Does Diabetes Control and the Means for Achieving Control Affect Various Phenotypes of NAFLD?

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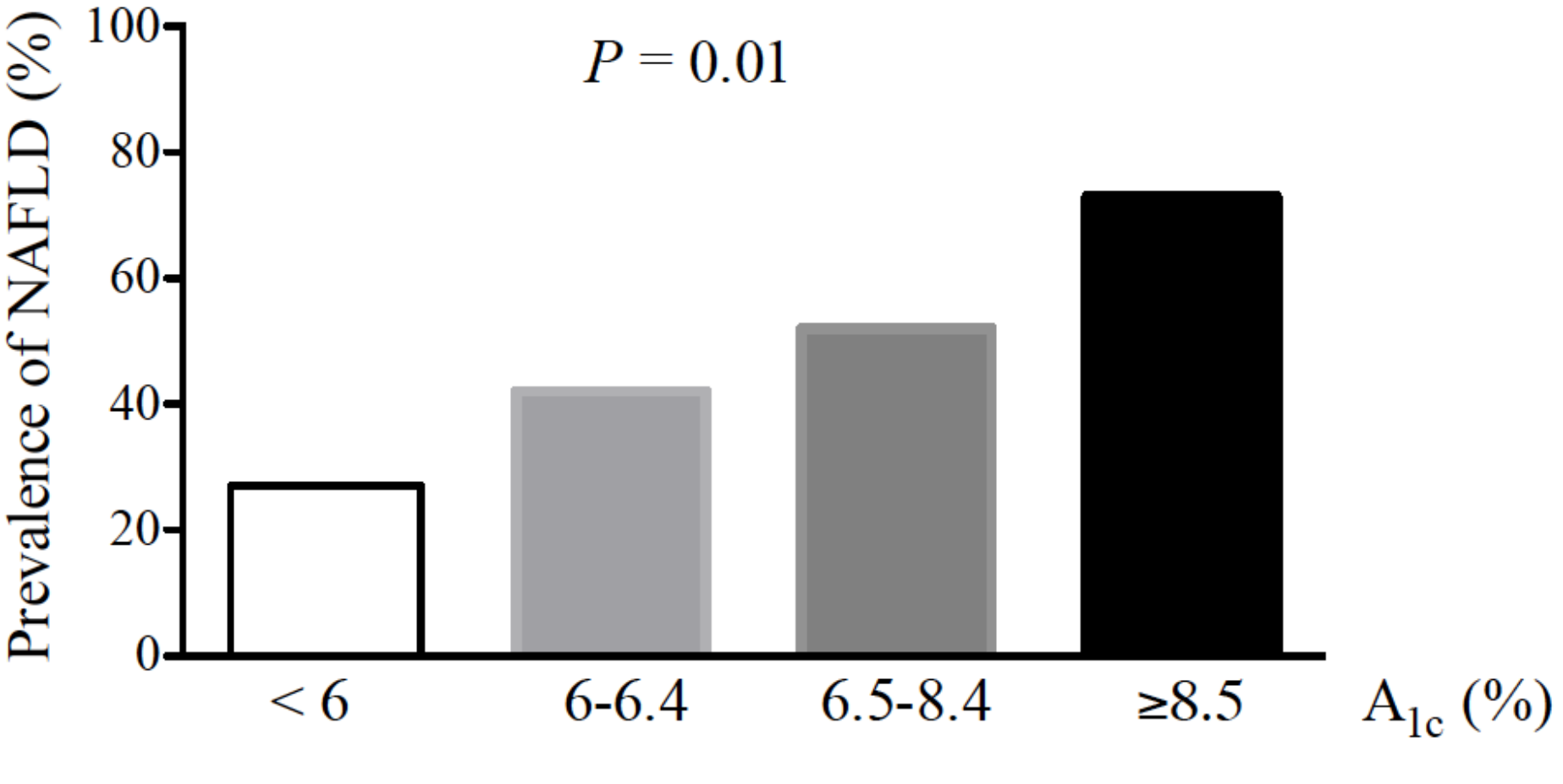
Diabetes Treatment and NAFLD/NASH

Does diabetes control, and the means for achieving it, affect various phenotypes of NAFLD?

1. **Does diabetes control improve NAFLD?**
   - Treating hyperglycemia
2. **What about the means of achieving control on NAFLD or NASH?**
   - Treating insulin resistance
3. **What about phenotypes: do they impact response to treatment?**
   - Path to individualized treatment?

The Prevalence of NAFLD* Increases with Hyperglycemia in Patients with T2DM and Normal AST/ALT Levels

n =103



*Screened by the gold-standard magnetic resonance and spectroscopy

Portillo et al, JCEM June 2015, 100:2231–2238.

Effect of Weight Loss on NAFLD/NASH: Few studies focused in T2DM

- **Reduction in hepatic steatosis (by ^{1}H-MRS): proportional to the degree of weight loss**
  - LOOK AHEAD (Lazo et al, Diabetes Care 2010)
  - Bacchi et al (in pts with T2DM, Hepatology 2013)
  - Bariatric surgery – many studies, few in T2DM only
- **Histological improvement proportional to weight loss** (Lomonaco et al, Drugs 2013)
  - Promrat et al, Hepatology 2010 (non-diabetics)
- **Mechanism(s) – multifactorial**
  - Decreased IR, lipotoxicity, subclinical inflammation

Effect of Lifestyle Intervention in NAFLD

Author (year)	Type of study (*n*)	Duration (weeks)	Main intervention	Weight loss	Change in liver fat by MRS
Tamura [28] (2005)	RCT ($n=14$)	2	Hypocaloric diet ± exercise Diet (−25% kcal)	↓1.5% vs. ↓2.3%^ ↓10%**^	↓21% vs. ↓20%^ ↓37%**^
Larson-Meyer [57] (2006)	RCT ($n=46$)	24	Diet + exercise Diet (−15% WR)	↓10%**^ ↓14%**^	↓29%**^ ↓40%**^
Kantartzis [31] (2008)	Uncontrolled ($n=50$)	39	Hypocaloric diet + aerobic exercise (moderate)	↓3.5%**	↓35%**
Shah [56] (2009)	RCT ($n=18$)	24	Hypocaloric diet ± exercise	↓9% vs. ↓10%^	↓46% vs. ↓45%^
Lazo [32] (2010)	RCT ($n=96$)	48	Hypocaloric diet + exercise	↓8%**	↓ 51%*
Wong [58] (2013)	RCT ($n=154$)	48	Hy		

MRS, magnetic resonance imaging and spectroscopy; RCT, randomized, controlle
n = based on number of completers.
* $p < 0.05$ and
** $p < 0.01$ when compared against control (vs. baseline for uncontrolled studies).
^ *p* NS between groups comparisons.

Lazo and Associate

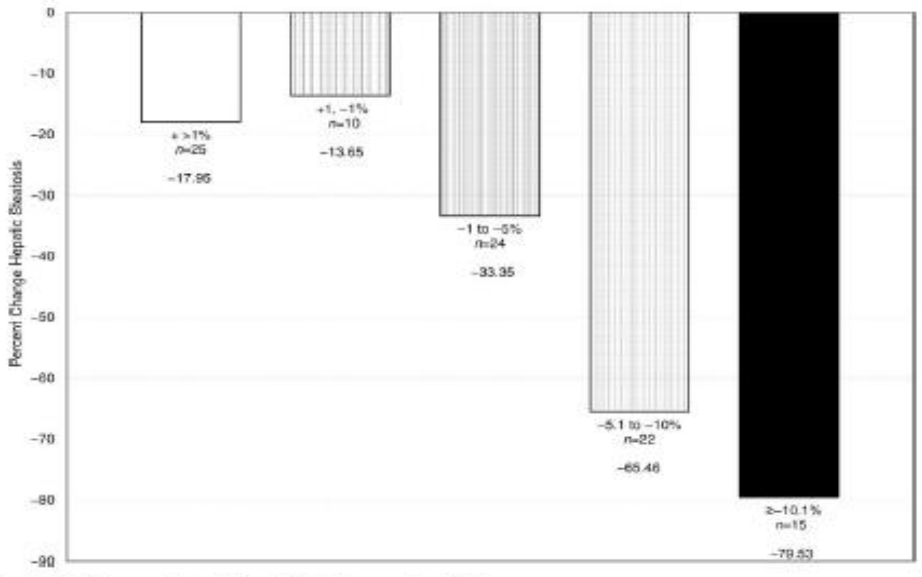
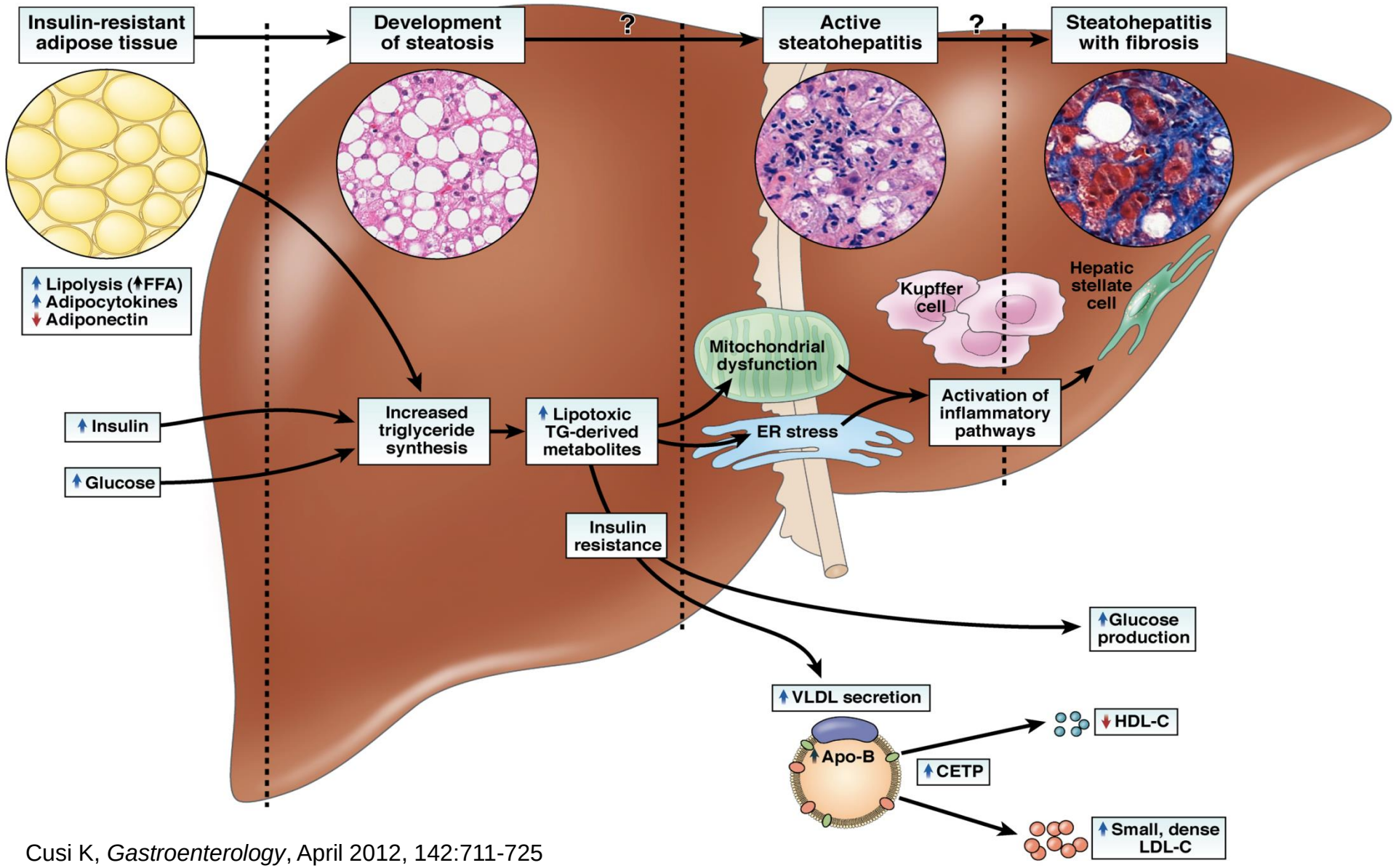


Figure 1—Median percent change in hepatic steatosis by percent weight change.

Fernando Bril, Kwame Ntim, Romina Lomonaco and Kenneth Cusi
University of Florida, Gainesville, FL, USA

International Textbook of Diabetes Mellitus. Fourth Edict
Ferrannini, and Paul Zimmet. 2015 John Wiley & Sons,

From Obesity/Lipotoxicity to NASH and Cirrhosis



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

Diabetes Treatment and NAFLD/NASH

1. **Does diabetes control improve NAFLD?**
   - Treating hyperglycemia

2. **What about the means of achieving control on NAFLD or NASH?**
   - Treating insulin resistance, subclinical inflammation

Current Therapeutic Agents in T2DM:
Effect on Liver Triglycerides and Histology

Treatment	Mechanism of action	AST/ALT	Liver fat by imaging	Liver histology
Oral				
Metformin [38,45-48]	Insulin-sensitizer	↓	↓*,↔^	Unchanged
Pioglitazone [52, 53, 55]	PPARγ agonist	↓	↓^	Improved
Sitagliptin [72, 80, 81]	DPP-4 inhibitor	↓	n/a	n/a
Vildagliptin [82]	DPP-4 inhibitor	↓	↓^	n/a
Canagliflozin [90]	Inhibits renal glucose reabsortion	↓	n/a	n/a
Dapagliflozin [91, 92]	Inhibits renal glucose reabsortion	↓	n/a	n/a
Injectable				
Exenatide [70]	GLP-1 receptor agonist	↓	↓^	n/a
Liraglutide [69-75]	GLP-1 receptor agonist	↓	↓**,^	Improved

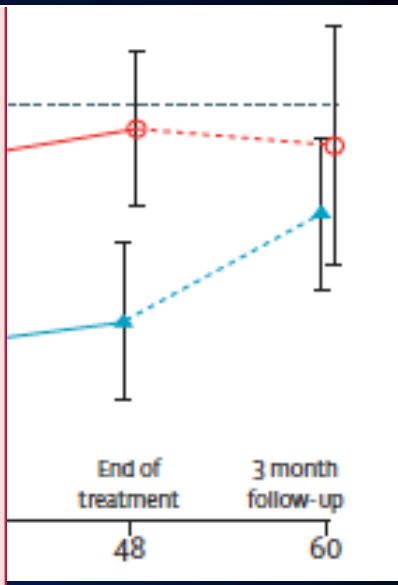
*NAFLD assessed by ultrasound, **NAFLD assessed by CT, ^NAFLD assessed by MRI/^{1}H-MRS, n/a: data not available

*** Insulin:** may lower intrahepatic triglycerides but no data on liver histology

Portillo-Sanchez and Cusi, Clinical Diabetes and Endocrinology 2:9, 2016

Liraglutide in NASH: LEAN study

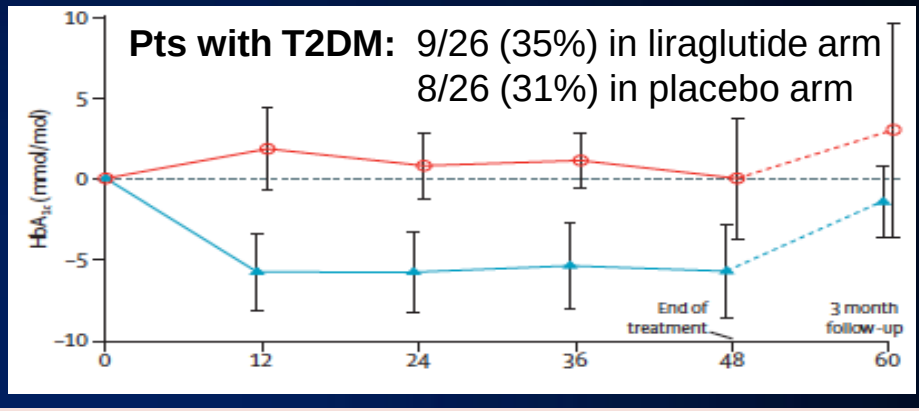
	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
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
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†



Armstrong et al. Lancet 2016 387:679-90.

Liraglutide in NASH: LEAN study

Metabolic factors		
Glucose (mmol/L)	6·0 (1·7)	6·1 (1·5)
Insulin (pmol/L)	166 (80)	257 (289)
HOMA-IR (glucose [mmol/L] × insulin [mmol × U/L])	6·7 (4·7)	9·6 (9·8)
Glycated haemoglobin A_{1c}		
Absolute concentration (mmol/mol)	41·2 (7·8)	42·4 (9·3)
Percentage of total haemoglobin (%)	5·9% (0·7%)	6·0% (0·9%)

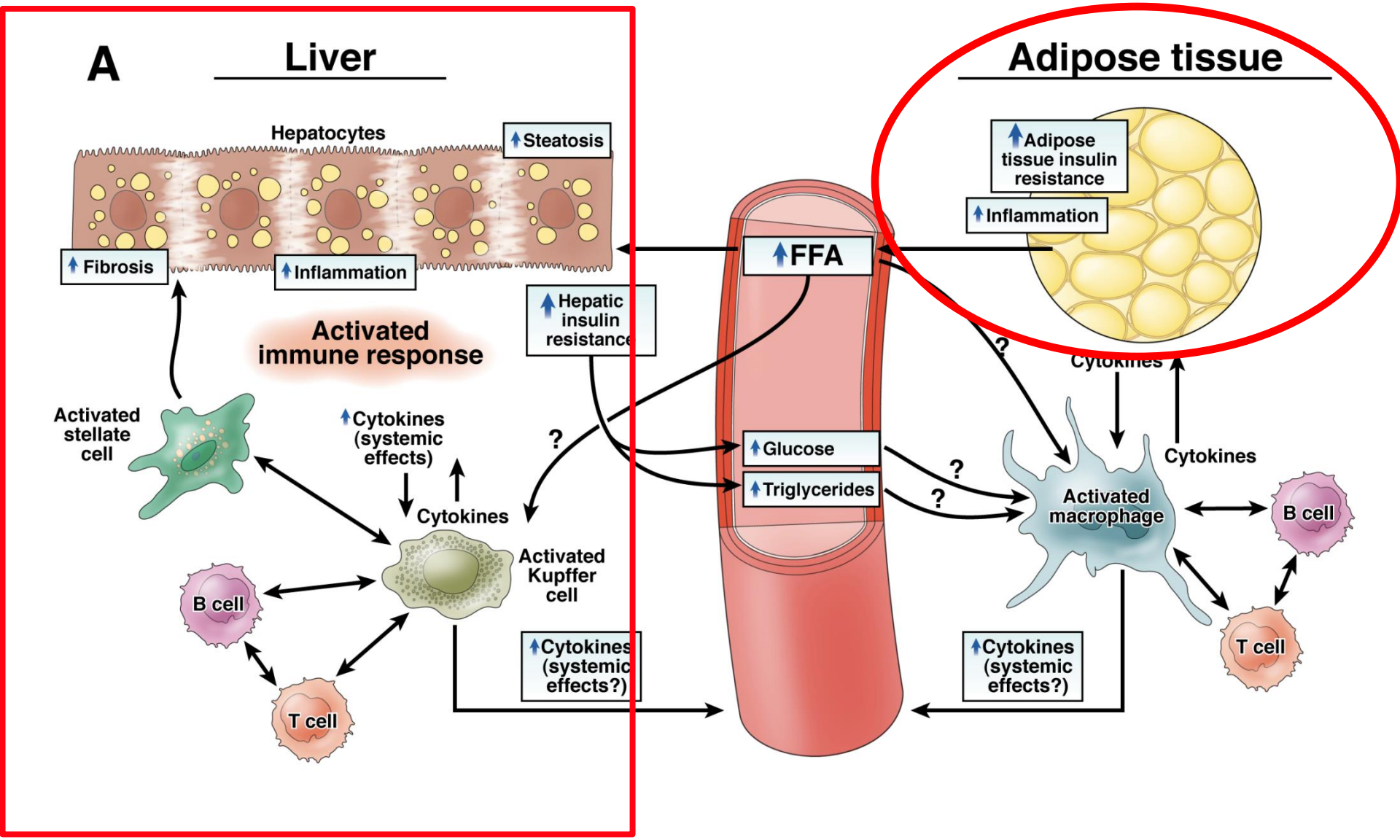


	Mean (SD) change from baseline to 48 weeks		Mean (95% CI) changes from baseline (liraglutide *vs* placebo)	p value*
	Liraglutide (n=23)	Placebo (n=22)		
Metabolic factors				
Glucose (mmol/L)	−1·0 (1·5)	0·72 (2·3)	−1·67 (−2·81 to −0·53)	0·005
Insulin (pmol/L)	−15·9 (54·7)	−34·7 (164·1)	−4·0 (−75·0 to 67·0)	0·91
HOMA-IR (glucose [mmol/L] × insulin [mmol × U/L])	−1·8 (3·7)	0·70 (9·49)	−2·74 (7·24 to 1·76)	0·23
Glycated haemoglobin A_{1c}				
Absolute concentration (mmol/mol)	−5·7 (6·9)	0·00 (8·7)	−5·18 (−9·91 to −0·44)	0·03
Percentage of total haemoglobin (%)	−0·53% (0·64%)	0·00% (0·80%)	−0·48% (−0·91% to −0·05%)	0·03
Non-esterified fatty acids (µmol/L)	−242 (374)	−121 (297)	−49 (−200 to 101)	0·51
ADIPO-IR (fasting non-essential fatty acid [mmol/L] × insulin [mmol × U/L])	−8·0 (10·1)	−7·6 (32·3)	−6·34 (−15·09 to 2·41)	0·15

Saxenda (liraglutide 3 mg)? Semaglutide?

Armstrong et al. Lancet 2016 387:679-90.

Rationale for Pioglitazone in NASH



Cusi K. Gastroenterology 2012, 142:711-25

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

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Jean Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulcini, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.

ABSTRACT

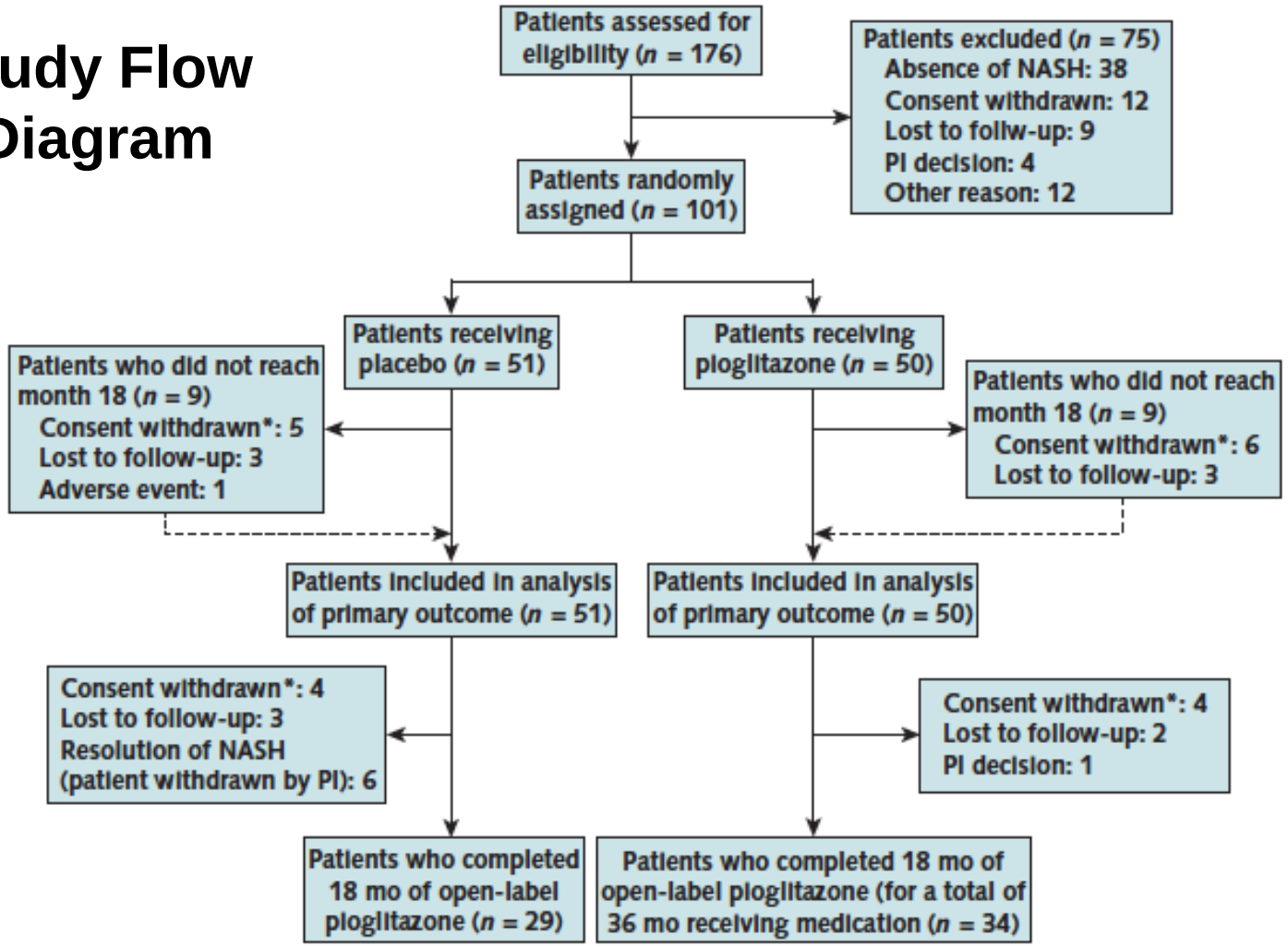
BACKGROUND

No pharmacologic therapy has conclusively proved to be effective for the treatment of nonalcoholic steatohepatitis, which is characterized by insulin resistance, steatosis, and necroinflammation with or without centrilobular fibrosis. Pioglita-

From the Un
ence Center
K.B., J.F., J.H
J.Z.M., S.D., F

Role of Long-Term Pioglitazone in Patients with Prediabetes or T2DM and NASH

Study Flow Diagram



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Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Role of Long-Term Pioglitazone in NASH

Methods - Study Design

Volunteer with presumable NASH

Screening

Run-in (4 weeks)

PIO 30 mg/day (8 weeks), then 45 mg/day

Randomization

Placebo

End of RCT (18 mo)

Continue open label (18 mo)

Followed at GCRC q2-4 weeks

Studies:

1) Liver biopsy

2) Liver fat by MRS

3) % body fat (DXA)

4) Insulin clamp, OGTT

Repeat baseline studies:

1) Liver biopsy

2) Liver fat by MRS

3) % body fat (by DXA)

4) Insulin clamp, OGTT

Patient Characteristics

Table 1. Baseline Patient Characteristics*

Characteristic	Placebo (*n* = 51)	Pioglitazone (*n* = 50)
Mean age (SD), *y*	49 (11)	52 (10)
Male, *n (%)*	35 (69)	36 (72)
T2DM, *n (%)*	28 (55)	24 (48)
Ethnicity, *n (%)*		
White	11 (22)	14 (28)
Hispanic	37 (73)	31 (62)
Other	3 (6)	5 (10)
Mean weight (SD), *kg*	99.2 (17.0)	98.2 (16.5)
Mean body mass index (SD), kg/m^2	34.5 (4.8)	34.3 (4.8)
Mean total body fat by DXA (SD), %	34 (8)	33 (7)
Mean fasting plasma glucose level (SD)		
mmol/L	6.7 (1.5)	6.9 (1.6)
mg/dL	121 (27)	124 (29)
Mean 2-h plasma glucose level (SD)		
mmol/L	11.3 (3.6)	11.7 (4.3)
mg/dL	203 (64)	211 (78)
Mean hemoglobin A_{1c} level (SD), %		
Patients without T2DM	5.7 (0.5)	5.7 (0.5)
Patients with T2DM	6.8 (1.0)	7.1 (0.9)

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Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Effect of 18 Months of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes*

Table 2. Effect of 18 mo of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes*

Outcome	Placebo (*n* = 51)	Pioglitazone (*n* = 50)	Treatment Difference (95% CI)	*P* Value
Primary outcome				
≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)*	9 (17)	29 (58)	41 (23 to 59)	<0.001
Secondary outcomes				
Resolution of NASH, *n (%)*†	10 (19)	26 (51)	32 (13 to 51)	<0.001
Steatosis				
≥1-point improvement, *n (%)*	13 (26)	35 (71)	44 (25 to 63)	<0.001
Mean change in score (SD)	−0.2 (0.8)	−1.1 (1.0)	−0.9 (−1.3 to −0.5)	<0.001
Inflammation				
≥1-point improvement, *n (%)*	11 (22)	25 (49)	27 (8 to 46)	0.004
Mean change in score (SD)	−0.1 (0.8)	−0.6 (0.9)	−0.6 (−0.9 to −0.2)	<0.001
Ballooning				
≥1-point improvement, *n (%)*	12 (24)	25 (51)	27 (7 to 47)	0.004
Mean change in score (SD)	−0.2 (0.7)	−0.6 (0.6)	−0.4 (−0.7 to −0.2)	0.001
Fibrosis				
≥1-point improvement, *n (%)*	13 (25)	20 (39)	14 (−6 to 34)	0.130
Mean change in score (SD)	0 (1.2)	−0.5 (1.0)	−0.5 (−0.9 to 0)	0.039

NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis.
* Multiple imputation was used to impute missing histologic data for patients who did not complete 18 mo of therapy (**Appendix**). Numbers of patients may not always seem to match the proportion because they were estimated from the combination of 40 imputed data sets.
† Defined as absence of NASH after 18 mo of therapy in patients with definite NASH at baseline.

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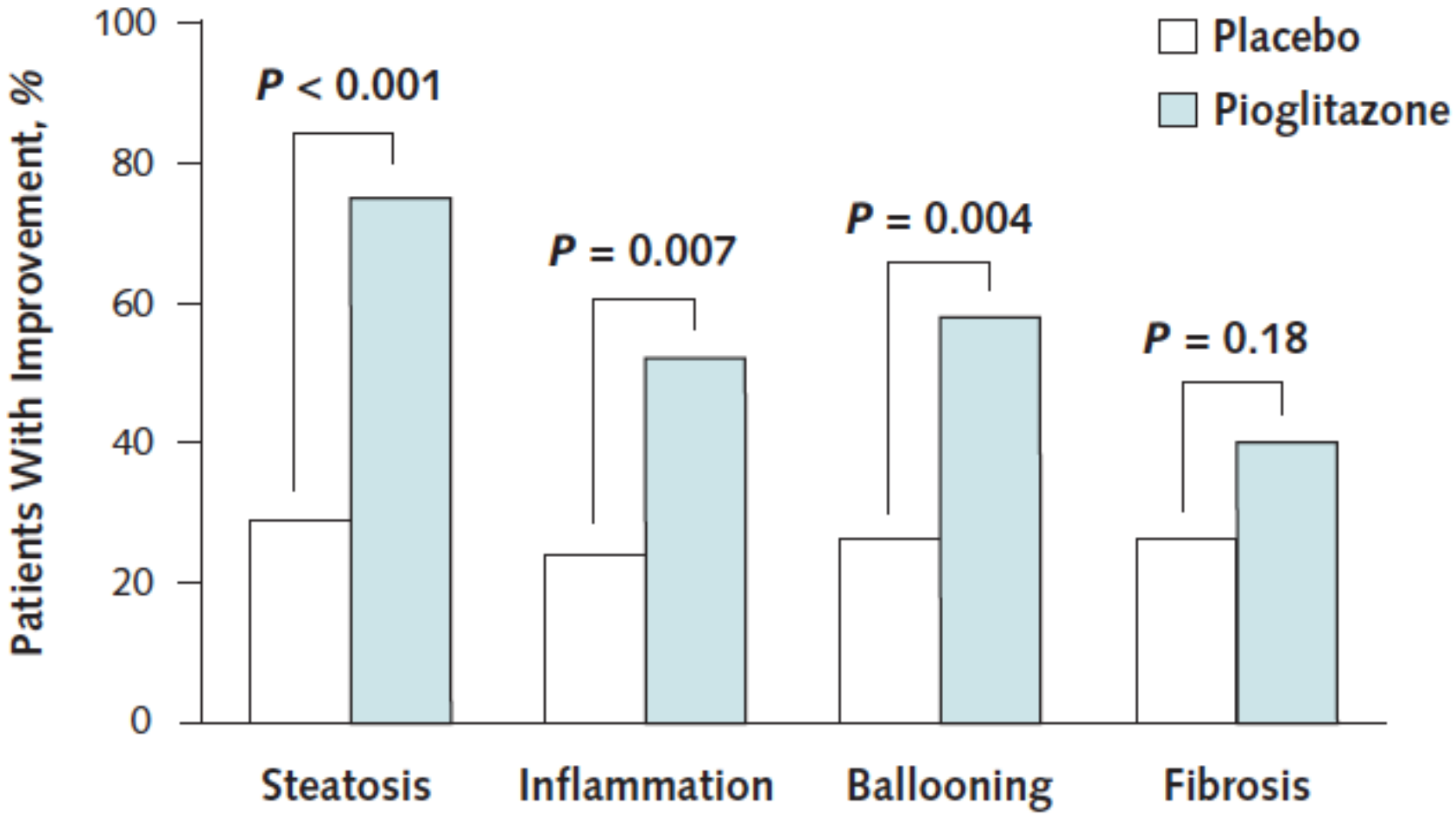
Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Effect of Pioglitazone on Primary and Secondary Liver Histologic Outcomes at 18 months*



* In patients with paired biopsies

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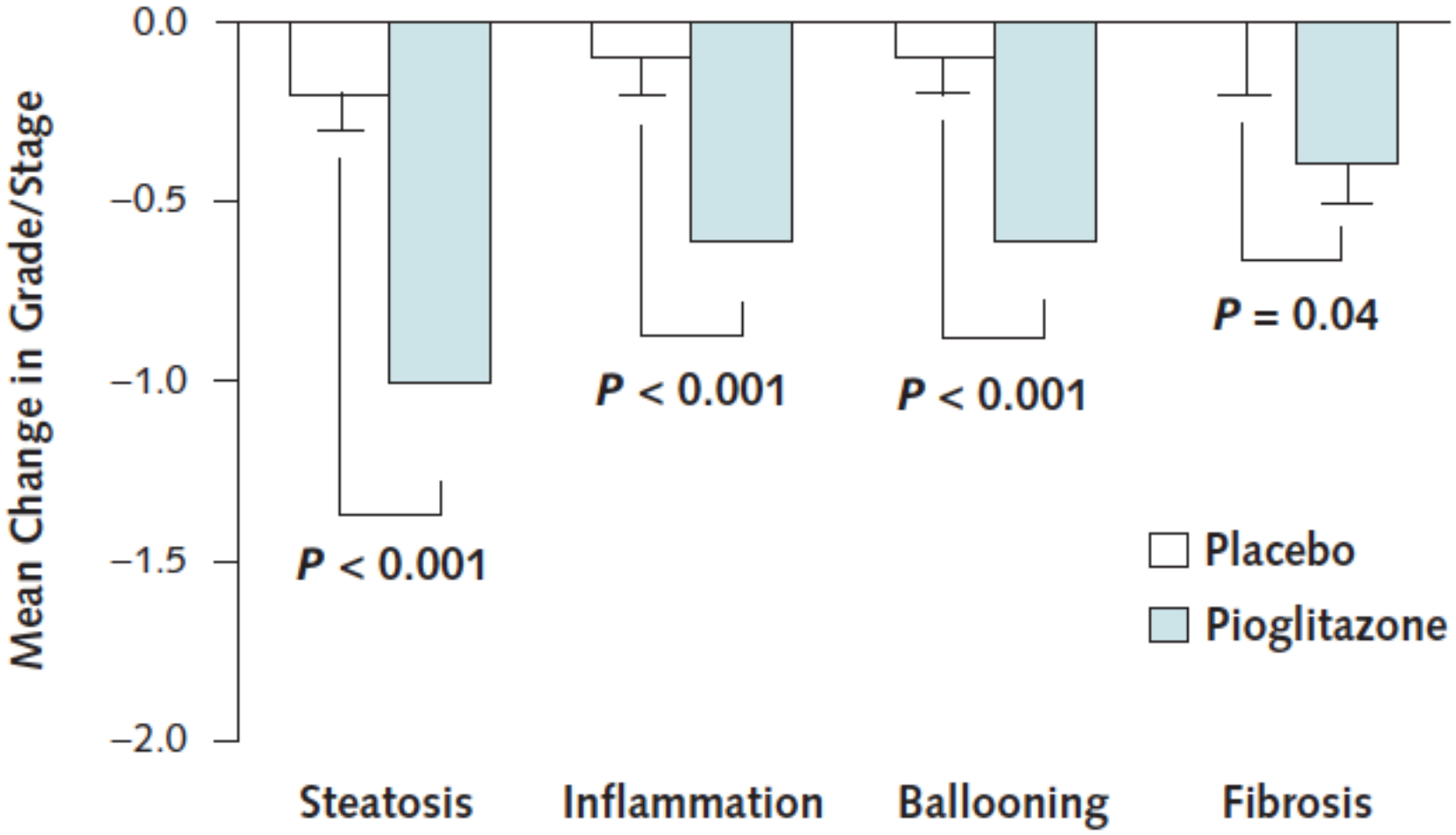
Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Effect of Pioglitazone on Primary and Secondary Liver Histologic Outcomes at 18 months*



* In patients with paired biopsies

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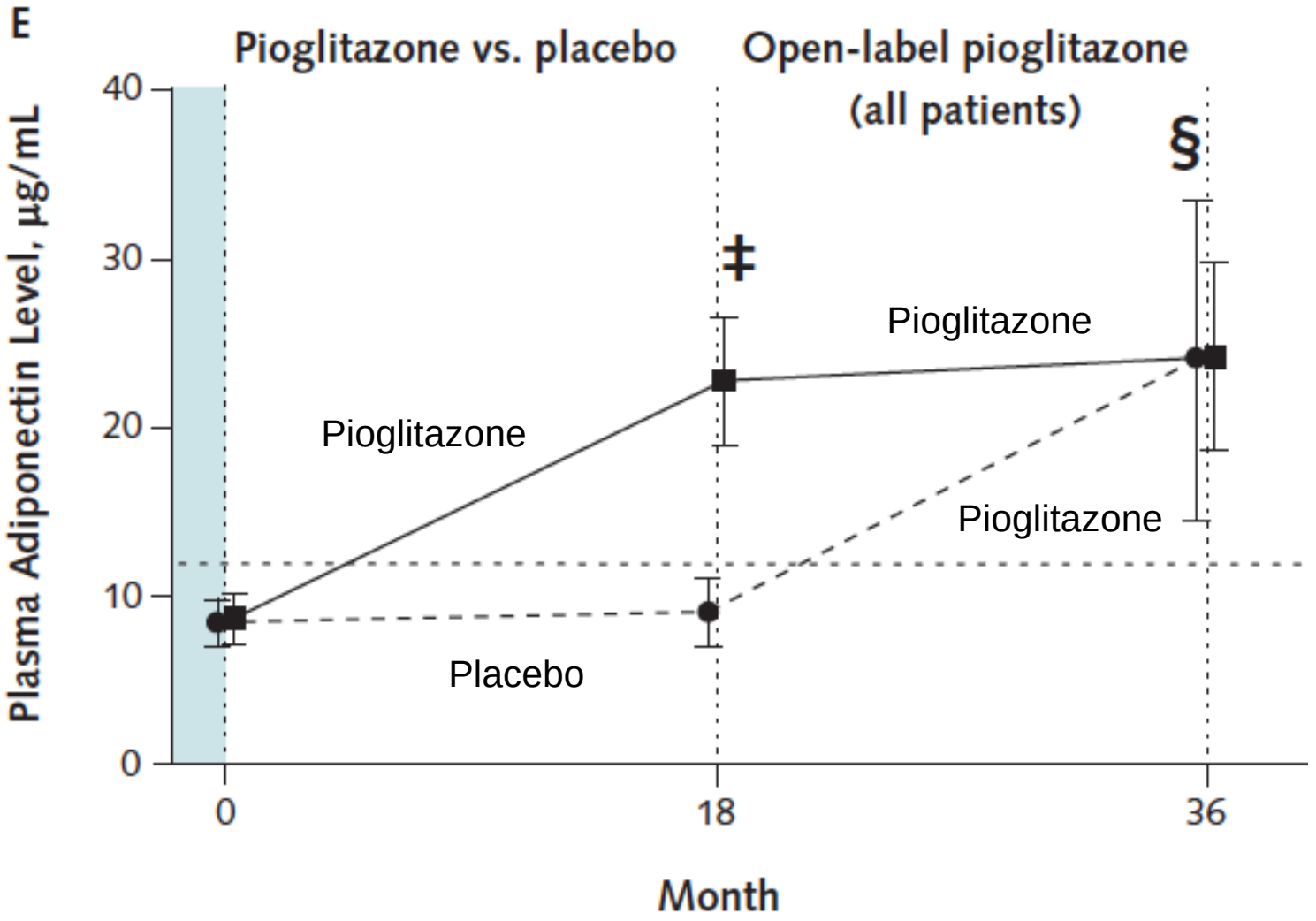
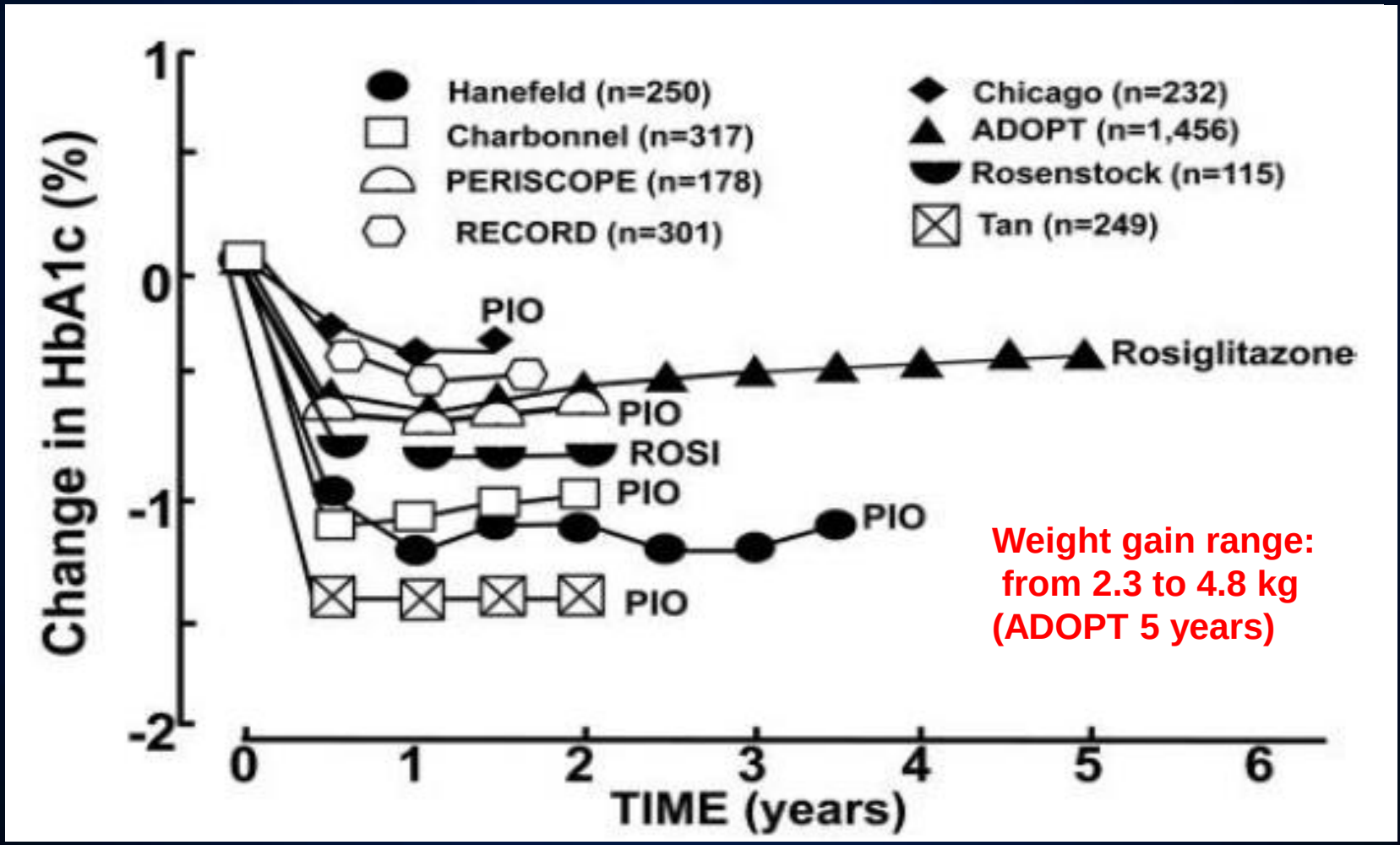
Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Plasma Adiponectin after 18 months of Pioglitazone or Placebo, and after 18 or 36 Months of Pioglitazone



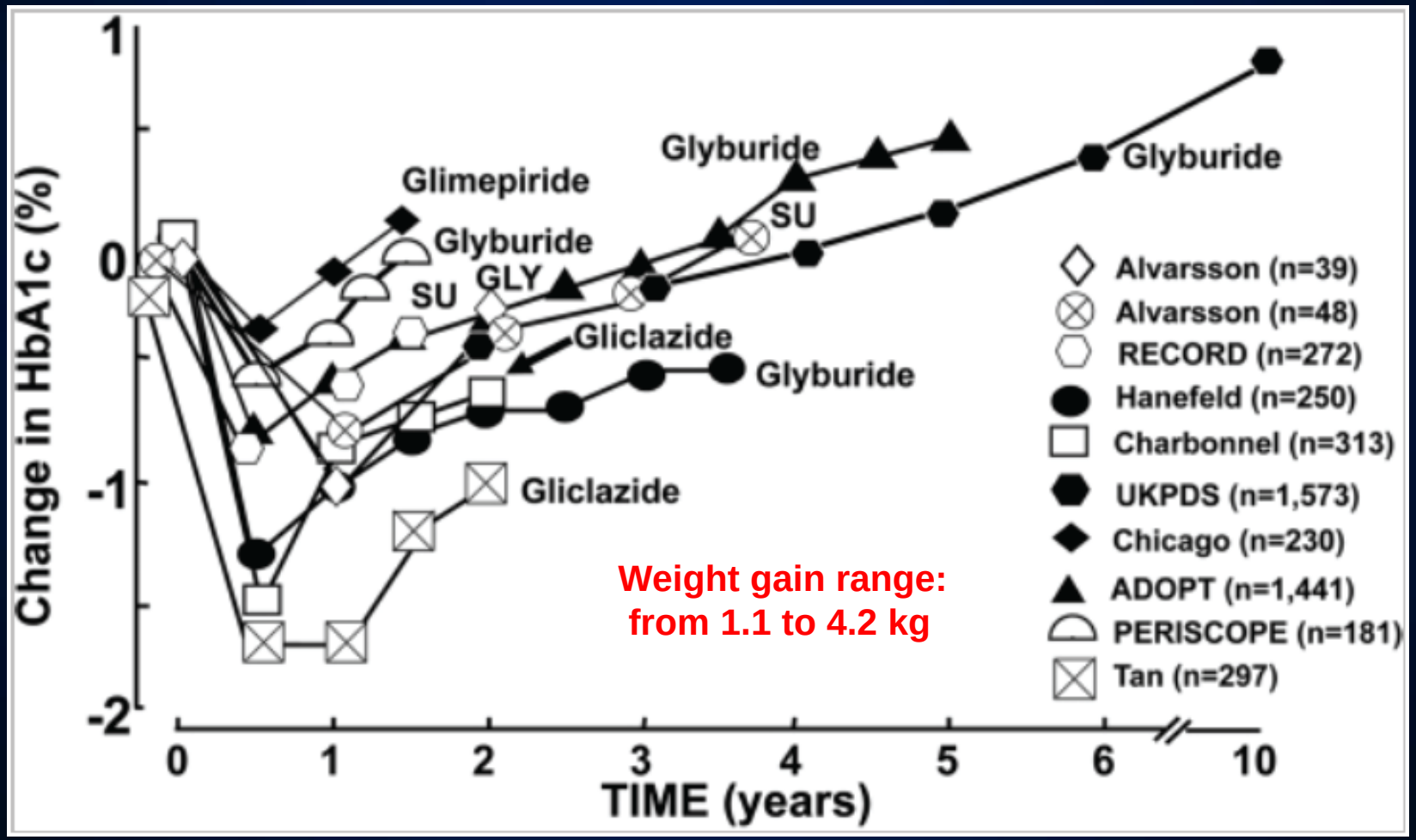
Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Long-term Durability of Thiazolidinediones on Glycemic Control

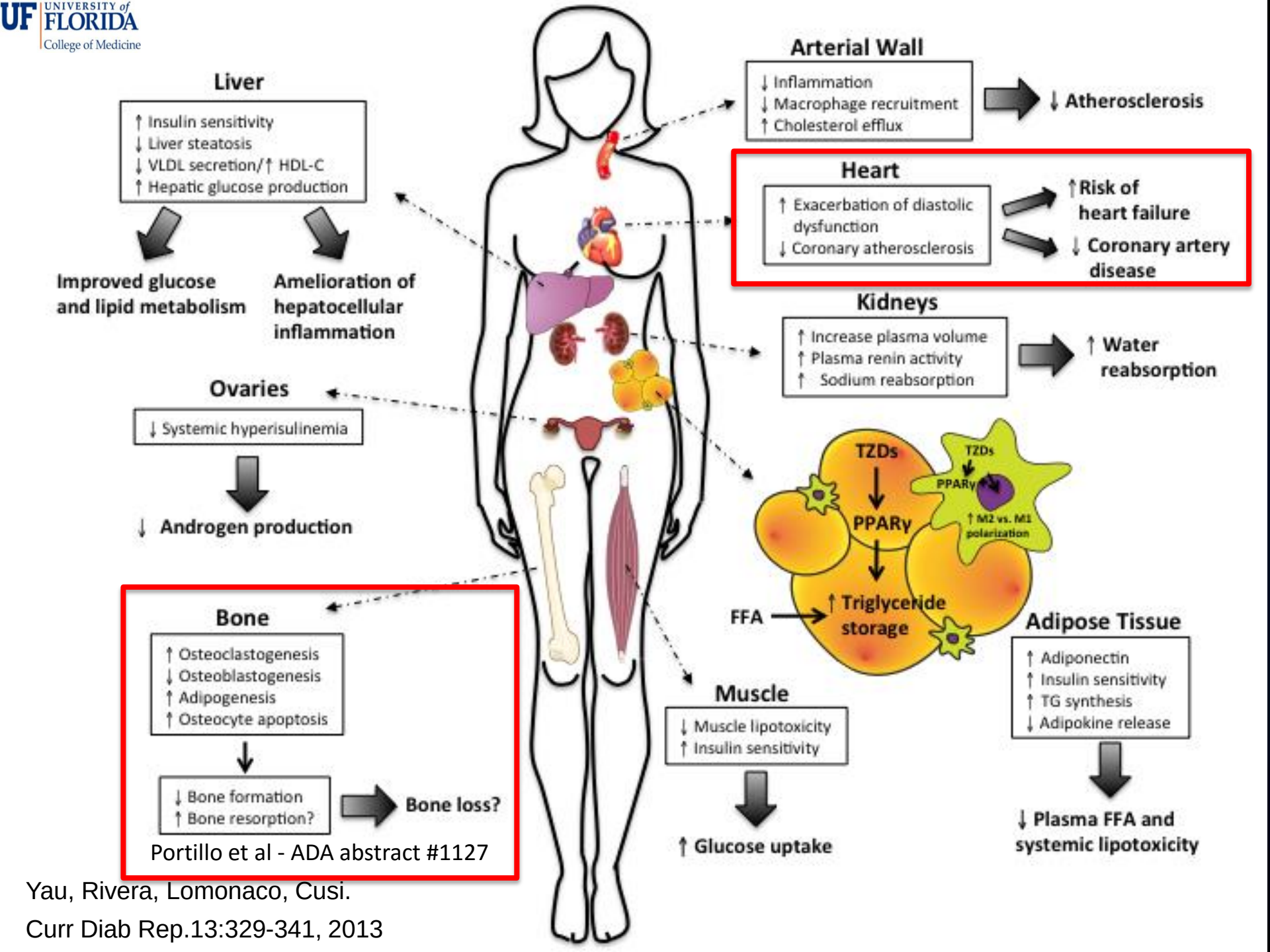


DeFronzo RA, Diabetes. 2009; 58:773–795.

Limited Durability of Sulfonylureas Compared to Thiazolidinediones on Glycemic Control



DeFronzo RA, Diabetes. 2009; 58:773–795.



Portillo et al - ADA abstract #1127

Yau, Rivera, Lomonaco, Cusi.

Curr Diab Rep.13:329-341, 2013

Adverse Events

	First 18 mo		Open-Label Phase	
	Placebo (n = 51)	Pioglitazone (n = 50)	Patients Starting Pioglitazone Therapy (n = 36)	Pioglitazone (months 18-36) (n = 40)
Mild adverse events, *n*				
Cardiovascular	6	2	10	6
Respiratory/otolaryngologic	12	14	15	14
Gastrointestinal	17	13	12	14
Endocrinologic	0	0	0	1
Neurologic	6	6	8	5
Gynecologic	2	1	0	0
Urologic	3	6	6	7
Hematologic	3	7	7	5
Dermatologic	6	6	3	7
Musculoskeletal	21	23	22	26
Asthenia	8	5	0	3
Other	11	8	4	7
Moderate to severe adverse events, *n*				
Cardiovascular				
Atypical chest pain	1	1	0	2
Pulmonary thromboembolism	0	0	1	0
Palpitations/arrhythmia	1	0	1	0
Hypertension/hypotension	0	0	1	2
Chronic lower limb edema	3	11	5	0
Gastrointestinal				
Pancreatitis	0	1	0	0
Cholelithiasis	0	0	1	2
Diverticulitis	0	0	2	0
Gastritis	1	0	1	2
Alanine/aspartate aminotransferase level elevations	1	0	0	1
Endocrinologic				
Hypoglycemic episodes	8*	4	16†	10
Osteoporotic fractures	0	0	0	0
≥0.5-point reduction in T-score in femoral neck	2	1	2	3
Diagnosis of adrenal carcinoma	0	0	1	0

* 2 patients (both receiving glipizide and 1 also receiving insulin) had 3 episodes each.
† 1 patient (also receiving glipizide) had 7 episodes, whereas another (also receiving glyburide and insulin) had 4.

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Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Adverse Events (continued)

Neurologic				
Dissociative amnesia	0	1	0	0
Newly diagnosed peripheric neuropathy	1	1	2	1
Cephalea/migraine	2	0	1	0
Dizziness	1	0	0	0
Insomnia	0	1	0	0
Gynecologic				
Ovarian cyst rupture	0	0	0	1
Uterine bleeding	0	1	0	0
Vaginal yeast infection	0	0	1	0
Urologic				
Diagnosis of bladder cancer	0	0	0	0
Diagnosis of prostate cancer	0	0	0	1
Urinary tract infection	1	1	1	1
Urine retention	0	0	2	0
Kidney stones	0	0	0	2
Hematologic				
Anemia	0	2	2	0
Thrombocytopenia	1	0	0	0
Other				
Biopsy-related	3	1	1	1
Motor vehicle accident	0	1	0	0
Perforation secondary to diverticulosis	0	0	1	0
Concussion	0	0	1	0

Cusi et al, Ann Intern Med June 21, 2016. [Epub].

PIOGLITAZONE:

CVD reduction or prevention of progression of atherosclerosis in T2DM

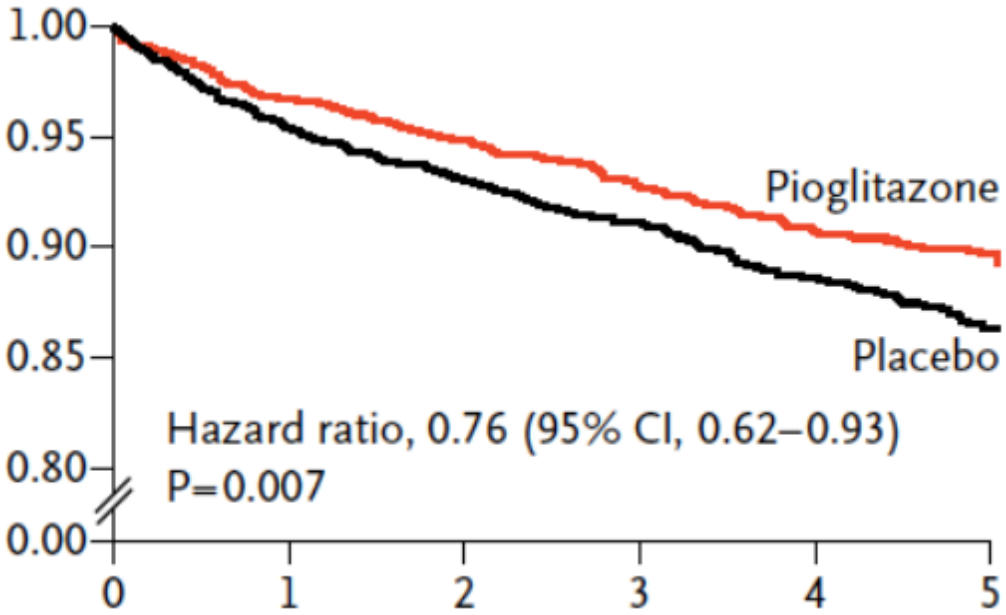
- PROACTIVE (Lancet 2006)
- CHICAGO (JAMA 2007)
- PERISCOPE (JAMA 2008)
- Ischemic stroke-TIA study (2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

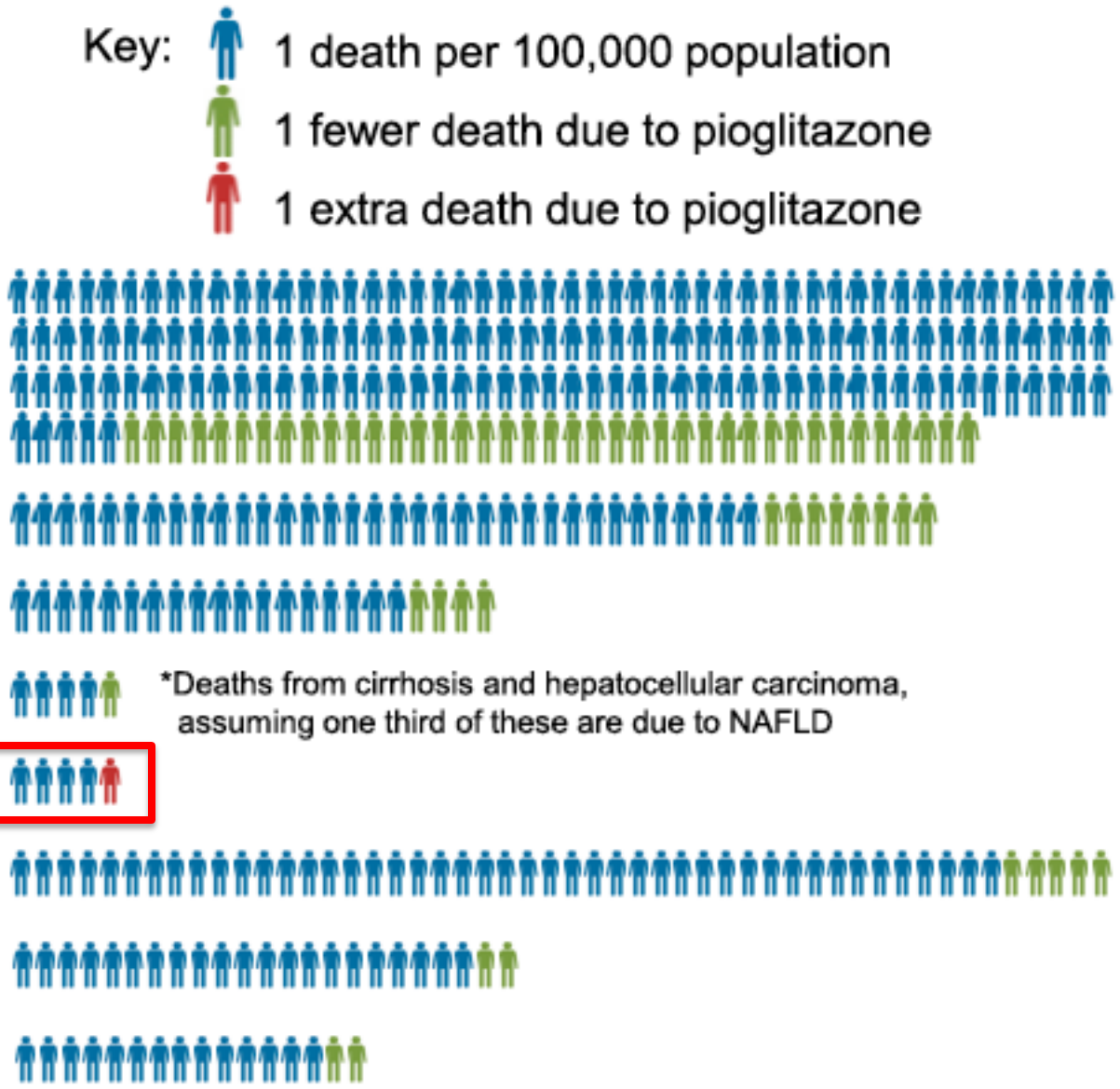
W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman,
[illegible]wit, L.M. Brass,* G.G. Schwartz,
. Coull, G.A. Ford, D. Kleindorfer,
.D. Spence, D. Tanne, D. Wang,
al Investigators†



Kernan et al, NEJM February 17, 2016

Weighing Mortality Risk and Benefits of Pioglitazone

Cause of death	Deaths per 100,000	Potential effect of pioglitazone	
		Risk	Deaths
Heart Disease	194	-20%	-39
Stroke	42	-20%	-8
Diabetes	22	-20%	-4
NAFLD-related*	5	-20%	-1
Bladder cancer	4	+20%	+1
Lung cancer	50	-10%	-5
Breast cancer	23	-10%	-2
Colon cancer	16	-10%	-2



Soccio et al, Cell Metabolism 2014, 20:573-591

Diabetes Treatment and NAFLD/NASH

1. **Does diabetes control improve NAFLD?**
   - Treating hyperglycemia
2. **What about the means of achieving control on NAFLD or NASH?**
   - Treating insulin resistance
3. **What about phenotypes: do they impact response to treatment?**
   - Path to individualized treatment?

The New York Times

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PHOTOGRAPHS BY NANCY BORowick FOR THE NEW YORK TIMES

Yubelkis Matias, 19, has a severe nonalcoholic fatty liver disease. Her symptoms include sharp abdominal pains that come and go.

Threat Grows From Liver Illness Tied to Obesity

By ANAHAD O'CONNOR

Despite major gains in fighting hepatitis C and other chronic liver conditions, public health officials are now faced with a growing epidemic of liver disease that is tightly linked to the obesity crisis.

In the past two decades, the prevalence of the disease, known as nonalcoholic fatty liver, has more than doubled in teenagers and adolescents, and climbed at a similar rate in adults. Studies

Epidemic Is Becoming a Major Cause of Transplants

to treat the disease, and it is quickly becoming a leading cause of liver transplants around the country.

Doctors say that the disease, which causes the liver to swell with fat, is particularly striking

chief of pediatric gastroenterology, hepatology and nutrition at NewYork-Presbyterian Morgan Stanley Children's Hospital. "You have to force feed ducks to get fatty liver, but people seem to be able to develop it on their own."

Gavin Owenby, a 13-year-old in Hiawassee, Ga., learned he had the disease two years ago after developing crippling abdominal pain. "It's like you're being stabbed in your stomach with a knife," he said.

An ultrasound revealed that Gavin's liver was enlarged and

States spent more than $1 trillion in an eight-year war that Mr. Obama had repeatedly claimed was history when the last troops left in 2011. While Mr. Obama said he would offer some help, it would not include troops, and he asserted that "we're not going to allow ourselves to be dragged back into a situation in which, while we're there, we're keeping a lid on things."

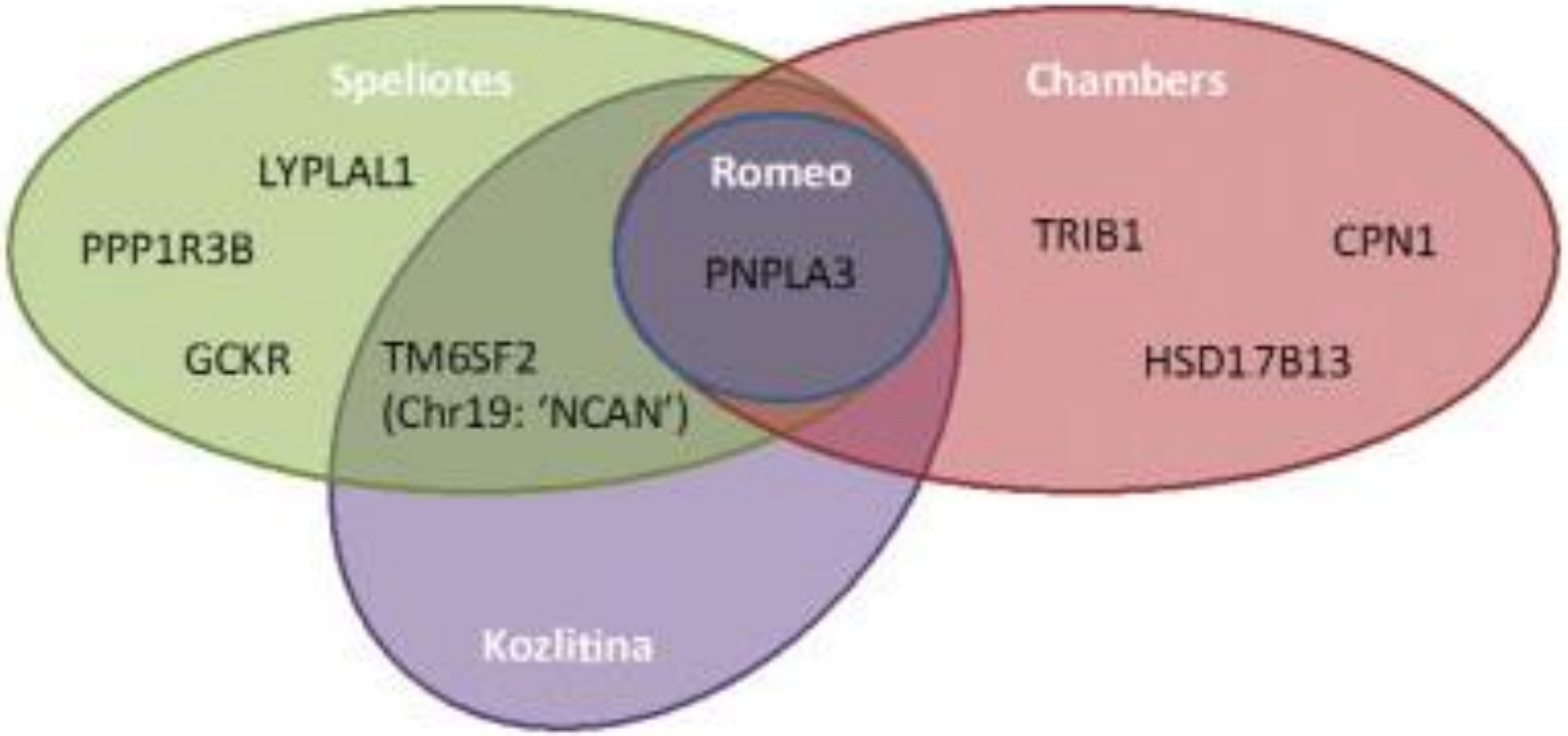
Heeding the call to arms by

Seeing Their C
Shiites Floc

The Evidence that NAFLD has a Genetic Component

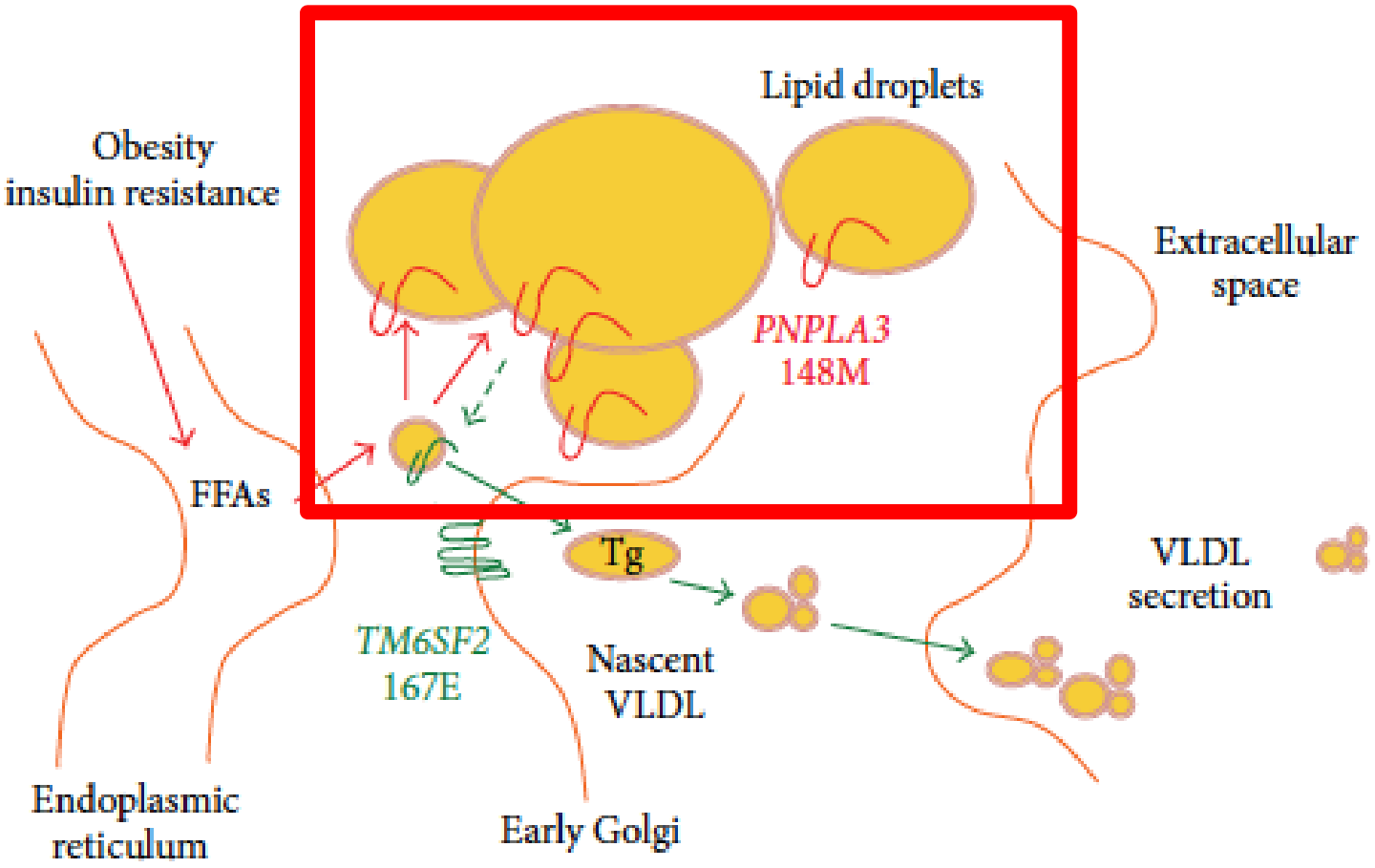
- Not all patients with a similar phenotype develop NAFLD
- Not all patients with NAFLD progress to NASH
- Progression to cirrhosis and HCC also highly variable
- Ethnic differences:
  - African Americans have less steatosis, but also develop NASH
  - Hispanics are believed to develop more NAFLD – but not when matched for prevalence of adiposity (Lomonaco, Hepatology 2011)
- Familial aggregation studies, twin studies
- Candidate-gene studies have only identified a small number of genes that are strongly associated with NAFLD
- GWAS approach has been more useful

Little Commonality in Genetic Variants Identified in GWASs that may Influence the Susceptibility to NAFLD and NASH



Anstee and Day, *Semin Liver Dis* 2015;35:270–290.

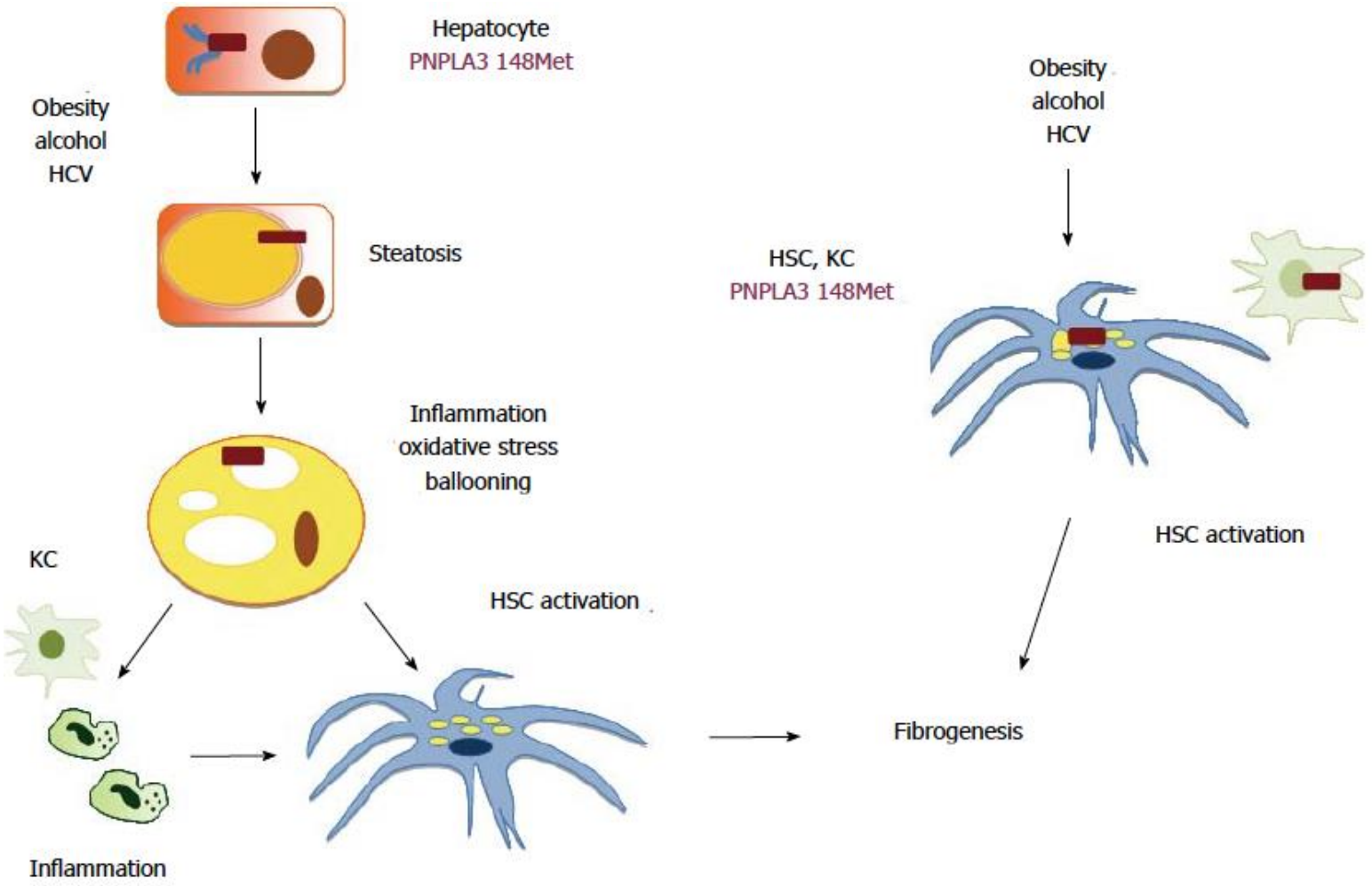
Role of PNLPA3 in the Development of Hepatic Steatosis



- Association with NAFLD replicated in many studies, including 8 GWAS studies

Dongiovanni, Romeo and Valenti *BioMed Research International* 2014: 1-10

Role of PNLPA3 in the Development of Fibrosis



Dongiovanni, et al. *World J Gastroenterol* 2013; 19: 6969-6978.

UF UNIVERSITY of FLORIDA College of Medicine

Treatment of Diabetes in NAFLD: Conclusions

- **Role of hyperglycemia on NAFLD/NASH:**
  - Hyperglycemia associated with worse steatosis.
  - Effect of controlling hyperglycemia unknown.
- **Role of treating IR in NASH:**
  - Pioglitazone and GLP-1RA have significant benefit on resolution of NASH, but confounded by changes in weight and other factors.
- **Effect of NAFLD phenotype on treatment response:**
  - Unknown, but potential to identify “higher risk” patients and develop improved intervention algorithms.