



UFRJ

Current management of NASH

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- Brazil

Disclosures

Partner of HEPATOSCAN Medical Services® -
Commercial interest in transient liver elastography
using FibroScan®.

NAFLD - Nonalcoholic Fatty Liver Disease

- Most common liver disease in western countries
- Hepatic manifestation of metabolic syndrome (MetS)
 - ✓ World prevalence: 6-46%
 - ✓ Obesity III: 90%
 - ✓ USA: 10-46%; NASH: 3-5%
 - ✓ Brazil: 19-35%

Vernon, et al. Aliment Pharmacol Ther 2011

Williams, et al. Gastroenterology 2011

Lazo, et al. Am J Epidemiol 2013

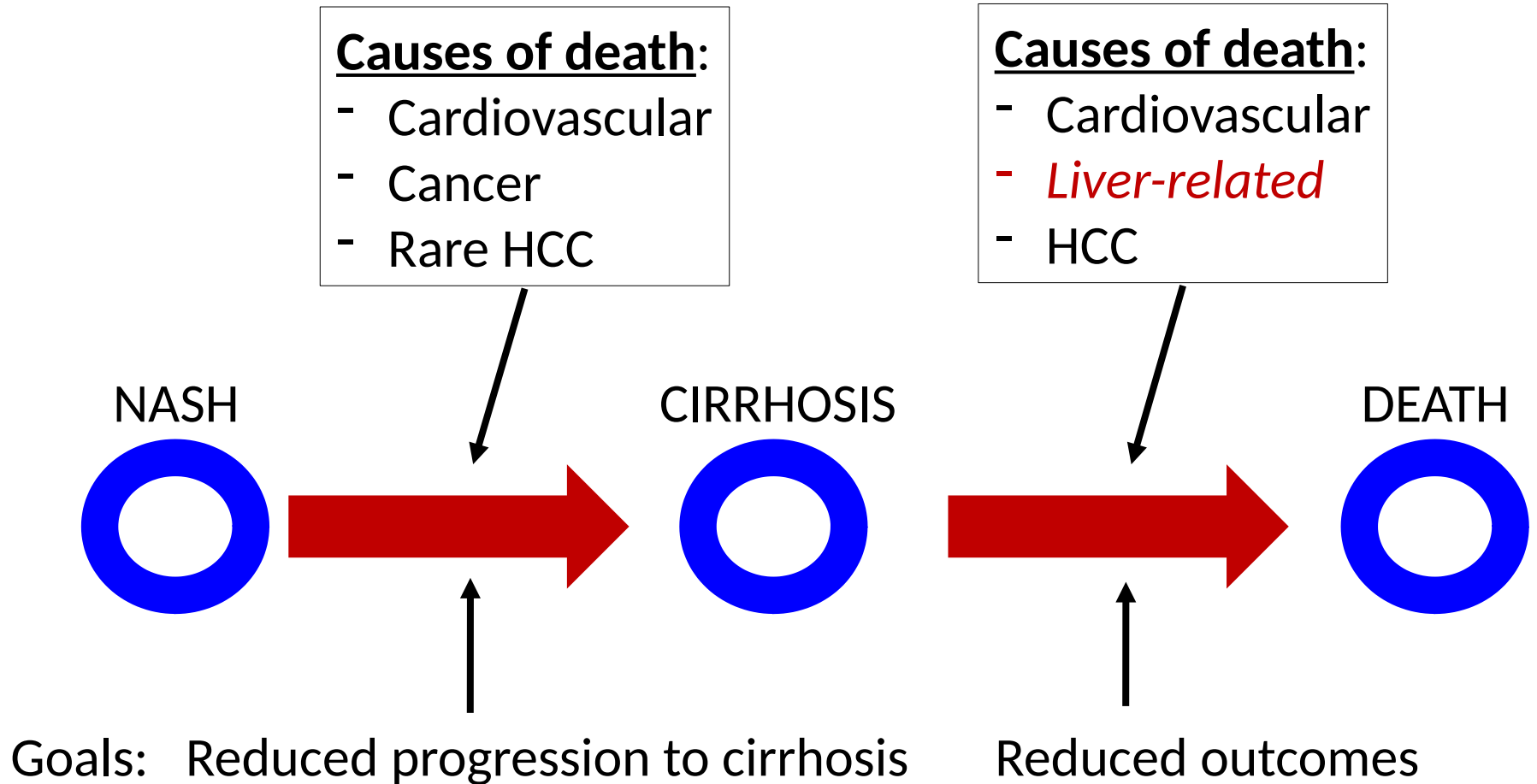
Parise, et al. 2003

Xarnikowski, et al. 2007

NAFLD - Nonalcoholic Fatty Liver Disease

- Major factors related to NAFLD:
 - ✓ Obesity
 - ✓ Type 2 diabetes (T2D)
 - ✓ Metabolic syndrome (MetS)

NAFLD clinical scenarios

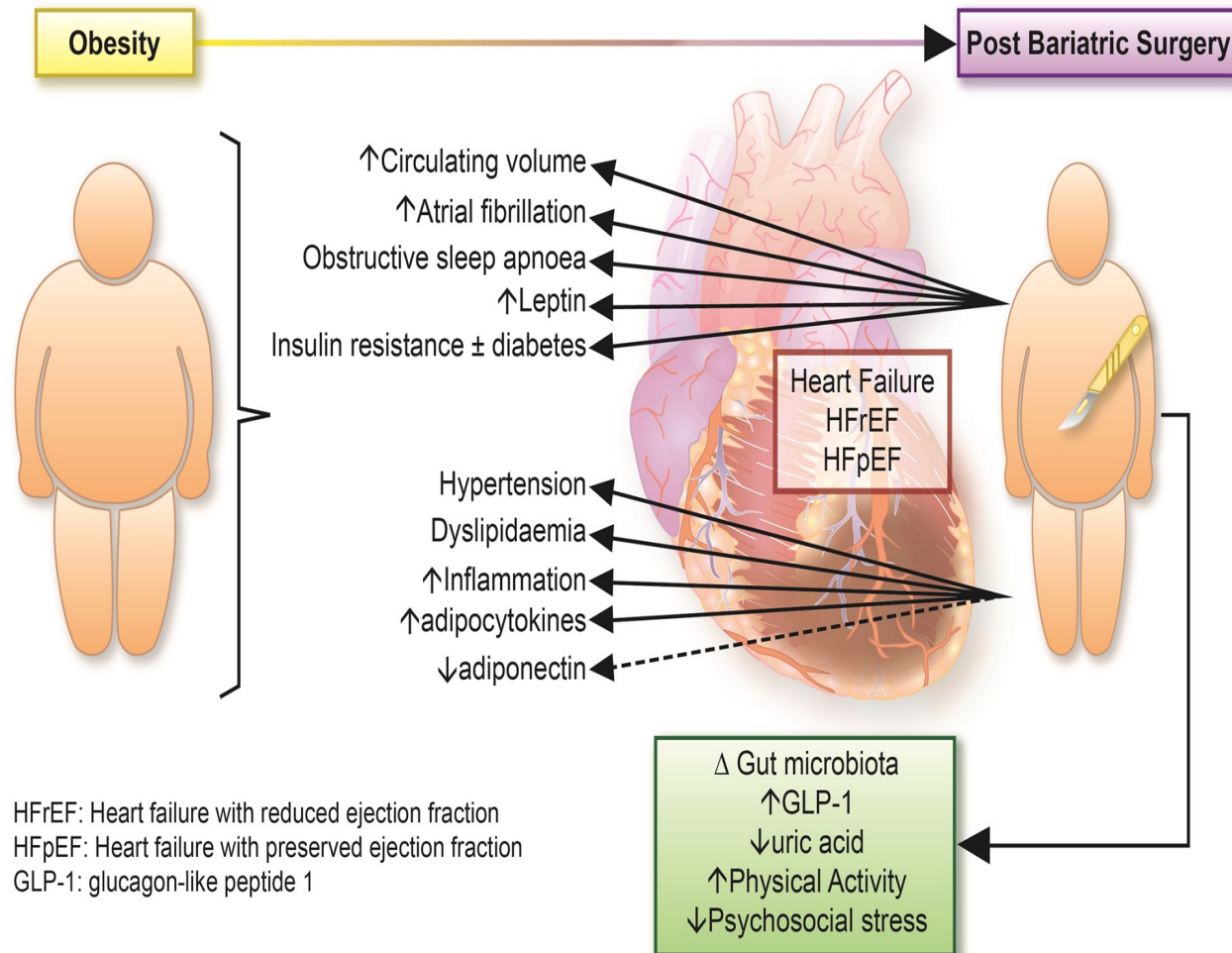




Diet and lifestyle changes



Weight loss benefits key outcomes associated with excess adiposity



Weight loss: the cornerstone of the treatment

3 randomized and 1 cohort studies (N = 293)

>10% weight loss

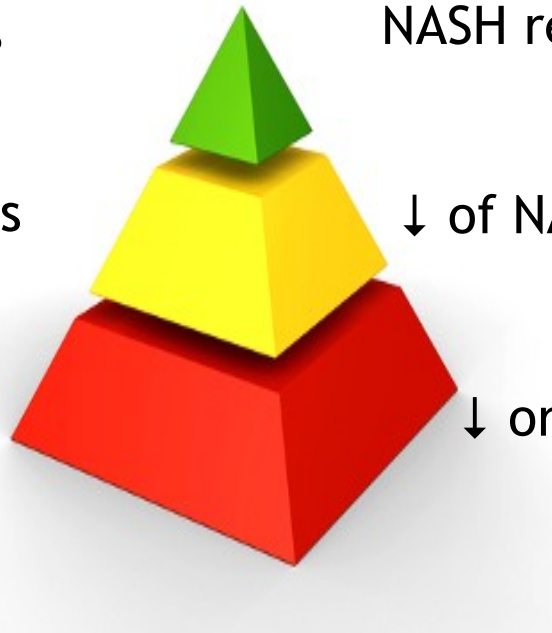
NASH remission (90%) and fibrosis (45%)⁴

7-10% weight loss

↓ of NASH score parameters (72%)^{1,3}

3-5% weight loss

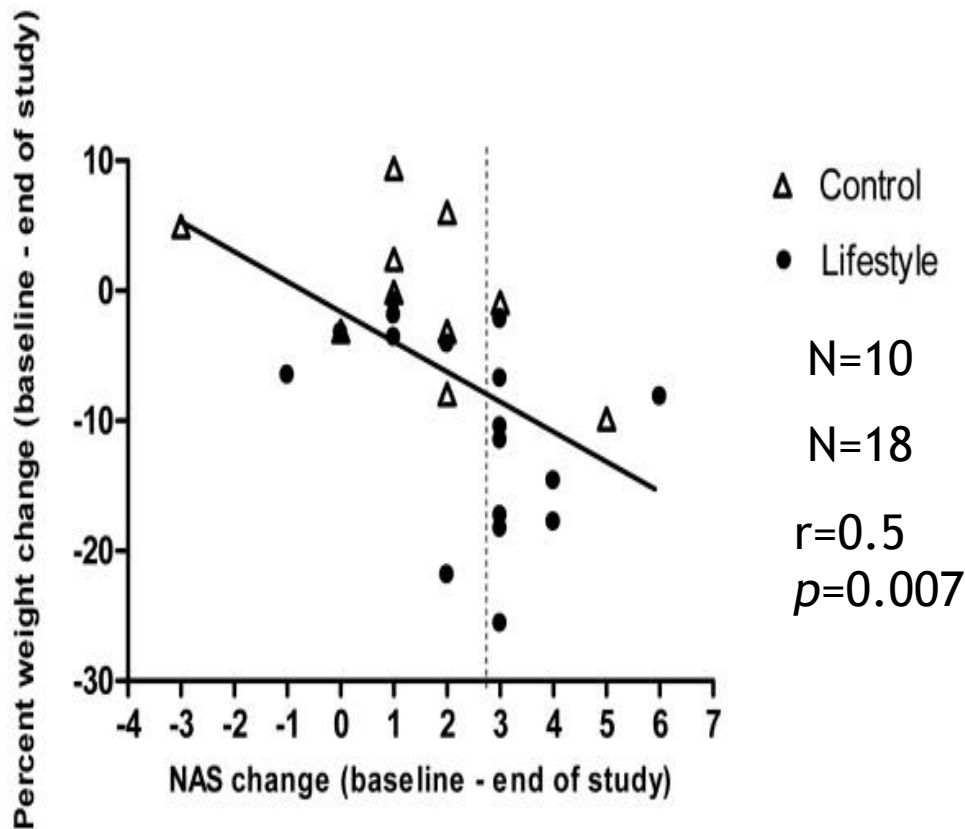
↓ or remission of steatosis (64%)^{1,2}



1. Harrison et al. *Hepatology* 2009; 2. Wong et al. *JHepatol.* 2013

3. Promrat et al. *Hepatology* 2010; 4. Vilar-Gomez et al. *Gastroenterology* 2015

Effect of combined diet and exercise on liver histology in NASH



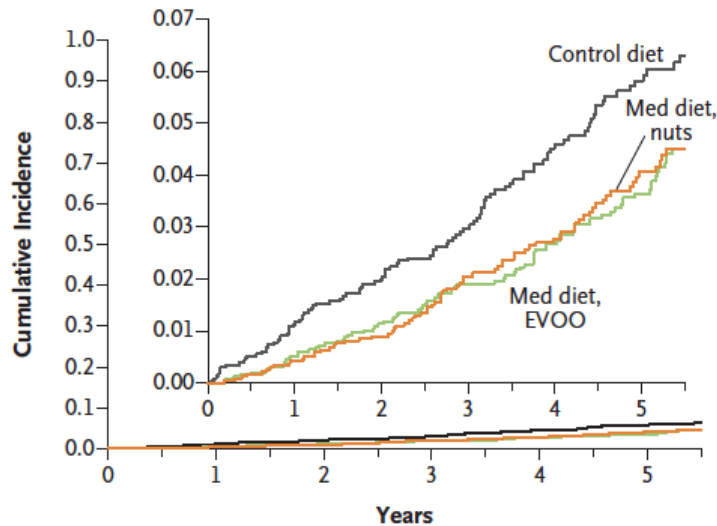
- 48 week diet and exercise intervention
- Steatosis improves with minimal wt loss but benefits to Inflammation/ballooning may require >7% body wt loss
- No effect on fibrosis

NAFLD - Nonalcoholic Fatty Liver Disease

N = 7447
Median FU 4,8y

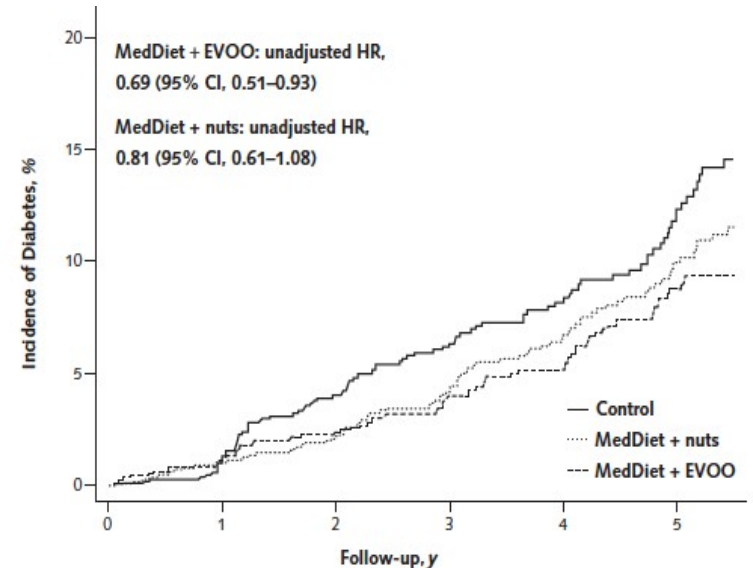
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)
Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)



No. at Risk

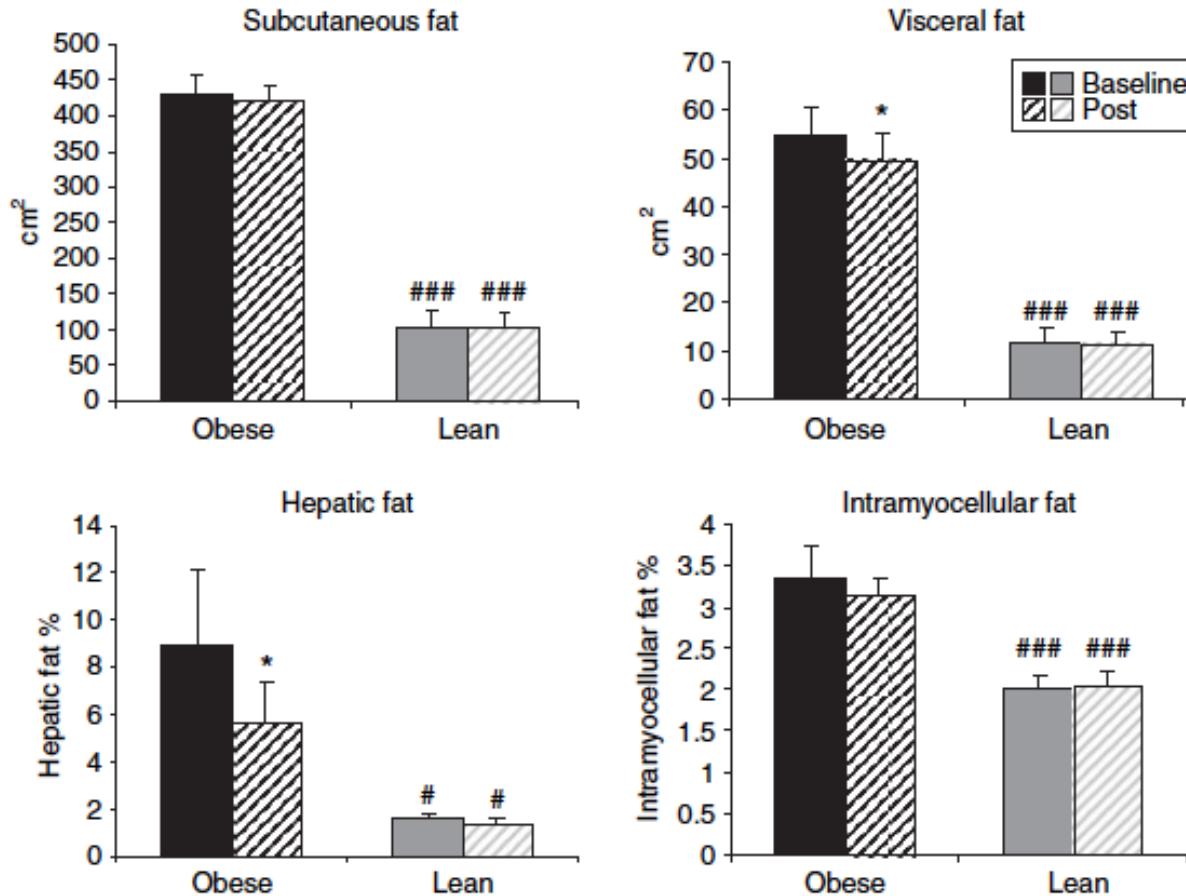
	0	1	2	3	4	5
Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031



Participants at risk, n

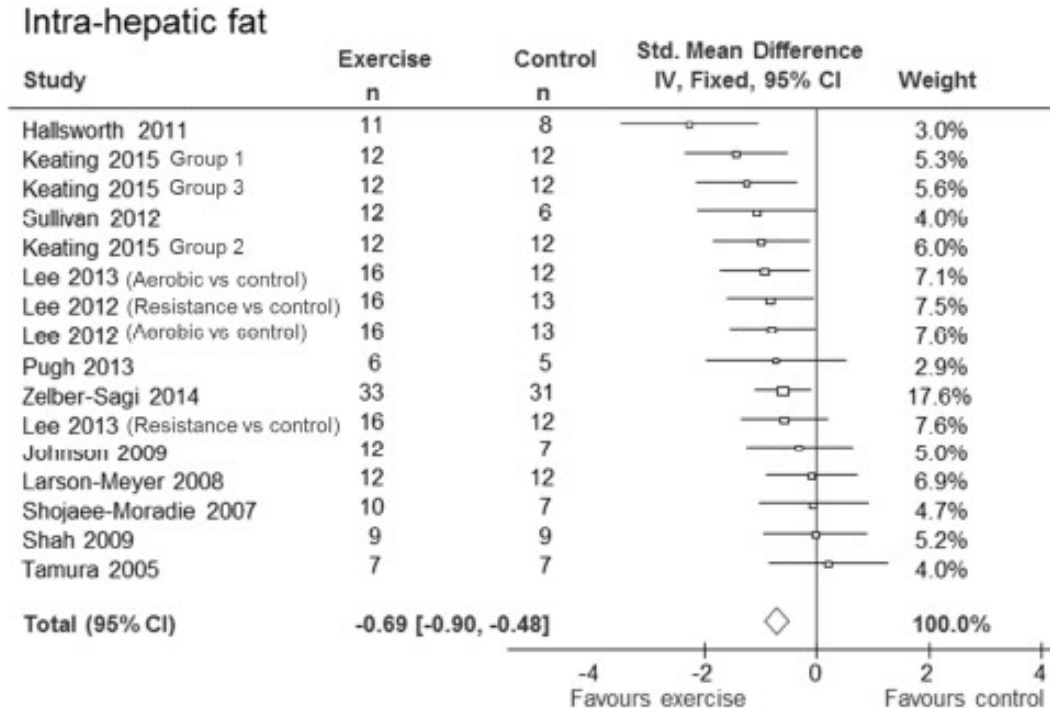
	0	1	2	3	4	5
MedDiet + EVOO	1154	1110	998	832	681	489
MedDiet + nuts	1240	1173	1000	775	629	427
Control	1147	1053	900	679	521	366

NAFLD - Nonalcoholic Fatty Liver Disease



N = 29 Hispanic adolescents (15 obese/14 lean) 12-week controlled aerobic exercise program

NAFLD - Nonalcoholic Fatty Liver Disease

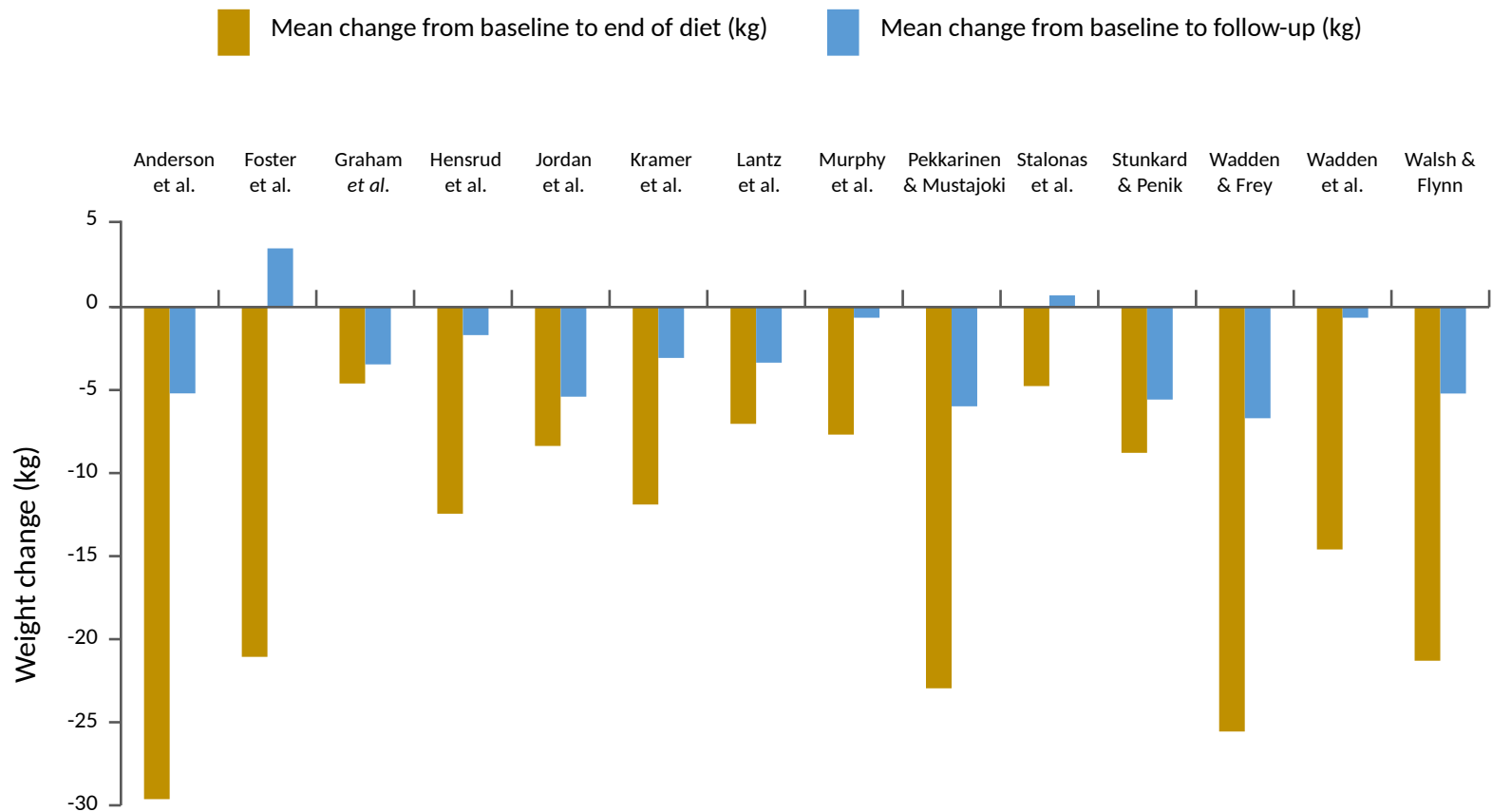


N= 1644
Physical activity-only
systematic review of 28
randomized clinical
trials

Heterogeneity: $\text{Chi}^2 = 21.22$, $\text{df} = 15$ ($P = 0.13$); $I^2 = 29\%$
Test for overall effect: $Z = 6.43$ ($P < 0.00001$)

The effect of physical activity on hepatic liver fat content was more prominent in young patients and patients with a higher baseline BMI

Maintaining weight loss is challenging



Follow-up range: from 4 to 7 years

Mann, et al. Am Psychol 2007

NAFLD - Nonalcoholic Fatty Liver Disease

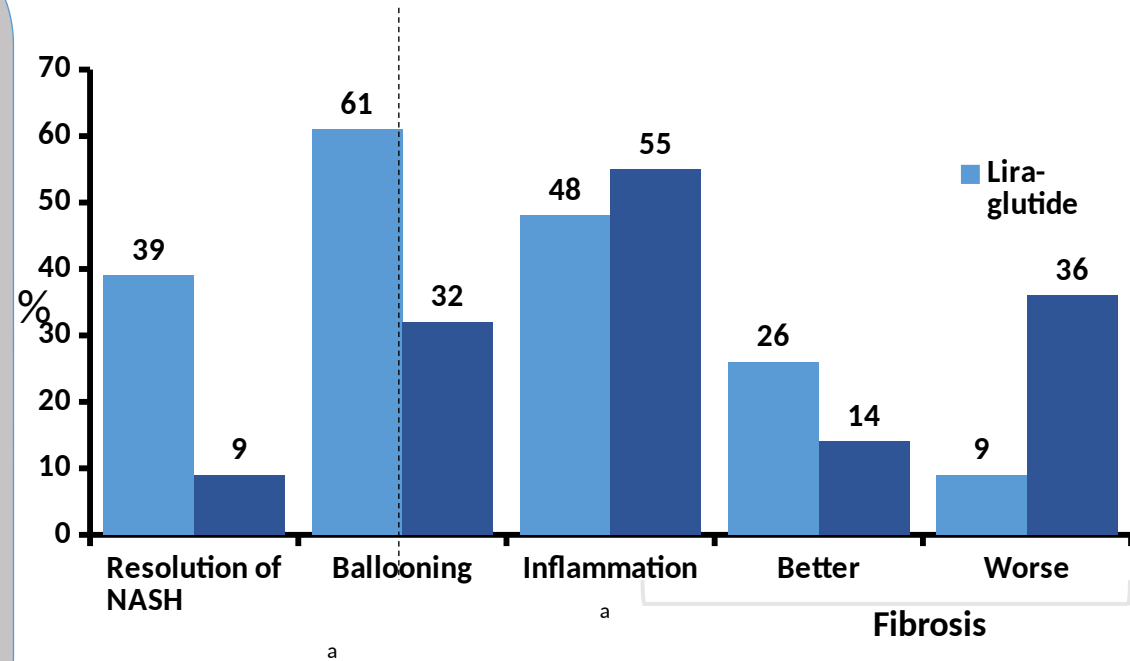
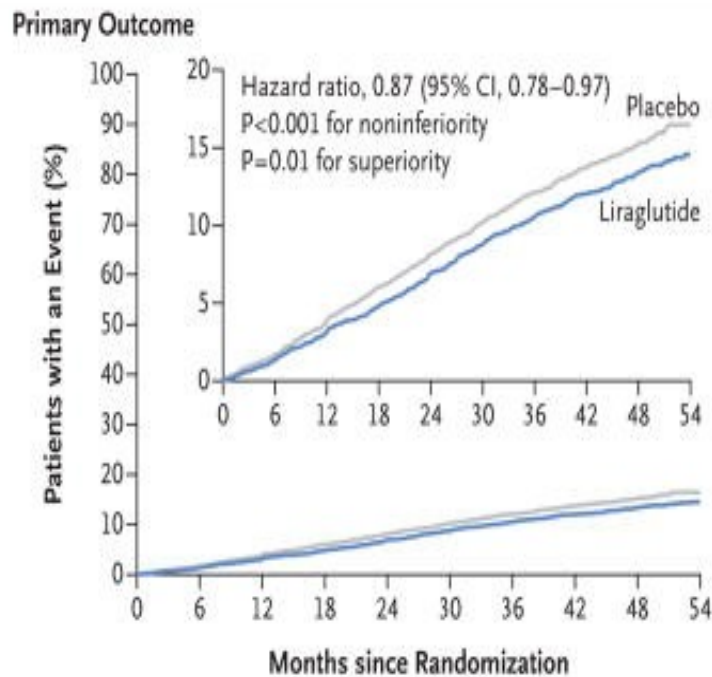
N = 540
FU = 7y

- NAFLD patients followed in a outpatients clinic of University Hospital - Federal University of Rio de Janeiro (HUCFF-UFRJ)
 - ✓ 7% weight maintenance
 - ✓ 49% increased weight
 - ✓ < 10% of total with reduction over 7% of initial weight

Management of obesity

	Mechanism of action	Available for chronic use		Mean percentage weight loss		Advantages	Disadvantages
		USA	European Union	Placebo	Drug		
Phentermine; 15-30 mg orally	Sympathomimetic	For short-term use	No	Not stated in label	Not stated in label	Inexpensive	Side-effect profile; no long-term data*
Orlistat; 120 mg orally three times a day before meals	Pancreatic lipase inhibitor	Yes	Yes	-2.6%†	-6.1%†	Not absorbed; long-term data*	Modest weight loss; side-effect profile
Lorcaserin; 10 mg orally twice a day	5-HT _{2c} serotonin agonist with little affinity for other serotonergic receptors	Yes	No	-2.5%	-5.8%	Mild side-effects; long-term data*	Expensive; modest weight loss
Phentermine/ topiramate ER; 7.5 mg/46 mg or 15 mg/92 mg orally indicated as rescue (requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Yes	No	-1.2%	-7.8% (mid-dose) -9.8% (full dose)	Robust weight loss; long-term data*	Expensive; teratogen
Naltrexone SR/ bupropion SR; 32 mg/360 mg orally (requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Yes	Yes	-1.3%	-5.4%	Reduces food craving; long-term data*	Moderately expensive; side-effect profile
Liraglutide; 3.0 mg Injection (requires titration)	GLP-1 receptor agonist	Yes	Yes	-3%	-7.4% (full dose)	Side-effect profile; long-term data*	Expensive; injectable

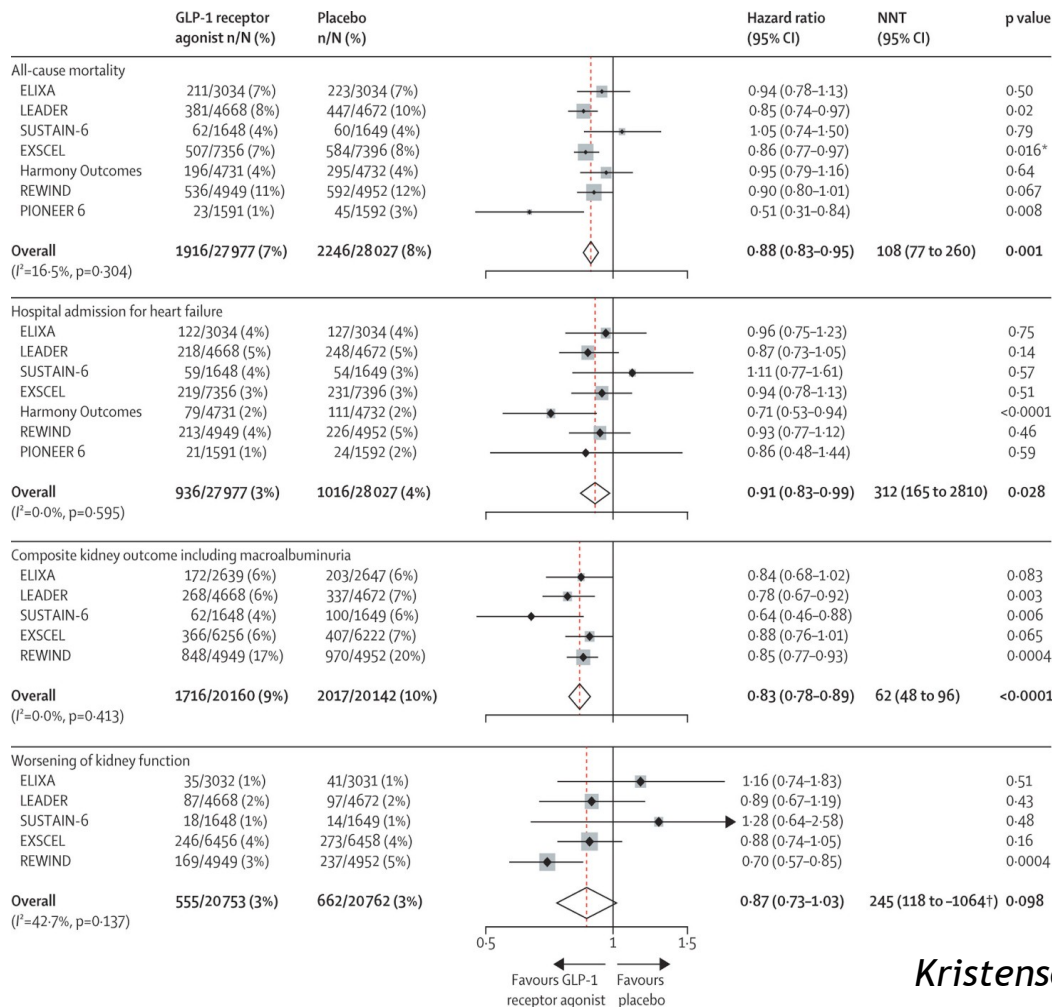
GLP-1 receptor agonists have the potential for cardio-metabolic as well as liver-benefits



Armstrong, et al. Lancet 2016

Marso et al, N Engl J Med 2016

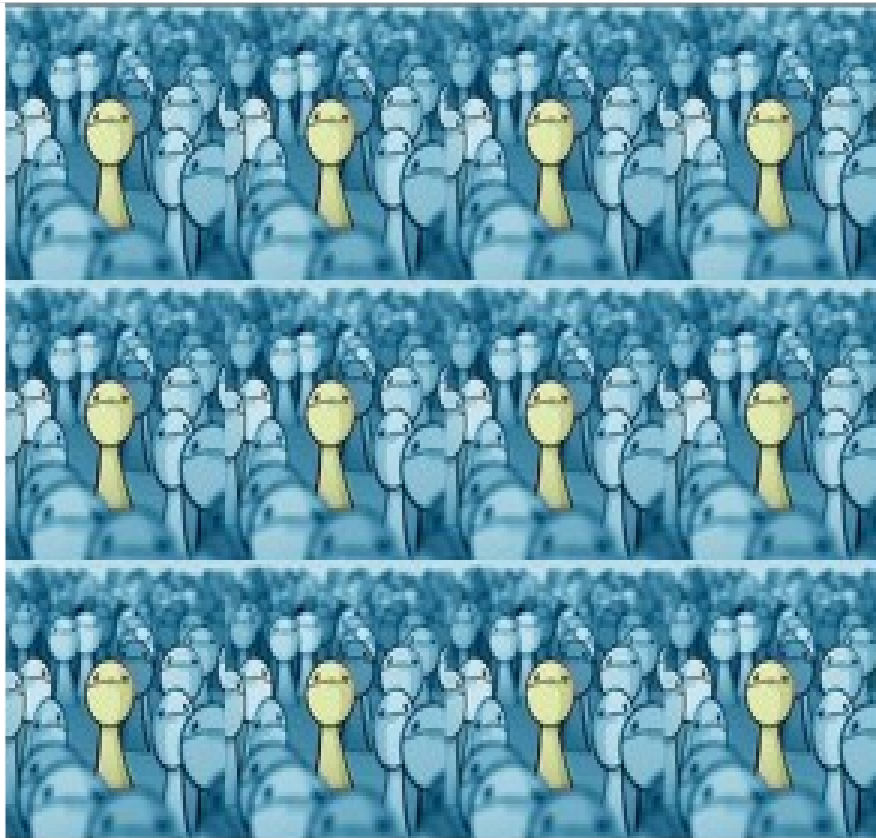
GLP-1 agonists reduce all cause mortality, hospitalization for heart failure and improve renal status in DM



NAFLD - Nonalcoholic Fatty Liver Disease

	N	Follow-up (m)	NAFLD Outcomes
<i>Mathurin et al, 2009 *</i>	381	50	48% NASH improvement Early stage fibrosis at 5y
<i>Taitano et al, 2015</i>	160	31	90% NASH remission 60% regression of fibrosis
<i>Lassailly et al, 2015</i>	109	12	85% NASH remission 34% regression of fibrosis
<i>Manco et al, 2016</i>	93	12	100% NASH remission 90% regression of fibrosis

Which would be the best candidates for pharmacological treatment for NAFLD?



Randomized Studies with Pioglitazone

↓ NAS
Score

100%

90%

80%

70%

60%

50%

40%

30%

20%

10%

0%

Belfort et al,2006

Aithal et al,2008

Sanyal et al,2010

Cusi et al, 2016

■ Pioglitazona

■ Placebo

Patients with or without
diabetes
30/45mg/daily
FU 6m-3y

0,73

$p = 0,001$

0,24

0,32

$p = 0,005$

0,1

0,34

$p = 0,004$

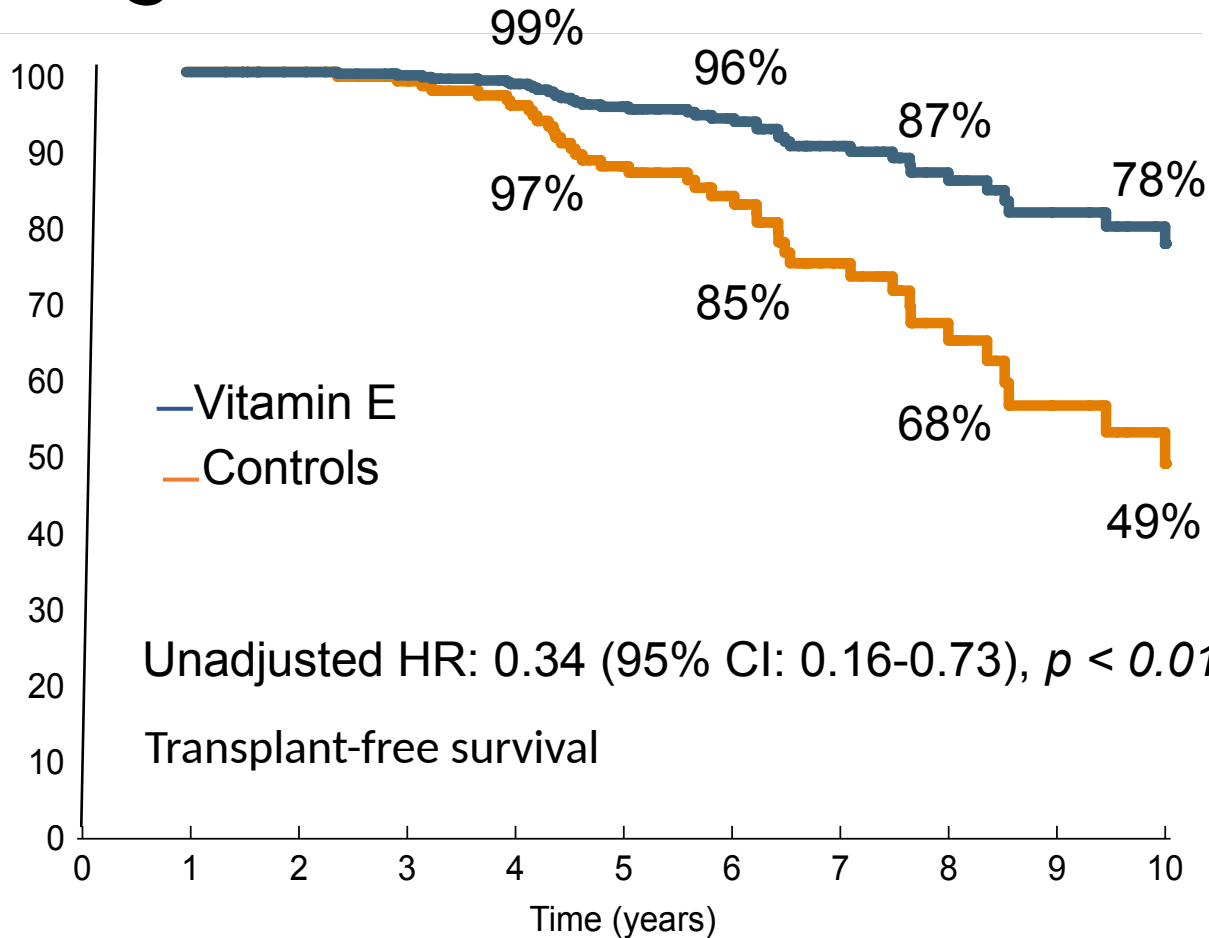
0,19

0,58

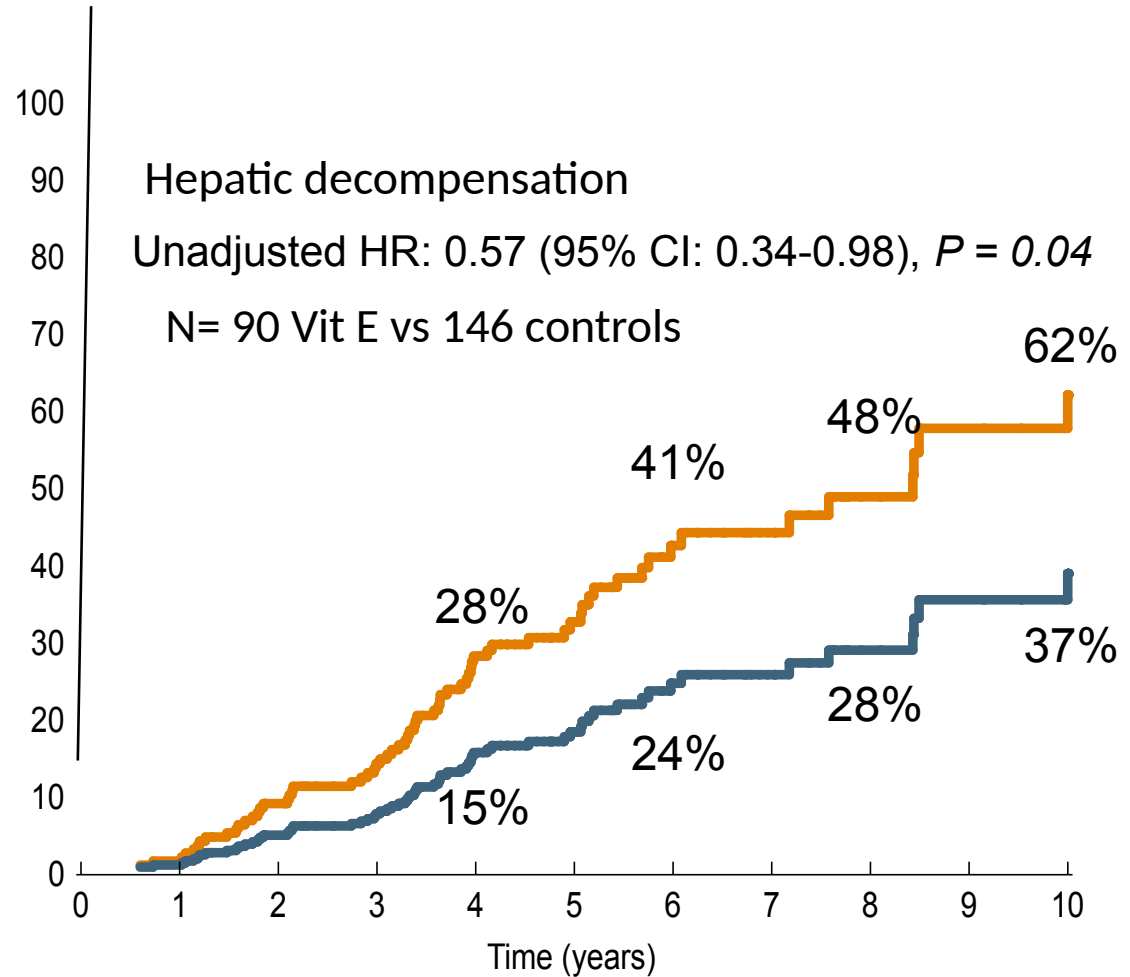
$p = 0,001$

0,17

Vitamin E improves transplant free survival and decompensation rates in NASH with stage 3 or 4 fibrosis



Vitamin E improves transplant free survival and decompensation rates in NASH with F3/4



NAFLD - Nonalcoholic Fatty Liver Disease

N = 132377
35-79y
FU = 8y
Non diabetic individuals

- ✓ A total of 6,555 incident diabetes (3,734 men and 2,821 women) were identified, on average, over 5.8 years of follow-up.
- ✓ The risk of incident diabetes was significantly associated with NAFLD [HR=2.08 (men) and 2.65 (women)].
- ✓ Elevated ALT, AST, GGT and ALP were also significantly associated with the increased risk of diabetes.

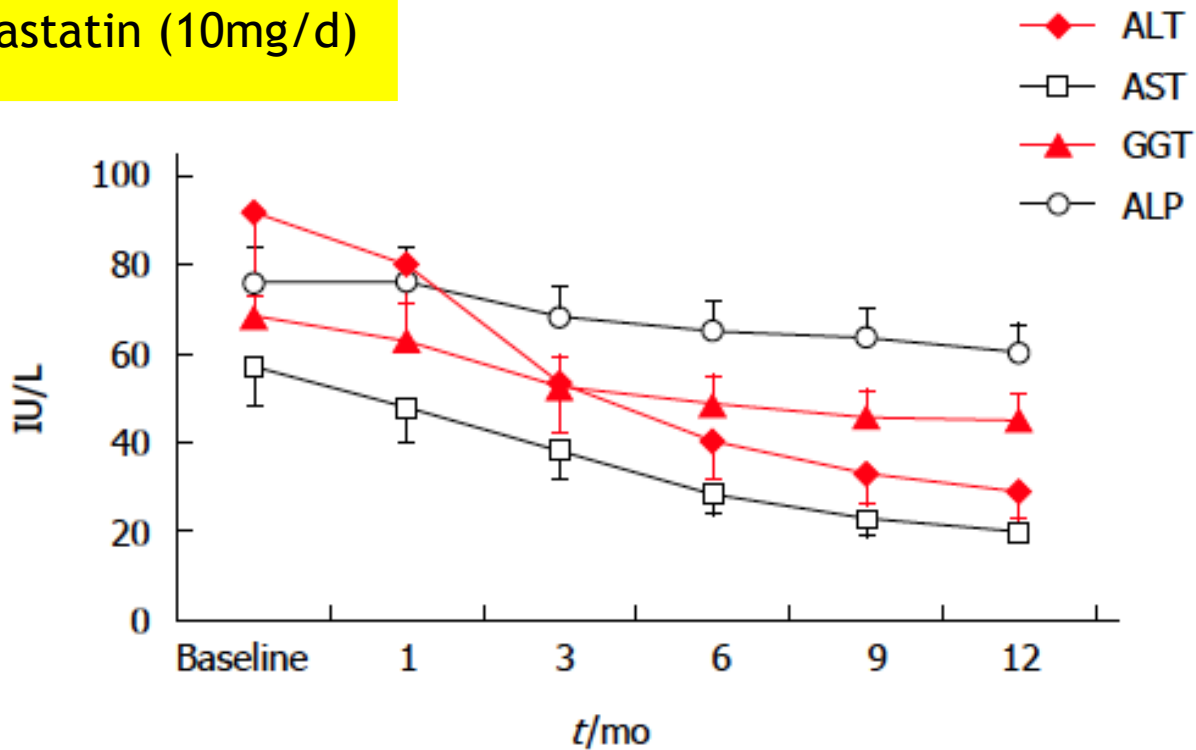
NAFLD - Nonalcoholic Fatty Liver Disease and diabetes

- Metformin
 - ✓ First-line drug in the treatment of diabetes and prevention of pre diabetes progression
 - ✓ No proven benefit in histological parameters
 - ✓ Anti-Tumor Effect - Limited Human Data (Retrospective Study)

Haukeland, et al. Scand J Gastroenterol 2009
Shields, et al. Therap Adv Gastroenterol 2009
Bhalla, et al. Cancer Prev Res 2012
Zhang, et al. J Clin Endocrinol Metab 2012

NAFLD - Nonalcoholic Fatty Liver Disease and dyslipidemia

N = 20
NASH biopsy proven
12m Rosuvastatin (10mg/d)



Take home messages

- NAFLD is a highly prevalent disease.
- There is no approved drugs.
- Diet and lifestyle changes are essential.
- Pioglitazone and Vitamin E still play a role.
- Statins are underused in NAFLD patients.

