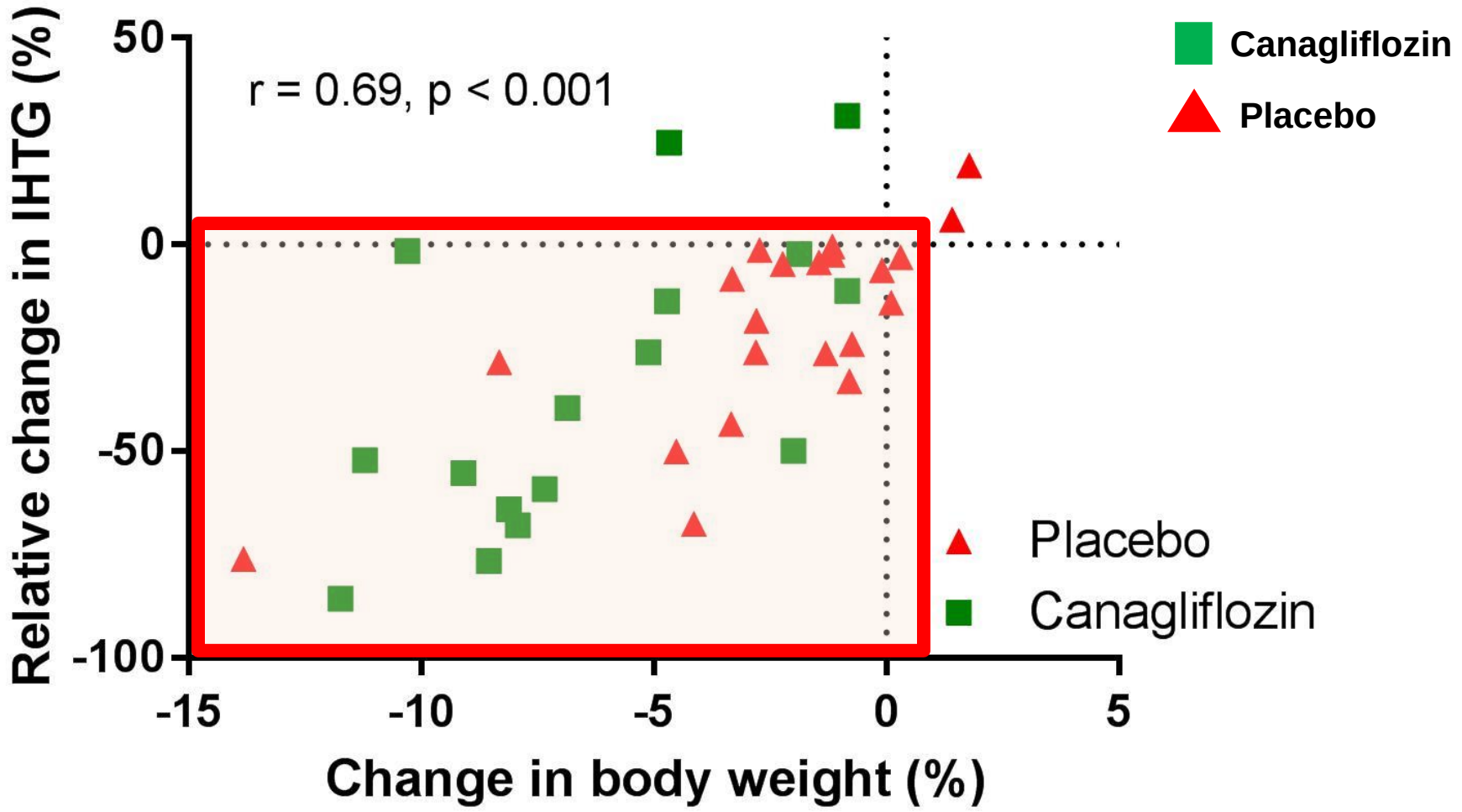
¶ Liver fat measured as liver-to-spleen attenuation ratio on computed tomography. Decrease similar to pioglitazone (comparator) in this trial (also ALT).

† Significant improvement in liver fat by controlled attenuation parameter (CAP; Fibroscan®).

§ Not significant compared to placebo.

Cusi KI, Diabetes Care 2020 (in press)

Effect of Canagliflozin on Intrahepatic Triglycerides is Proportional to Weight Loss in Patients with Type 2 Diabetes



Cusi et al, Diabetes, Obesity and Metabolism 2019

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Role of Pioglitazone in NASH Resolution

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Impact of Weight Gain from Excess Caloric Intake vs. Weight Loss vs. Weight Gain from PPARg Agonists in NAFLD

	Weight gain from overnutrition (i.e., in obesity)	Weight loss by different methods (lifestyle, medications, bariatric surgery)	Mild weight gain from PPARγ agonists (pioglitazone, lanifibranor)
Insulin resistance ○ Liver fat content ○ Visceral fat mass ○ Adipocyte function (insulin sensitivity, FFA, adiponectin secretion)	**Worse**	**Better**	**Better**
Type 2 diabetes ○ Glycemia ○ Atherogenic dyslipidemia	**Worse**	**Better**	**Better**
Cardiometabolic risk ○ Cardiovascular disease ○ Endothelial dysfunction ○ Subclinical inflammation	**Worse**	**Better**	**Better**

Cusi K, in press (2021)

The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2006, 355, 2297-2307

ORIGINAL ARTICLE

A Placebo-Controlled Tr
in Subjects with Nonalcol

Renata Belfort, M.D., Stephen A. Harriso
Celia Darland, R.D., Joan Finch, R.N., Jean H
Amalia Gastaldelli, Ph.D., Fermin Tio,
Rachele Berria, M.D., Jennie Z. Ma, F
Russell Havranek, M.D., Chris Fincke, I
George A. Bannayan, M.D., Steven Schenk

GASTROENTEROLOGY 2008;135:1176–1184

Randomized, Placebo-
Subjects With Nonalco

The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2010;362:1675–1685

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

Annals of Internal Medicine

ORIGINAL RESEARCH

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD

Background: The metabolic defects of nonalcoholic steatohepatitis (NASH) and prediabetes or type 2 diabetes mellitus (T2DM) seem to be specifically targeted by pioglitazone. However, information about its long-term use in this population is limited.

Objective: To determine the efficacy and safety of long-term pioglitazone treatment in patients with NASH and prediabetes or T2DM.

Design: Randomized, double-blind, placebo-controlled trial. (ClinicalTrials.gov: NCT00994682)

Setting: University hospital.

Participants: Patients (n = 101) with prediabetes or T2DM and biopsy-proven NASH were recruited from the general population and outpatient clinics.

Intervention: All patients were prescribed a hypocaloric diet (500–kcal/d deficit from weight-maintaining caloric intake) and then randomly assigned to pioglitazone, 45 mg/d, or placebo for 18 months, followed by an 18-month open-label phase with pioglitazone treatment.

Measurements: The primary outcome was a reduction of at least 2 points in the nonalcoholic fatty liver disease activity score (NAS) (in 2 histologic categories) without worsening of fibrosis. Secondary outcomes included other histologic outcomes, hepatic triglyceride content measured by magnetic resonance and proton spectroscopy, and metabolic parameters.

Results: Among patients randomly assigned to pioglitazone, 58% achieved the primary outcome (treatment difference, 41 percentage points [95% CI, 23 to 59 percentage points]) and 51% had resolution of NASH (treatment difference, 32 percentage points [CI, 13 to 51 percentage points]) (P < 0.001 for each). Pioglitazone treatment also was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, −0.5 [CI, −0.9 to 0.0]; P = 0.039); reduced hepatic triglyceride content from 19% to 7% (treatment difference, −7 percentage points [CI, −10 to −4 percentage points]; P < 0.001); and improved adipose tissue, hepatic, and muscle insulin sensitivity (P < 0.001 vs. placebo for all). All 18-month metabolic and histologic improvements persisted over 36 months of therapy. The overall rate of adverse ev
groups, although weight gain was g
kg vs. placebo).

Limitation: Single-center study.

Conclusion: Long-term pioglitazon
tive in patients with prediabetes or

Primary Funding Source: Burro
American Diabetes Association.

Annals of Intern Med, 2

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial

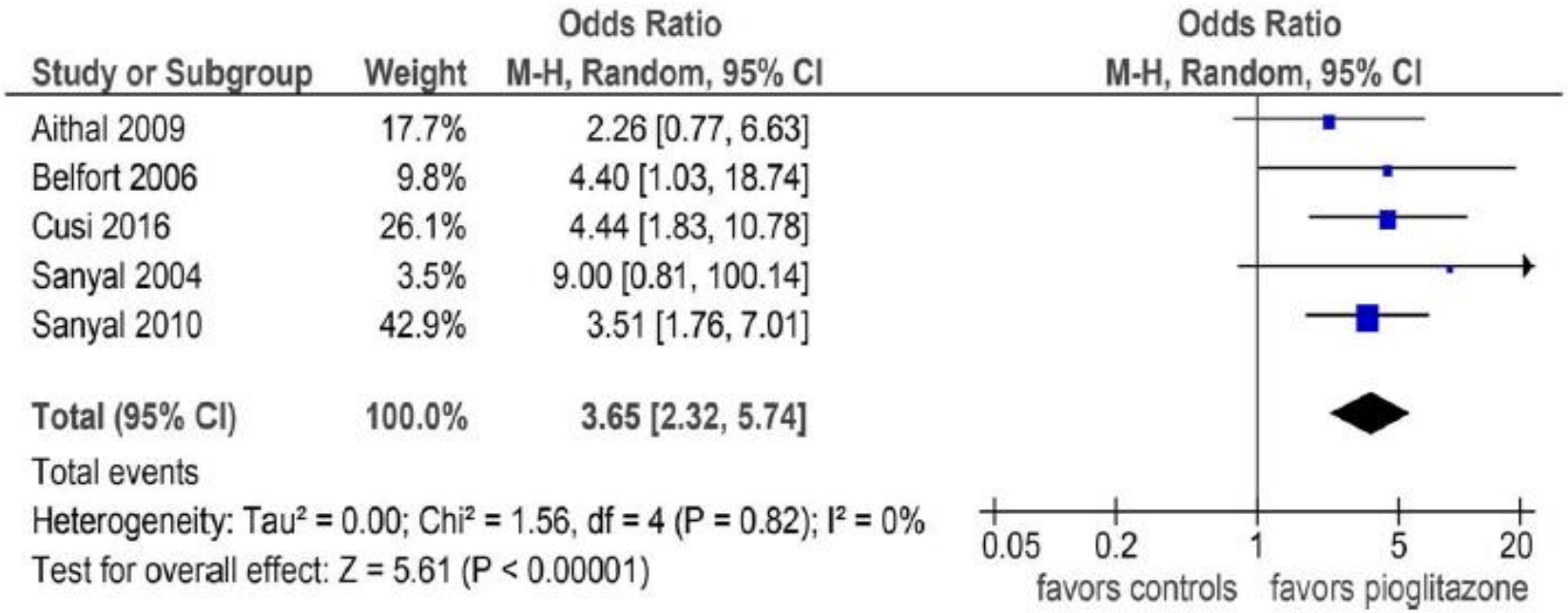
Fernando Bril,[1] Diane M. Biernacki,[1] Srilaxmi Kalavalapalli,[1] Romina Lomonaco,[1] Sreevidya K. Subbarayan,[1] Jinping Lai,[2] Fermin Tio,[3] Amitabh Suman,[4] Beverly K. Orsak,[5] Joan Hecht,[6] and Kenneth Cusi[1,7]

Diabetes Care 2019;42:1481–1488 | https://doi.org/10.2337/dc19-0167

Pioglitazone is not approved for treatment of NAFLD or NASH.

Effect on Pioglitazone on Resolution of NASH in RCTs:

Odds ratio for NASH resolution in all patients included in RCTs

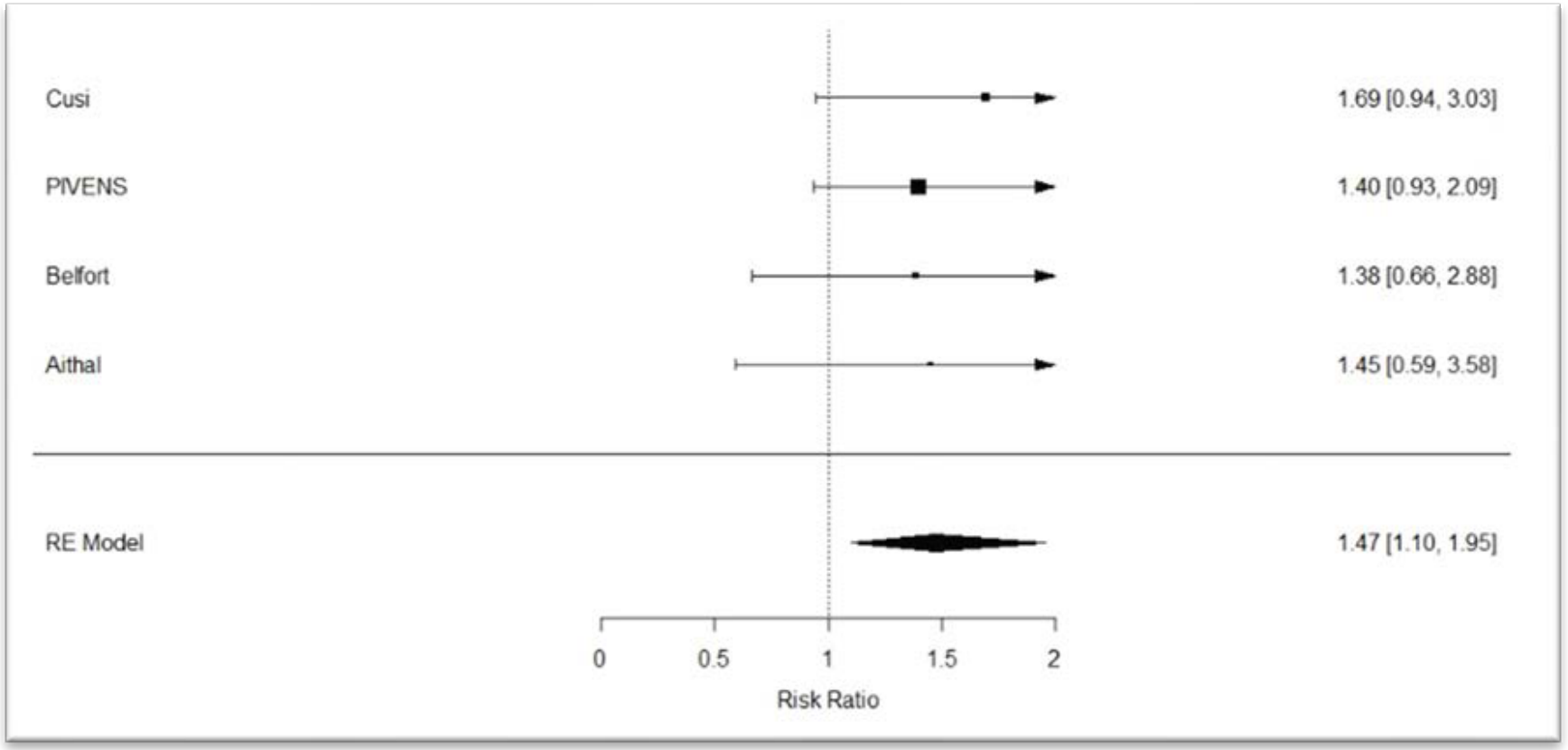


* Not head-to-head RCTs (not for comparison among pharmacological agents)

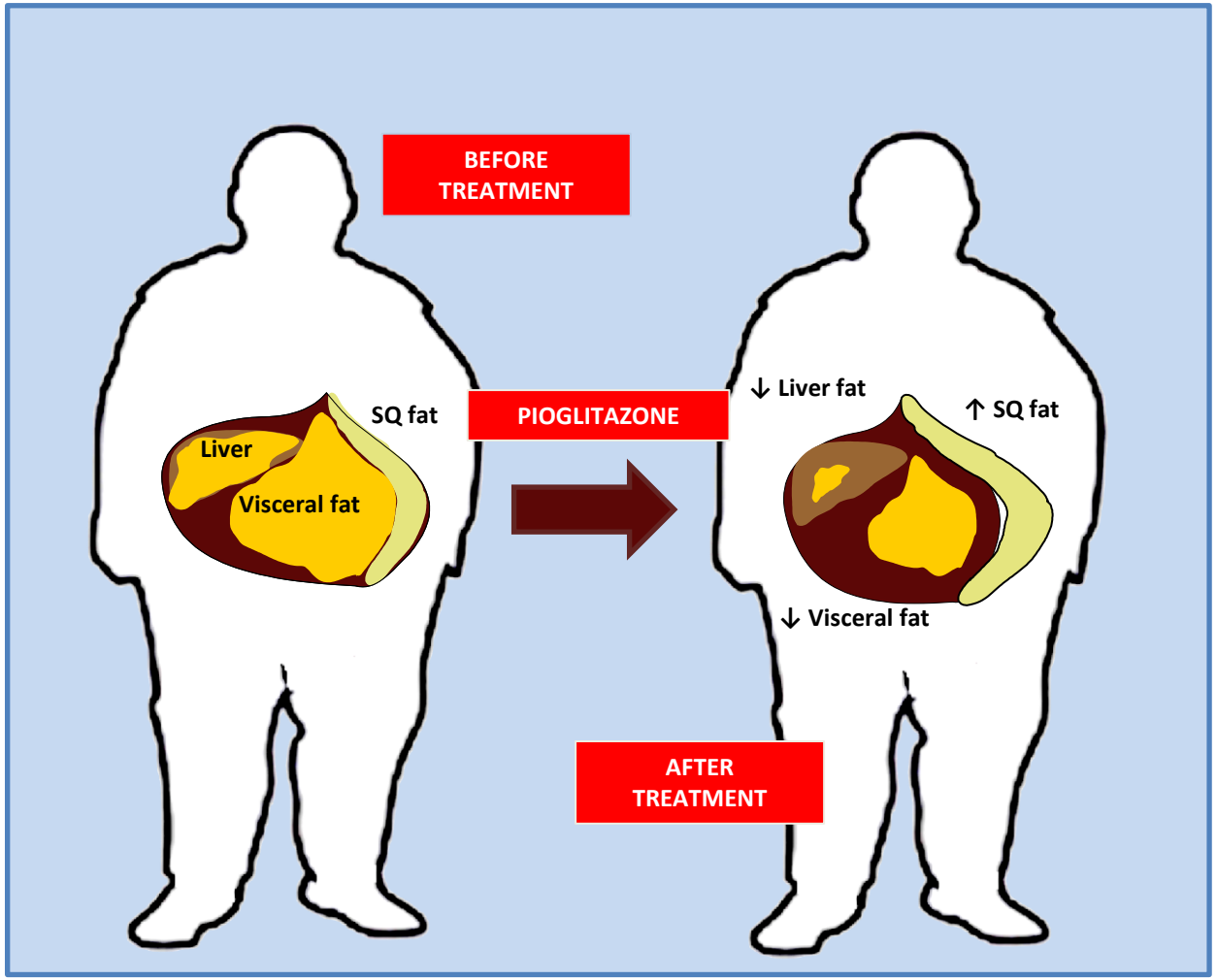
Musso et al, Hepatology 2016

Effect of Pioglitazone on Liver Fibrosis in Patients with NASH

Figure 4.2



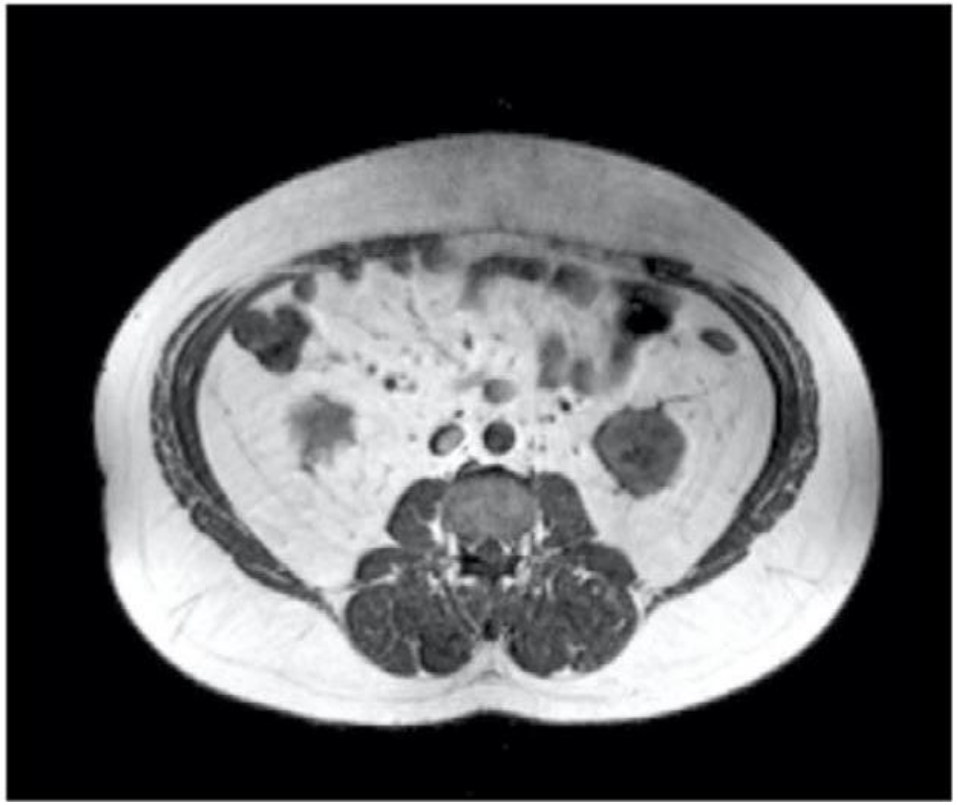
Improving Adipose Tissue Function (↑ adiponectin) and Reducing Visceral Fat (depot-specific effects) Explain the Effect of Pioglitazone in NASH



Gastaldelli/Cusi et al,
June 2021 (doi: 10.1111/liv.15005)

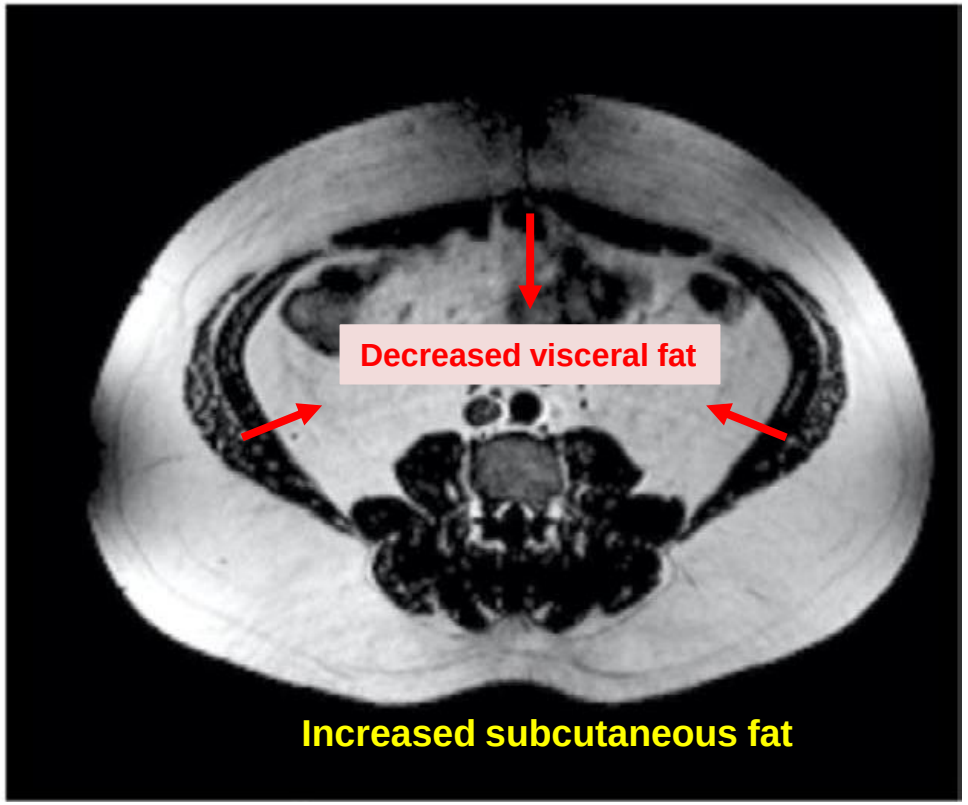
Clinical case: 39 year old male with type 2 diabetes

Before pioglitazone treatment



Fasting plasma glucose:	158 mg/dL
HbA1c:	7.9%
BMI:	35.6 kg/m^2

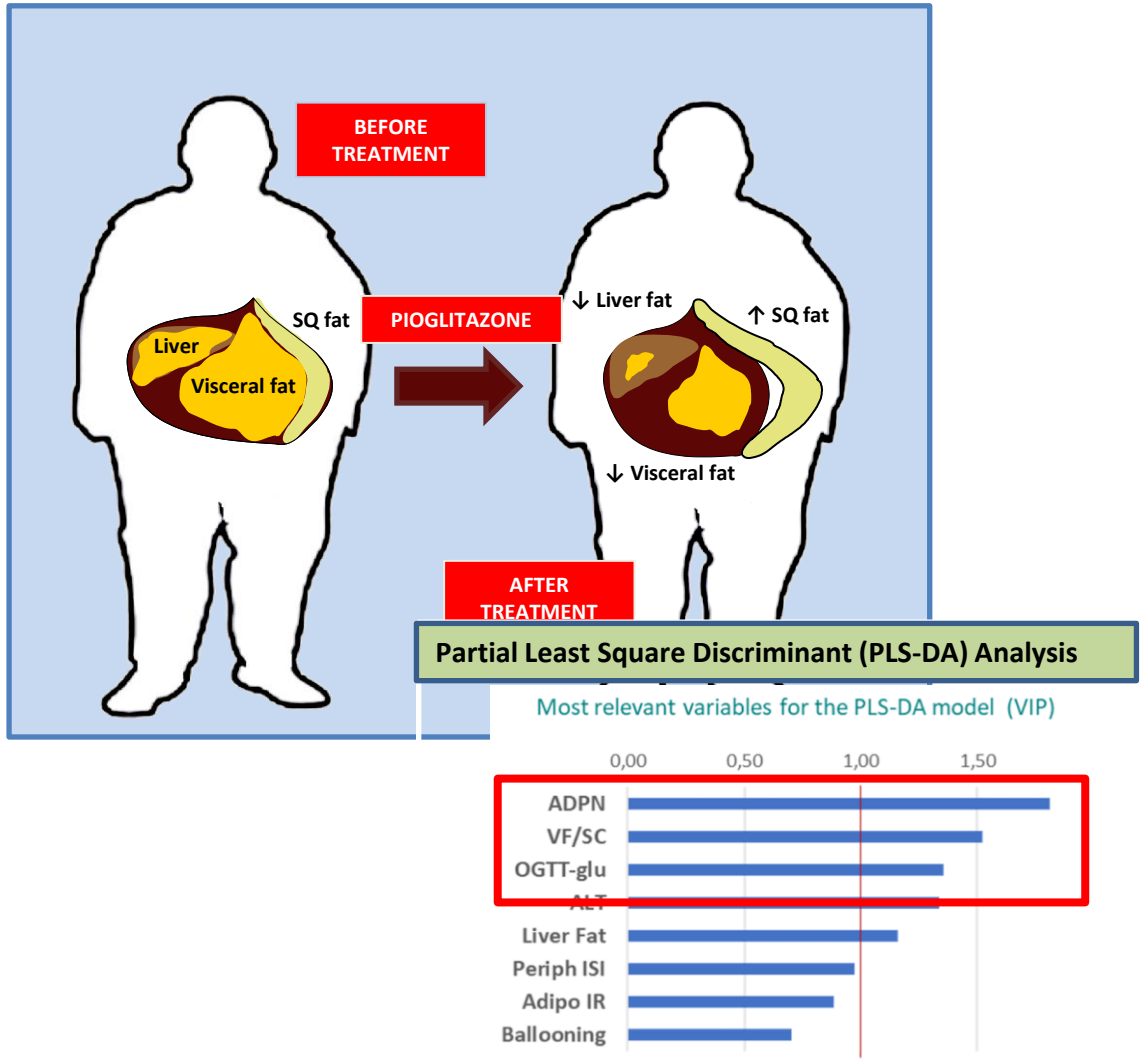
After pioglitazone treatment

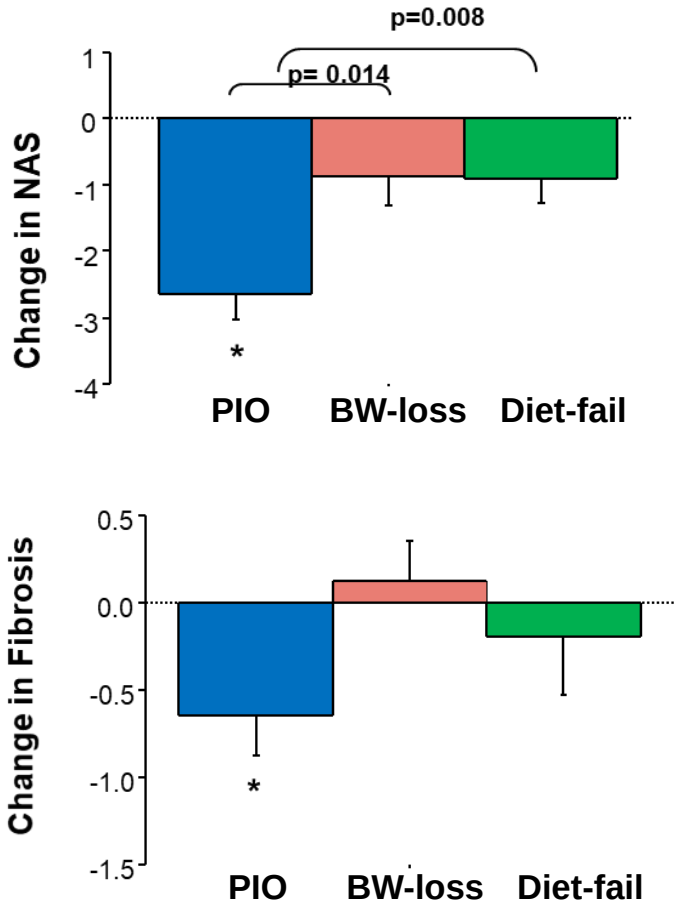


Fasting plasma glucose:	126 mg/dL
HbA1c:	6.2%
BMI:	37.3 kg/m^2

Gastaldelli/Cusi et al, June 2021 Liver International; doi: 10.1111/liv.15005

Pioglitazone Increases Adiponectin (Adipose Tissue Function) and Reduces Visceral and Hepatic Fat in Subjects with NASH



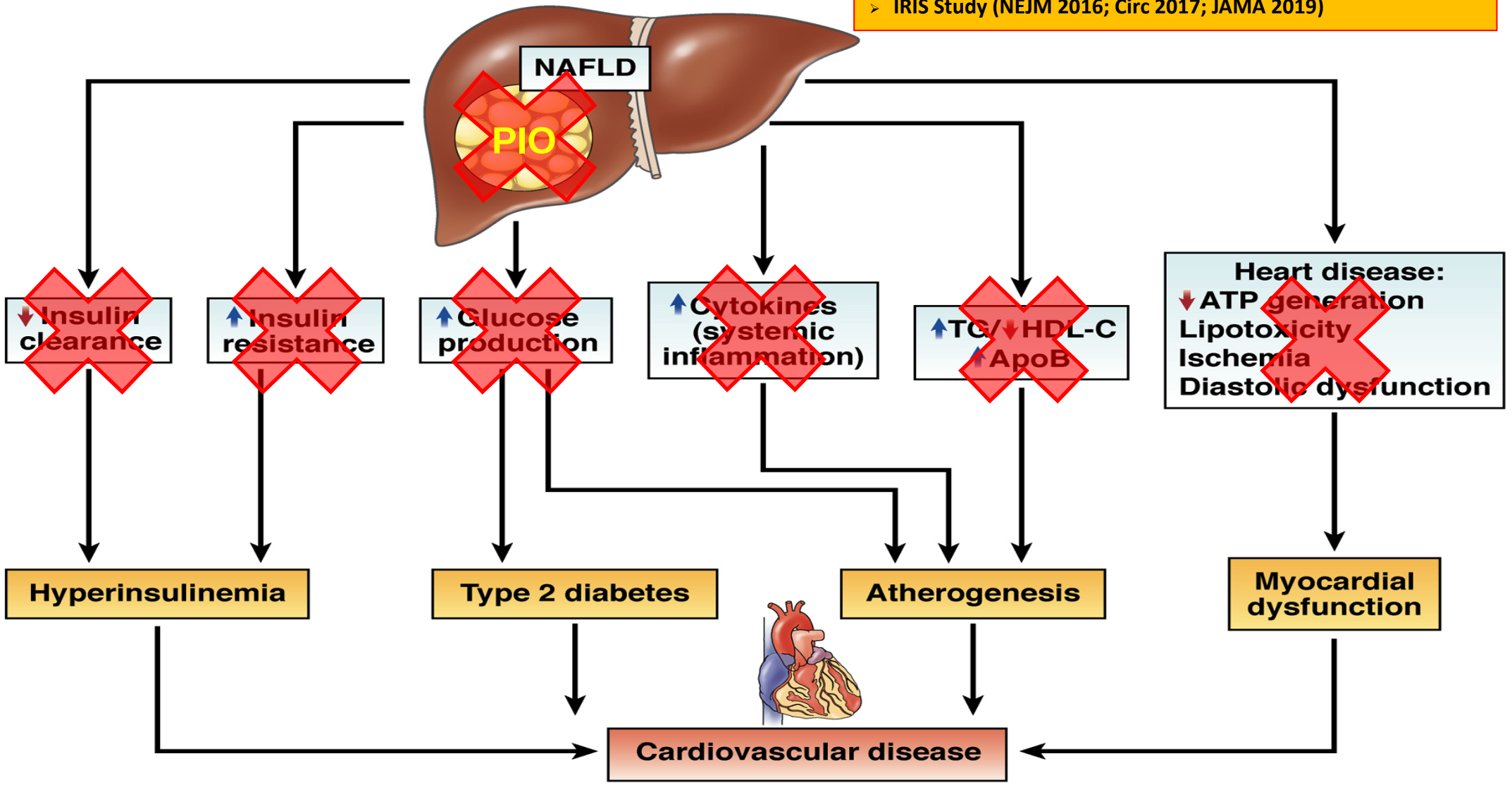


Gastaldelli/Cusi et al,June 2021 (doi: 10.1111/liv.15005)

Cardiovascular Impact of PPARg/a like Pioglitazone in NASH

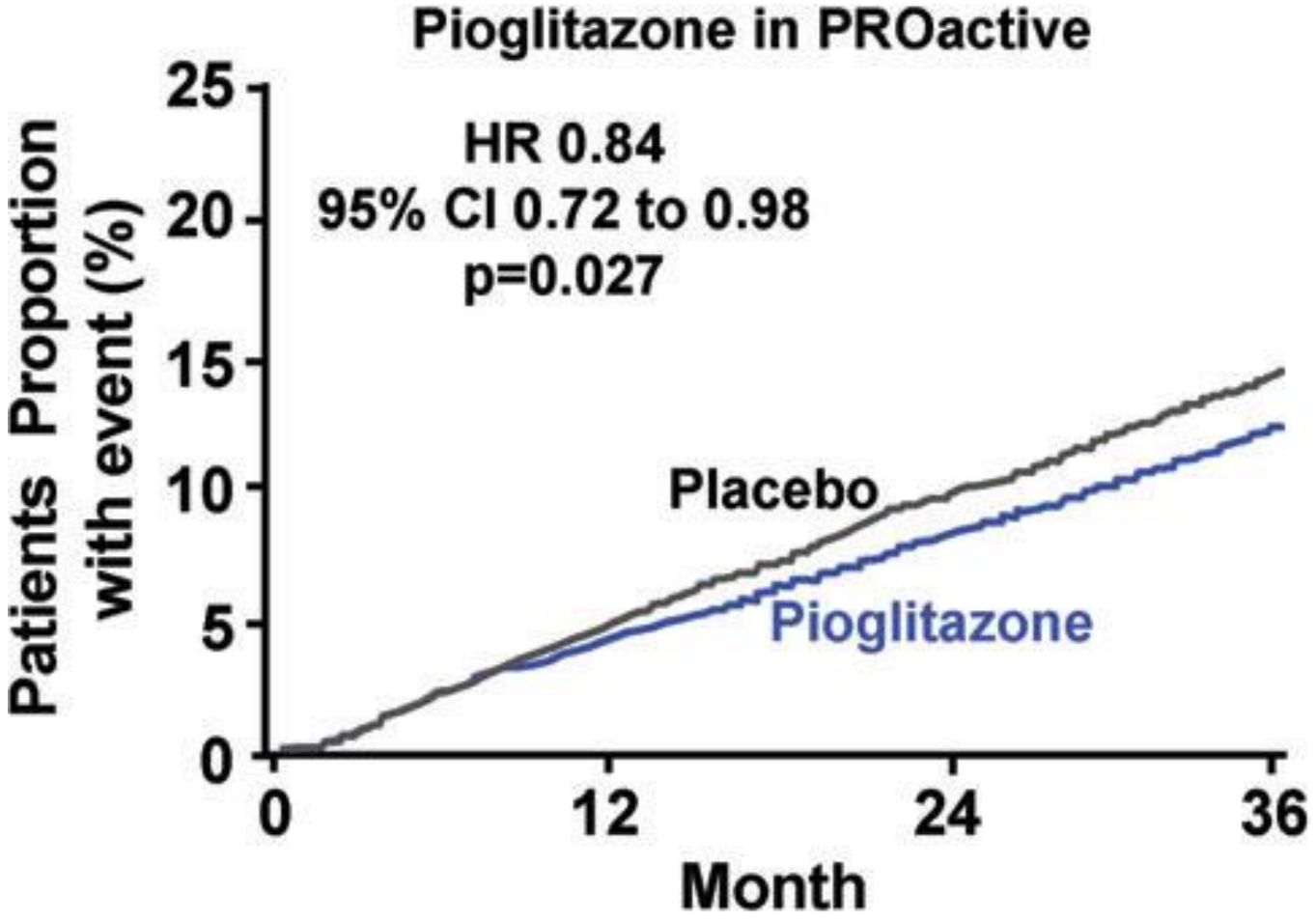
Reduction of CVD with pioglitazone:

- PROACTIVE (Lancet 2006)
- CHICAGO (JAMA 2007); PERISCOPE (JAMA 2008)
- IRIS Study (NEJM 2016; Circ 2017; JAMA 2019)



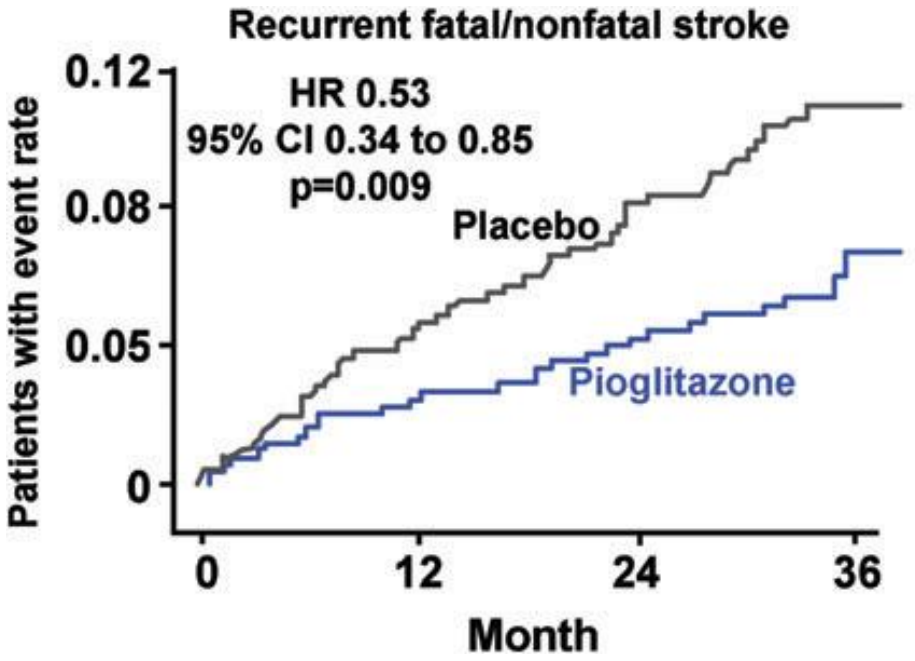
Cusi K, Gastroenterology, April 2012, 142:711-725

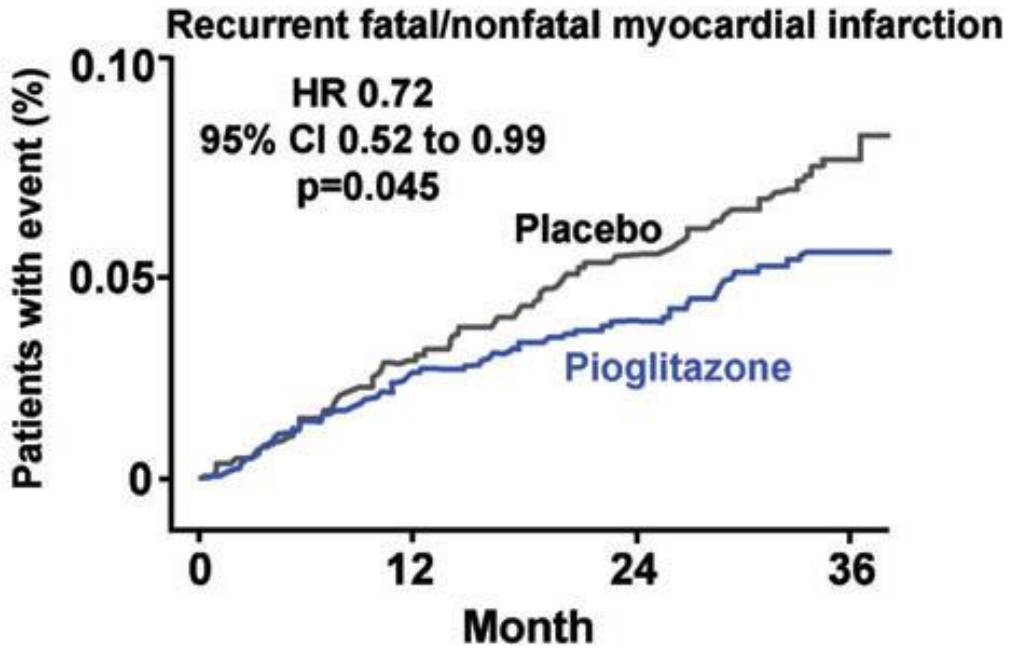
Effect of Pioglitazone (PROactive) on Major Adverse Cardiac Events (cardiovascular death, stroke, myocardial infarction)



Dormandy JA et al. Lancet 2005; 366: 1279–1289.

Effect of Pioglitazone (PROactive) on Major Adverse Cardiac Events (cardiovascular death, stroke, myocardial infarction)





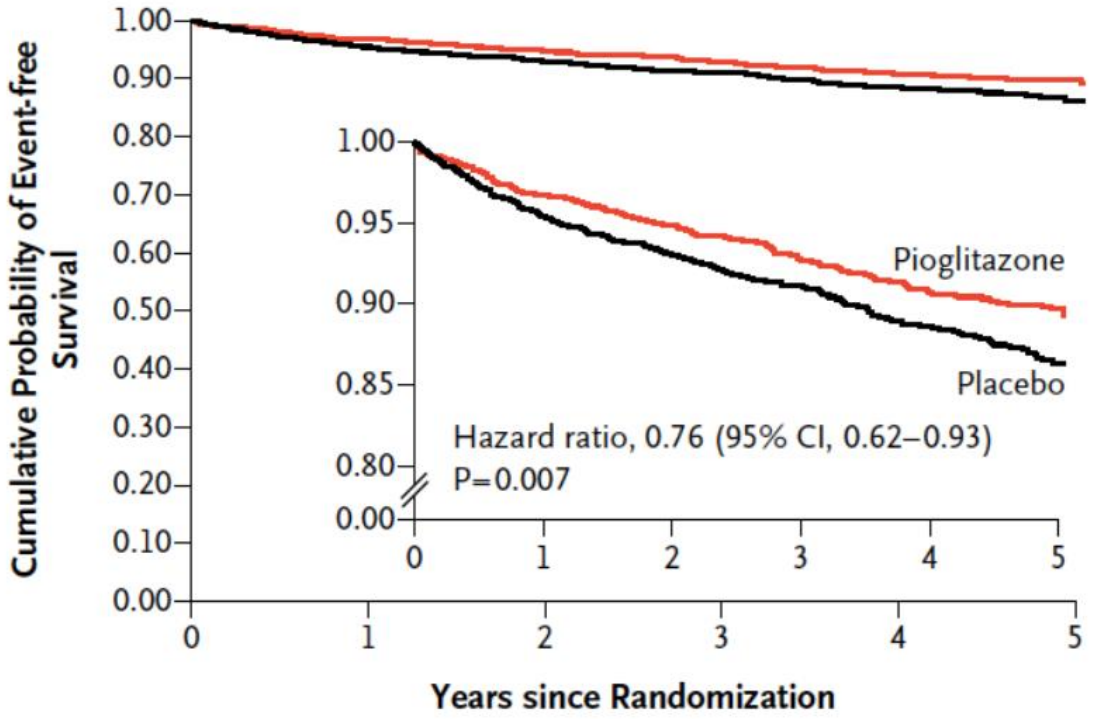
Dormandy JA et al. Lancet 2005; 366: 1279–1289.

Pioglitazone Reduces CVD and Improves LV Function

- PROACTIVE (Lancet 2006)
- CHICAGO (JAMA 2007)
- PERISCOPE (JAMA 2008)
- **IRIS Study**
  - **NEJM 2016**
  - **Circulation 2017**
  - **JAMA 2019**

Effect of Pioglitazone on Major Adverse Cardiac Events in Patients without T2DM with Cerebrovascular Disease (IRIS study)

- 3876 participants were randomly assigned to receive pioglitazone (45 mg/d target dose) or placebo within 180 days of a qualifying ischemic stroke or transient ischemic attack.
- Followed for a maximum of 5 years.



No. at Risk						
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

Kernan JA et al. N Engl J Med 2016;374, 1321-1331.

Pioglitazone for Secondary Stroke Prevention

A Systematic Review and Meta-Analysis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Hazard Rati IV, Random, 95%
IRIS	-0.1984509	0.12855306	46.8%	0.82 [0.64, 1.
J SPIRIT	-0.4155154	0.31533507	17.9%	0.66 [0.36, 1.
PROactive	-0.6348783	0.18197701	35.3%	0.53 [0.37, 0.
Total (95% CI)			**100.0%**	**0.68 [0.50, 0.**

Heterogeneity: Tau² = 0.03; Chi² = 3.88, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 2.53 (P = 0.01)

IRIS study: Pioglitazone reduced risk for ischemic strokes (HR, 0.72; 95% CI, 0.57–0.91; P=0.005) but had no effect on risk for hemorrhagic events (HR, 1.00; 95% CI, 0.50–2.00; P=1.00).

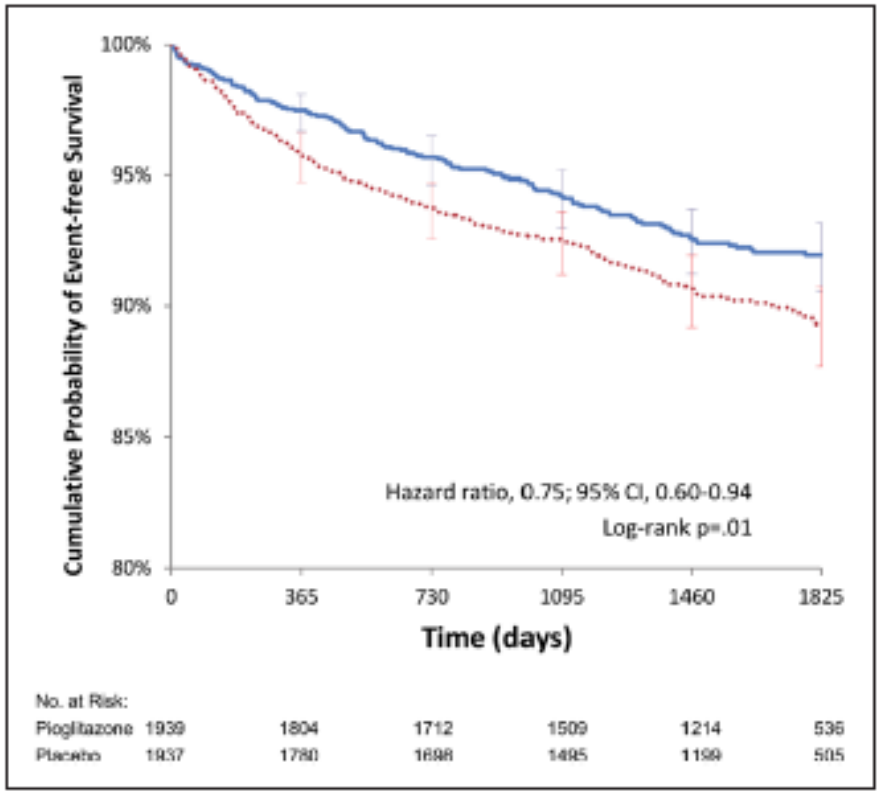


Figure 1. Time to first stroke by treatment group.
Pioglitazone, solid line; placebo, dashed line. CI indicates confidence interval.

Yaghi, Shadi, et al. Circulation 137.5 (2018): 455-463.

Pioglitazone Therapy in Patients With Stroke and Prediabetes A Post Hoc Analysis of the IRIS Randomized Clinical Trial

Table 2. Hazard Ratios in Cox Regression for On-Treatment and Intention-to-Treat Analyses

Variable	Hazard Ratio (95% CI)	*P* Value	NNT
Adherence ≥80%			
Stroke/MI	0.57 (0.39-0.84)	.004	24
Stroke	0.64 (0.42-0.99)	.04	39
Acute coronary syndrome	0.47 (0.26-0.85)	.01	40
Stroke/MI/HF hospitalization	0.61 (0.42-0.88)	.008	26
New-onset diabetes	0.18 (0.10-0.33)	<.001	12
Intention to treat			
Stroke/MI	0.70 (0.56-0.88)	.002	28
Stroke	0.72 (0.56-0.93)	.01	39
Acute coronary syndrome	0.72 (0.52-1.00)	.052	62
Stroke/MI/HF hospitalization	0.78 (0.63-0.96)	.02	34
New-onset diabetes	0.46 (0.35-0.61)	<.001	19

CONCLUSIONS AND RELEVANCE Pioglitazone may be effective for secondary prevention in patients with stroke/transient ischemic attack and with prediabetes, particularly in those with good adherence.

JAMA Neurology, February 2019

Heart Failure and Pioglitazone

Studies that have not observed an increase in heart failure:

- Mazzone et al. JAMA 2006;296, 2572-2581.
- Nissen et al. JAMA 2008;299, 1561-1573.
- Sanyal et al. N Engl J Med 2010;362, 1675-1685.
- DeFronzo et al. N Engl J Med 2011;364, 1104-1115.
- **Kernan et al. N Engl J Med 2016;374, 1321-1331 (IRIS study)**
- Cusi et al. Ann Intern Med 2016;165, 305-315.
- Vaccaro et al. Lancet Diabetes Endocrinol. 2017;5:887-897.
- Strongman et al. BMJ Open Diab Res Care 2018;6:e000481.

Cusi K, 2019 (unpublished)

Cohort Studies of the Association of Bladder Cancer and Pioglitazone Exposure (dependent variable)

Most (18 out of 23) Published Studies are Negative

Author	PIO Bladder Cancer, %	Control Bladder Cancer, %	HR*	
Lewis et al, 2011 (5-year follow-up)	0.30†	0.48	1.2	✔
Neumann et al, 2012	0.11	0.14	1.22*	
We L, 2012	0.28	o.44	1.16	
Tseng C-H, 2012			1.30	
Mamtani et al, 2012			0.93	
Vallarino et al, 2013			0.92	
Fujimoto et al, 2013			1.75	
Jin et al, 2014			1.14	
Lin et al, 2014			0.46	
Lee et al, 2014			1.03	
Levin et al, 2015	0.33	0.34	1.03	
Lewis et al, 2015 (10-year follow-up)	0.62**	0.66	1.06	✔
Korhonen et al, 2015	0.23	0.27	0.99	

Pioglitazone and bladder cancer?

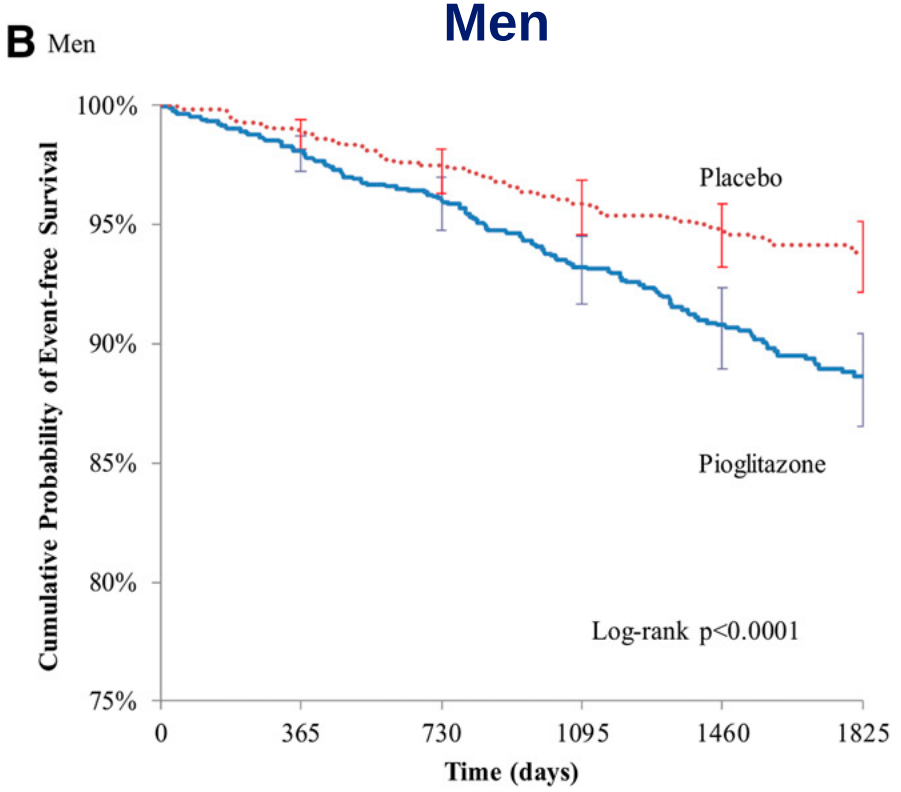
- Most studies = 18 of 23 studies are negative.
- In the 5 positive studies, several design flaws and effect small: number needed to treat for ~3 years for 1 bladder cancer between 877 to 4500.
- If any potential long-term effect is believed dose-dependent and rare.

P <0.05; †HR = 1.4; **HR = 1.16 for exposure > 4 years; ‡HR = 0.82 for exposure > 1 year, no trend with > 2 years.

Mayer, J Diabetes & Complications 2016; 30:981-985

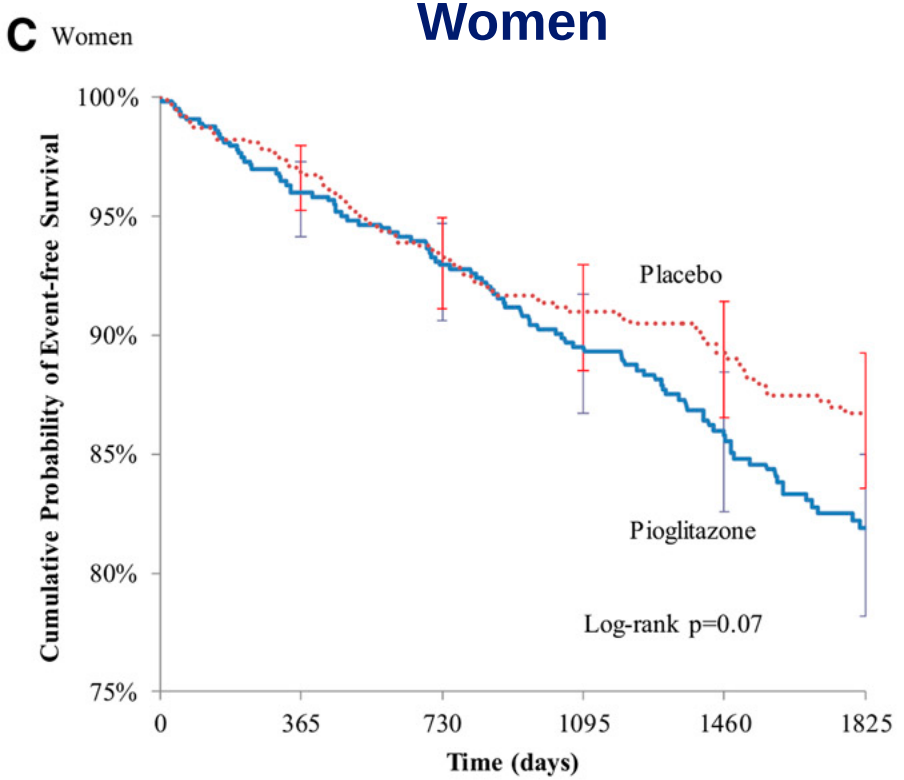
Pioglitazone and Risk for Bone Fracture: Safety Data From the IRIS Study

Men



No. at Risk:						
Pioglitazone	1293	1222	1160	1002	787	340
Placebo	1245	1177	1127	987	783	340

Women



No. at Risk:						
Pioglitazone	646	576	534	467	377	154
Placebo	692	632	590	512	425	171

IRIS study: At 5 years, the increment in fracture risk between pioglitazone and placebo groups was 4.9% [13.6% vs 8.8%; hazard ratio (HR), 1.53; 95% confidence interval (CI), 1.24 to 1.89).

Viscoli JA et al. JCEM 2017, 102(3):914–922.

How to Use Pioglitazone in Patients with T2DM?

- Beyond glycemia, PIO treats NASH, CVD and prediabetes
- Avoid if:
  - BMI ≥40 kg/m^2
  - LE edema at baseline or on amlodipine (edema +++)
  - Long-standing DM or high-insulin doses
  - If HF suspected (echocardiogram, BNP?, consult cardiology)
  - Osteoporosis
- Start pioglitazone at 15 mg/day
- Follow patient every 3-4 months:
  - ALT, A1c, if good tolerance (>90% pts) increase from 15 to 30 mg/day
  - Check for ankle swelling (~5-8%; more if on high-dose insulin)
  - Check for shortness of breath or easy fatigability (~1%) or excessive wt gain

Future options to reduce weight gain and increase efficacy of pioglitazone

1. Low-dose pioglitazone (15 mg/day)
2. Combination therapy:
    a) SGLT2i (many studies)
    b) GLP-1RA (e.g., AWARD-1: PIO + dulagutide and exenatide;
       SUSTAIN-2: PIO + semagutide)

Cusi K, 2021

Low-Dose Pioglitazone is Associated with Minimal Weight Gain in Patients with T2DM

Author Dose response studies	Dose (mg/day)	Population	n	Duration (weeks)	diff FPG (mg/dL)	diff A1c %	diff TG %	diff HDL %	Weight change %
Aronoff et al, 2000	15	USA	80	26	−39	−1.0%	−14%	6%	1%
	30		79		−41	−1.0%	−14%	4%	1%
Miyazaki et al, 2002	15	USA	12	26	−31	−1.3%	−28%	6%	2%
	30		11		−66	−2.0%	−40%	7%	3%
Rosenstock, 2002	15	USA	188	16	−35	−1.0%	−21%	7%	2%
	30		187		−48	−1.3%	−23%	9%	4%
Rajagopalan, 2015	15	India	28	26	−40	−0.6%	−18%	3%	1%
	30		29		−41	−0.7%	−24%	4%	2%

A1c, glycated haemoglobin; FPG, fasting plasma glucose; HDL, high-density lipoprotein; TG, triglycerides.

Cusi, 2021 (unpublished)

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

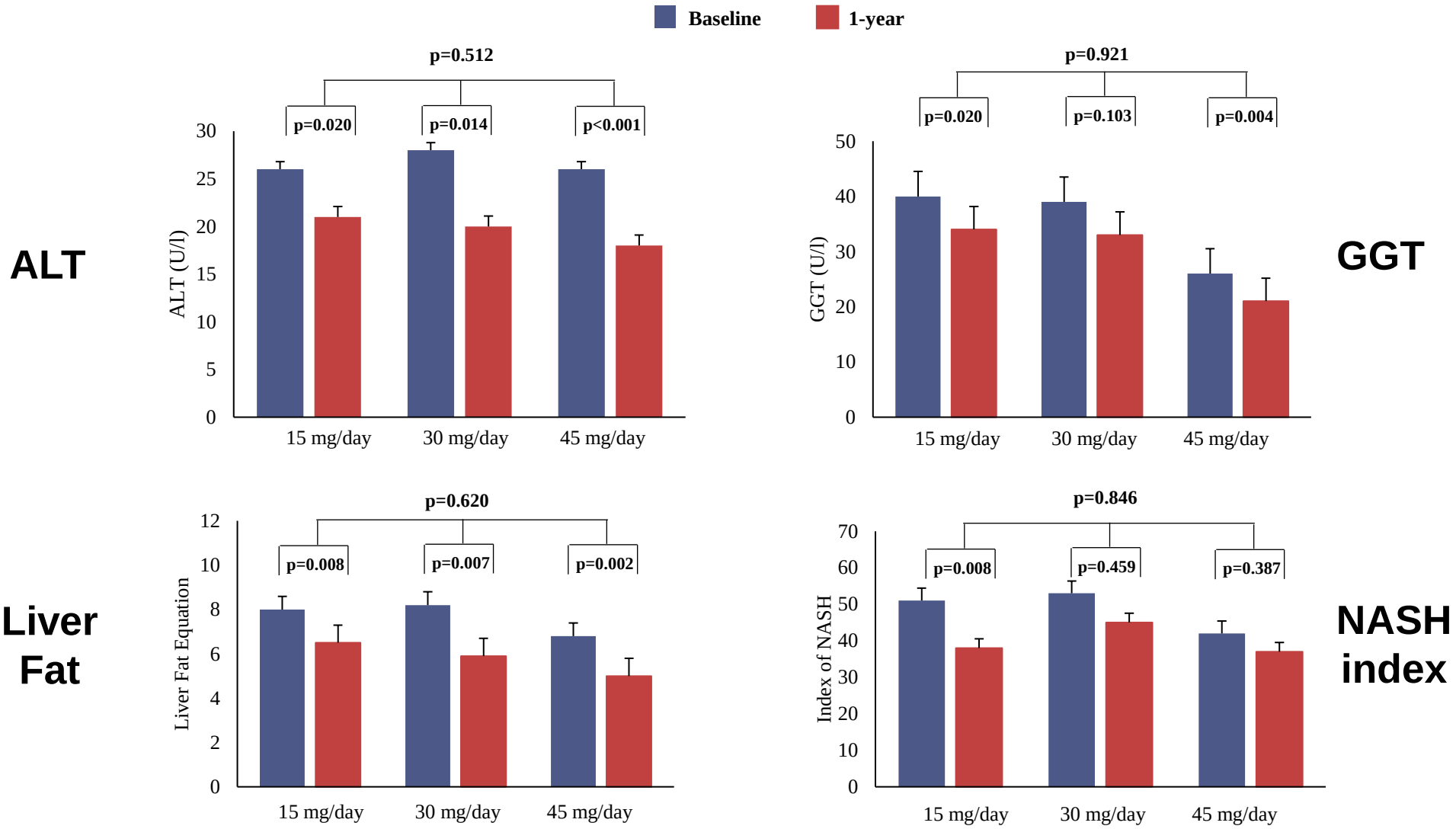
Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial

Giuseppe Della Pepa [a,1], Marco Russo [b,c,1], Marilena Vitale [a], Fabrizia Carli [b], Claudia Vetrani [a], Maria Masulli [a], Gabriele Riccardi [a], Olga Vaccaro [d], Amalia Gastaldelli [b,*], Angela A. Rivellese [a,*], Lutgarda Bozzetto [a]

[a] Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
[b] Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Pisa, Italy
[c] University of Siena, Siena, Italy
[d] Department of Pharmacy, University of Naples Federico II, Naples, Italy

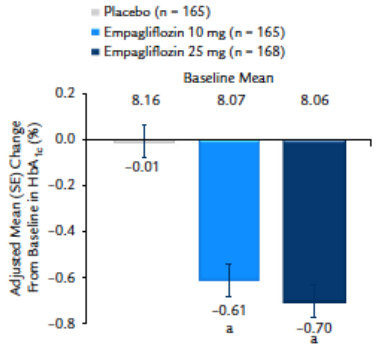
Della Pepa et al, Diabetes Res Clin Pract. 2021 Aug;178:108984. doi: 10.1016/j.diabres.2021.108984.

Effect of Pioglitazone 15 vs. 30 vs. 45 mg/day Treatment on Plasma ALT and indices of NAFLD



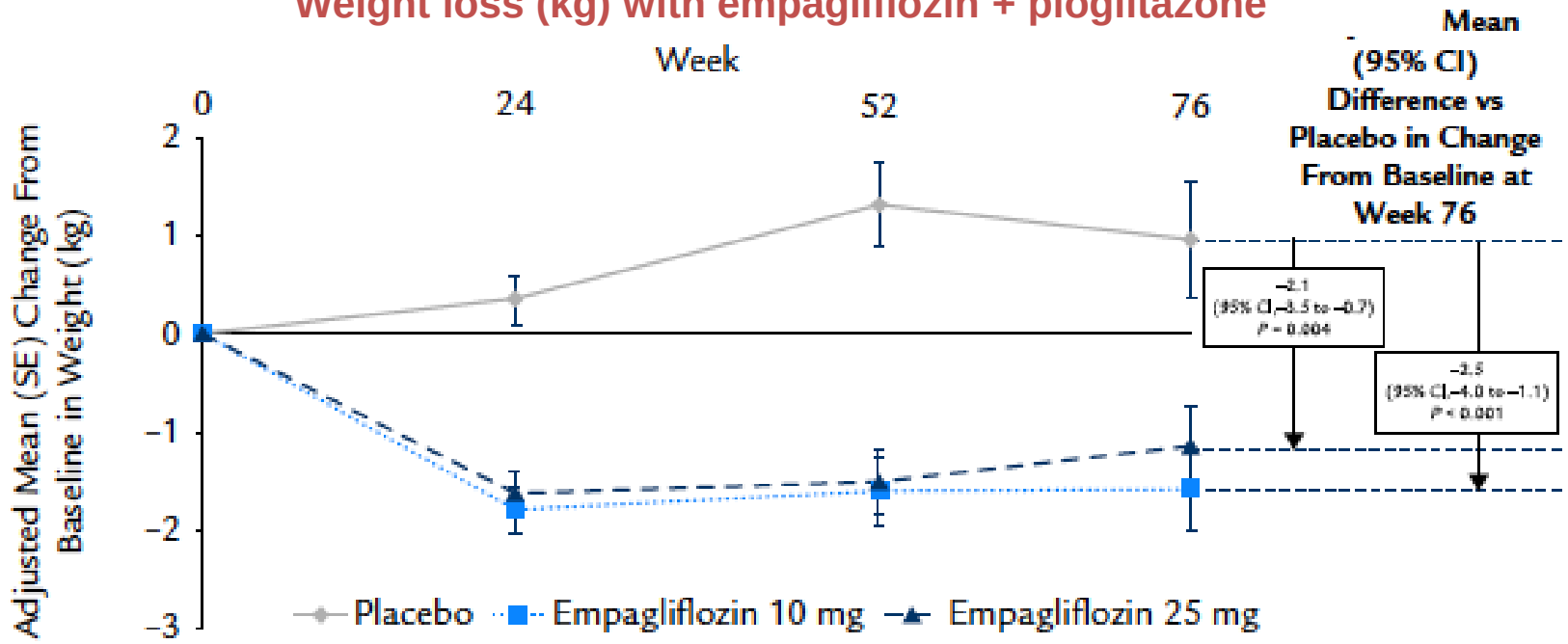
Della Pepa et al, Diabetes Res Clin Pract. 2021 Aug;178:108984. doi: 10.1016/j.diabres.2021.108984.

Weight loss with the Addition of Empagliflozin to Pioglitazone in Patients with T2DM (EMPA-REG EXTEND)



HbA1c

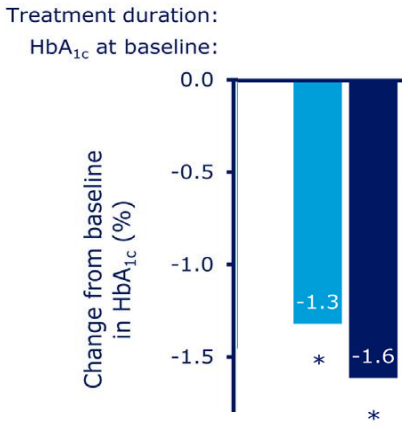
Weight loss (kg) with empagliflozin + pioglitazone



Kovacks et al, Clin Ther. 2015;37:1773–1788.

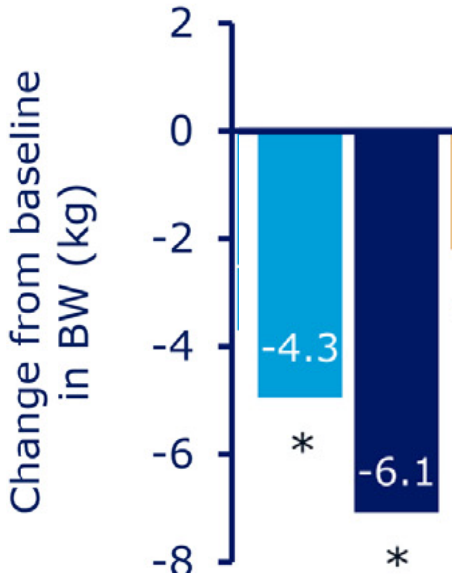
Weight loss with the Addition of the GLP-1RA Semaglutide to Pioglitazone in Patients with T2DM (SUSTAIN-2)

HbA1c

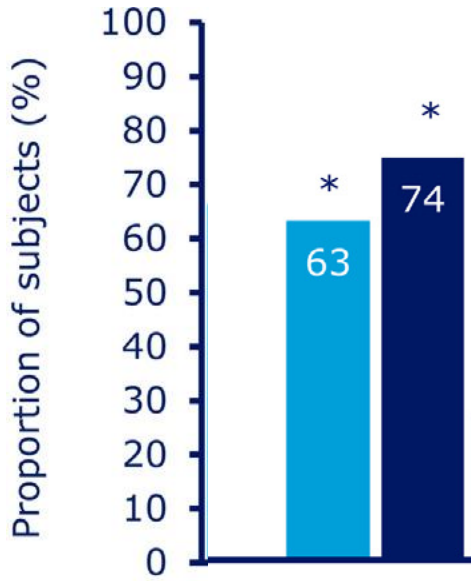


Background: (MET, TZD, MET/TZD)
Treatment duration: 56 weeks

Weight loss (kg) with semaglutide added to pioglitazone



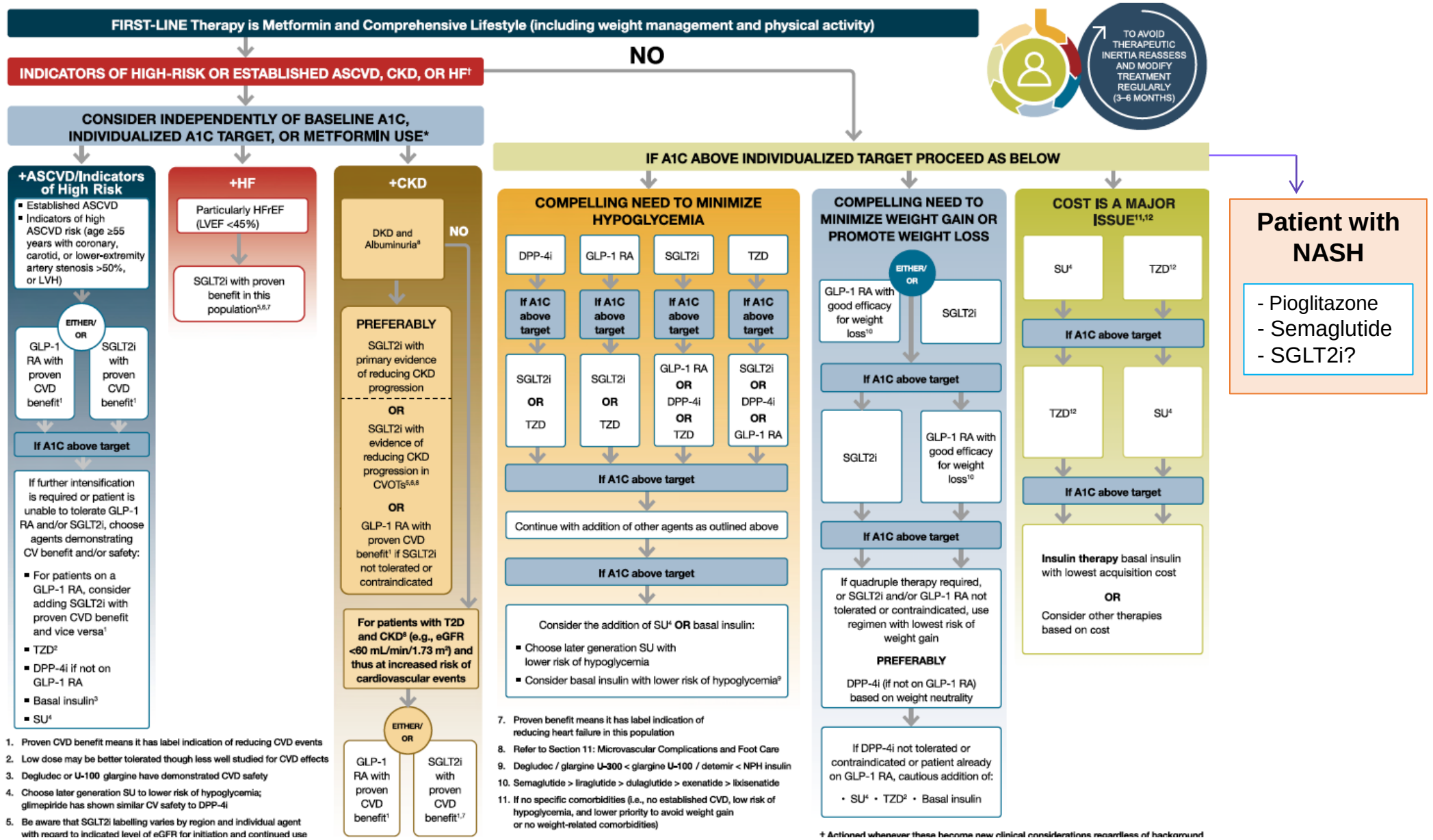
Patients achieving HbA1c <7.0% with no weight gain and no hypoglycemia



■ Semaglutide 0.5 mg ■ Semaglutide 1.0 mg

Ahren et al, Lancet Diabetes Endocrinol 2017;5:341–54.

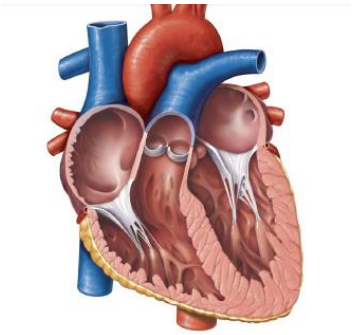
Glucose-lowering Medications in Type 2 Diabetes - 2021



American Diabetes Association, Diabetes Care 2021; 44(suppl. 1): S111-S124

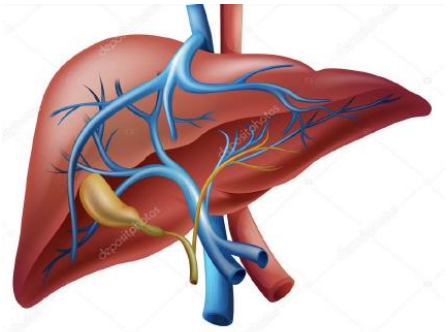
Cardiometabolic Risk Reduction in obesity and T2DM: A “triangle of care”…

CVD



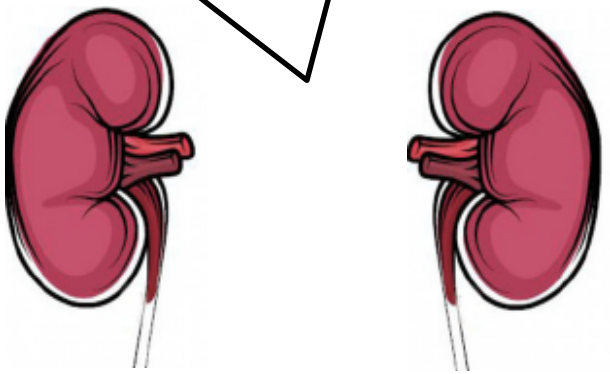
- ✓GLP-1RAs
- ✓SGLT2i
- ✓Pioglitazone

NASH



- ✓ Pioglitazone
- ✓ GLP-1RAs
- ✓ SGLT2i (?)

Nephropathy



- ✓ SGLT2i
- ✓ GLP-1RAs

Cusi K (unpublished 2021)