Terapia del Diabete Mellito Tipo 2 oltre la glicemia: le promesse dei nuovi farmaci:

FEGATO

Fabrizio Febo MD, PhD

CHIETI – 12 NOVEMBRE 2022

MENU of the DAY

NAFLD, NASH o MAFLD… ci vuole fegato!

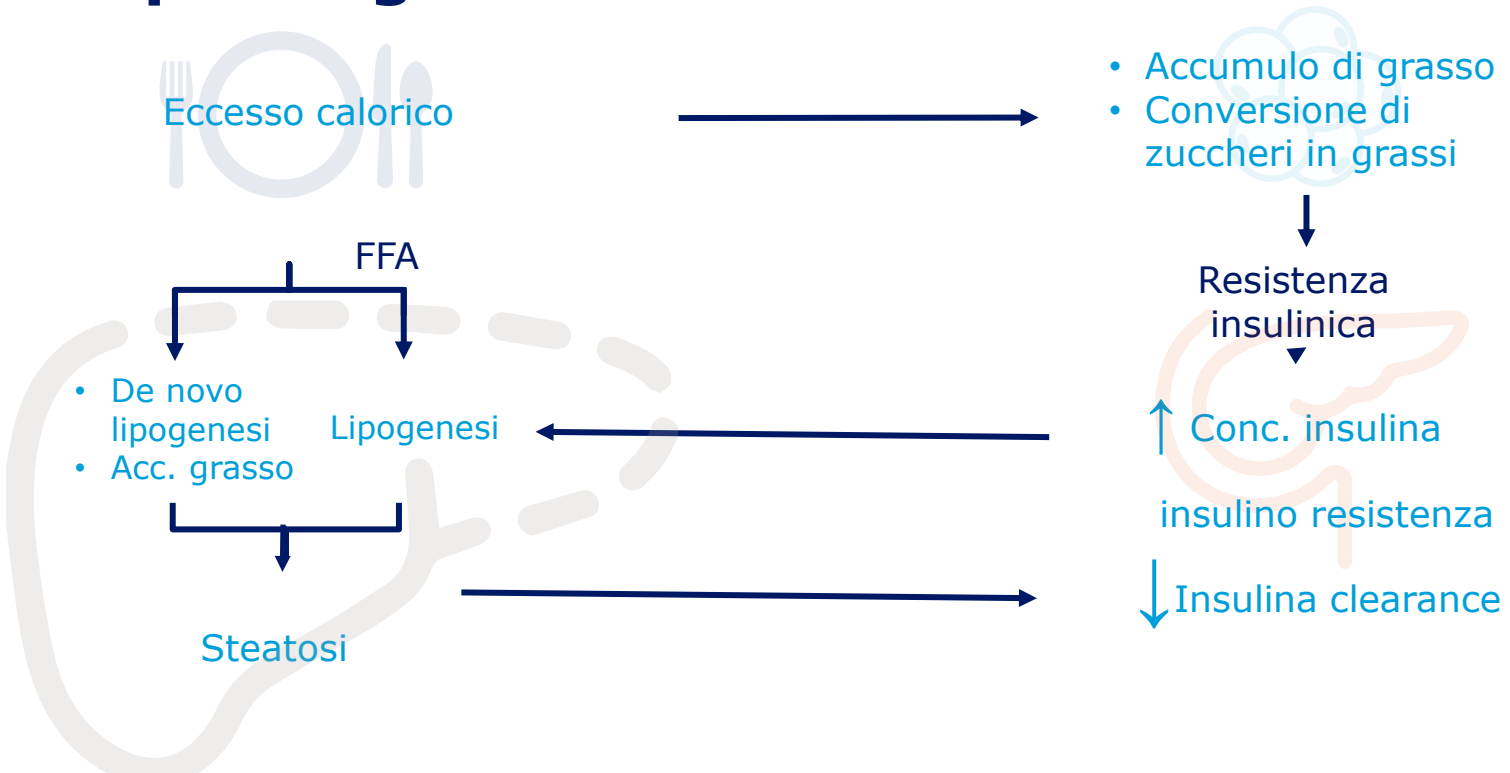
Presente da sfruttare…

…futuro da sperare!

Cos’è la NAFLD?

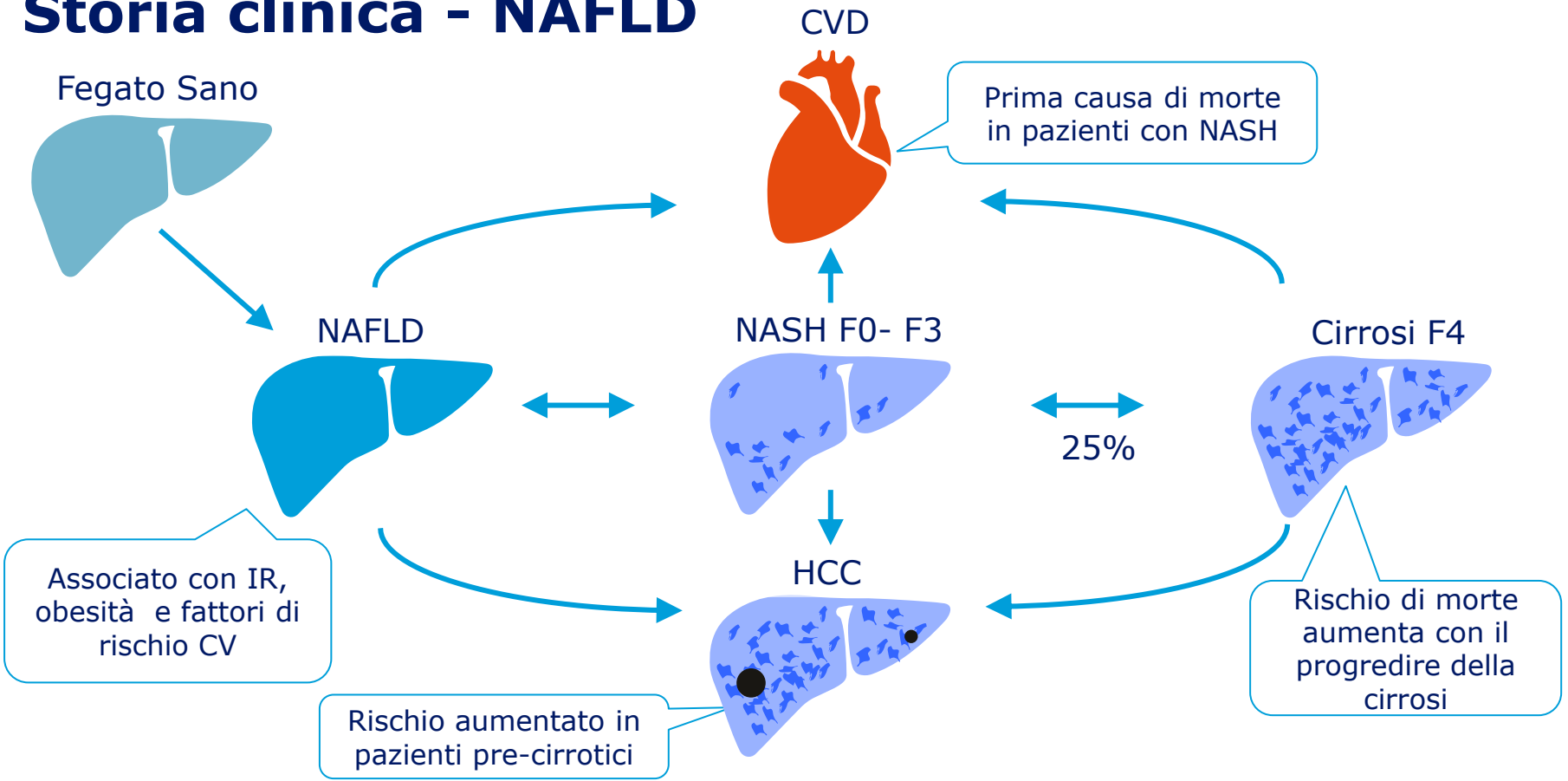
Non-alcoholic Fatty Liver Disease

Fisiopatologia NAFLD



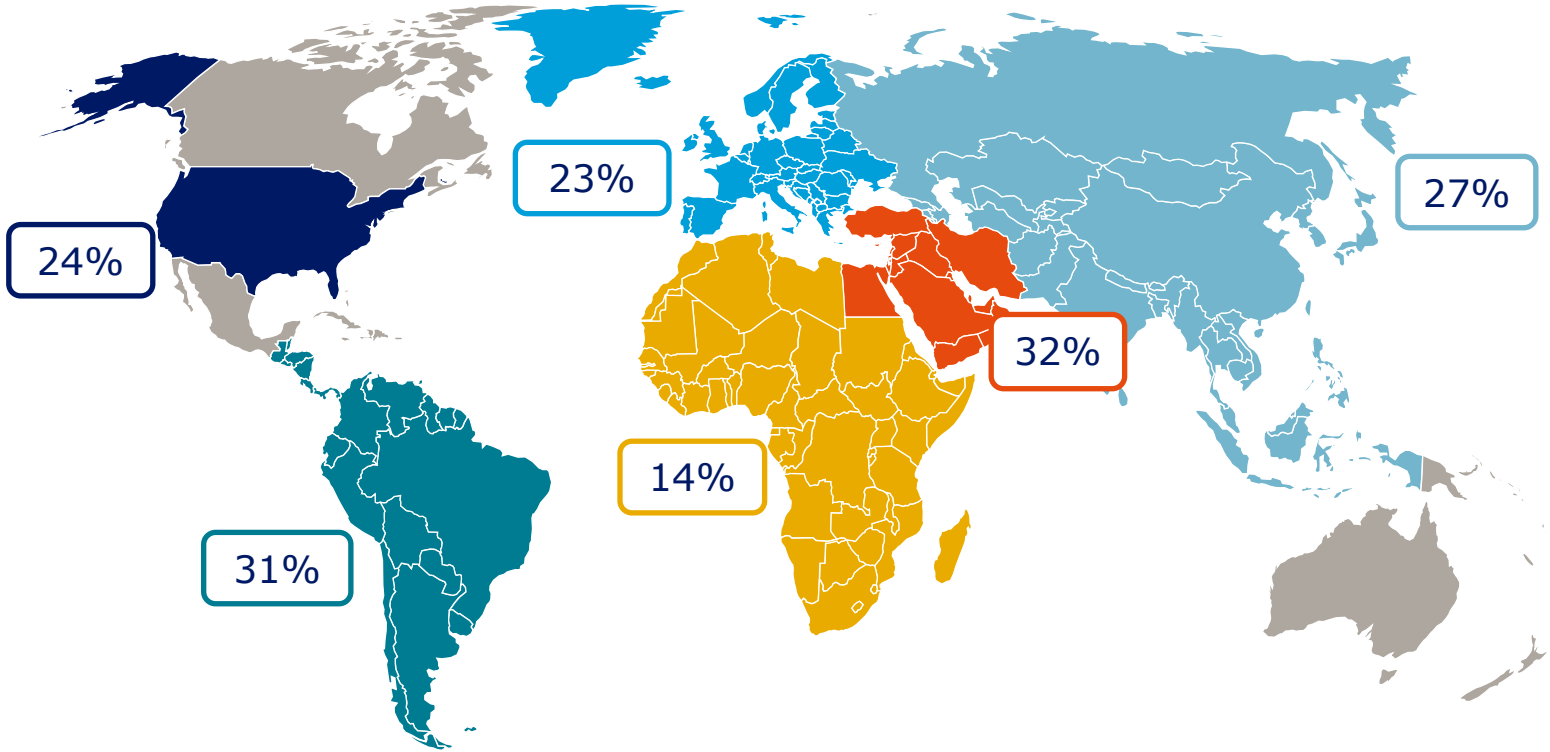
FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease.
Gaggini et al. Nutrients. 2013;5:1544–60.

Storia clinica - NAFLD



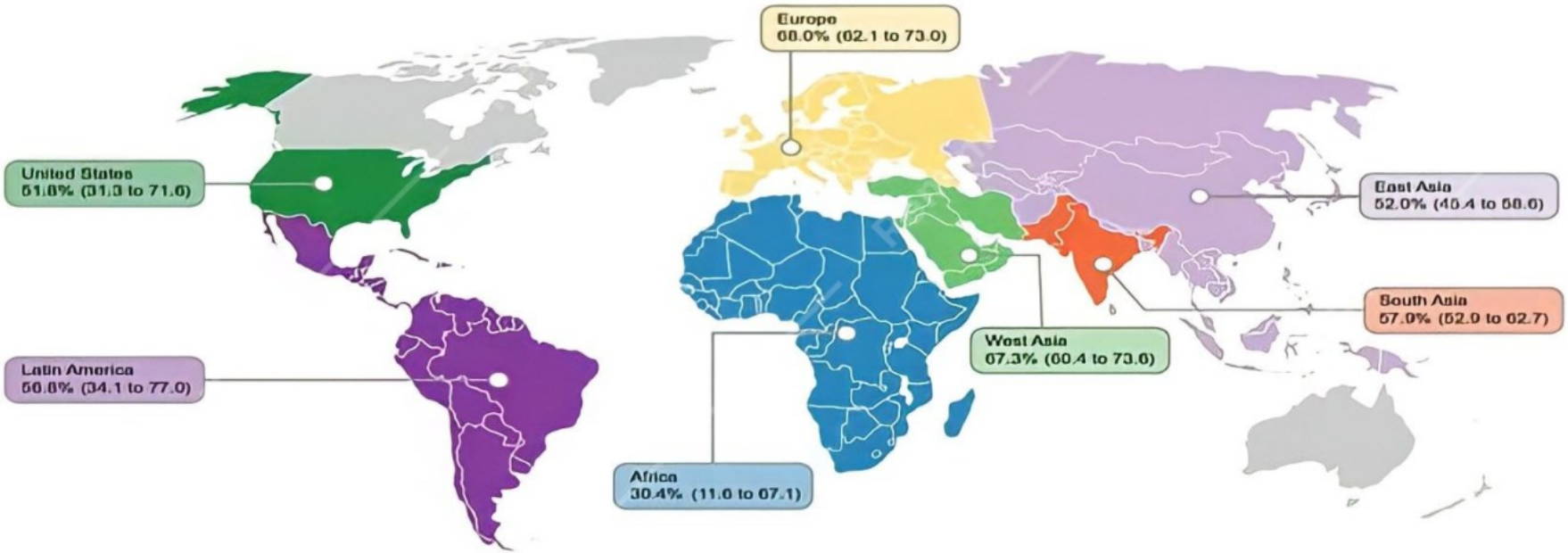
NASH may involve varying stages of liver fibrosis, represented by stages F0 (non-cirrhotic) to F4 (cirrhotic).
CV, cardiovascular; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Prevalenza globale di NAFLD



NAFLD, non-alcoholic fatty liver disease.
Younossi Z et al. *Nat Rev Gastroenterol Hepatol.* 2017;doi: 10.1038/nrgastro.2017.109; Bertot LC et al. *Int J Mol Sci* 2016;17:774.

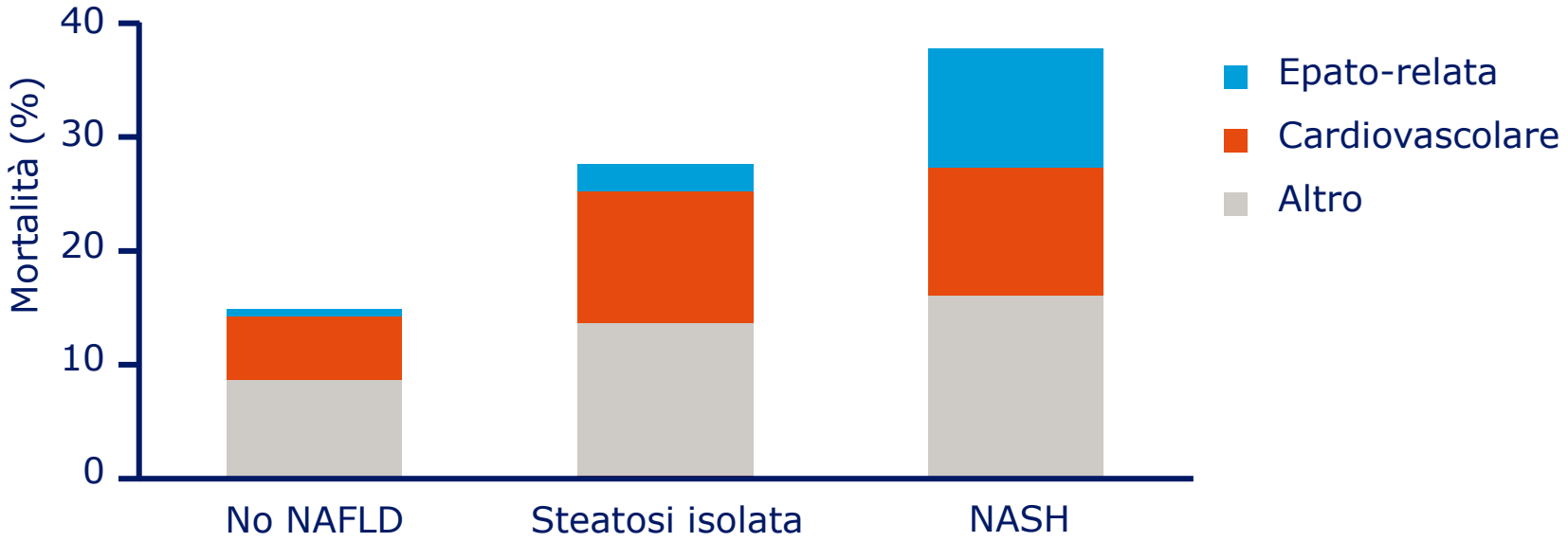
Prevalenza globale di NAFLD nel DM2



Global prevalence of NAFLD among T2DM patients 55.5%
(95% confidence interval: 47.3-63.7)

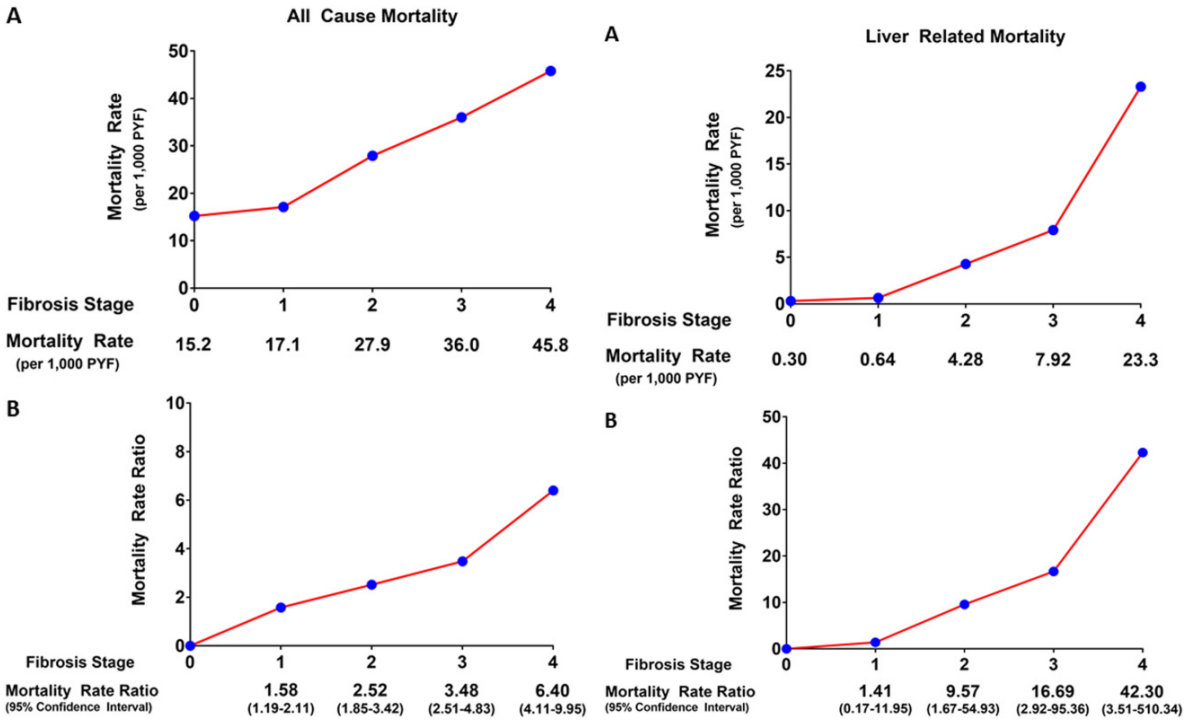
NAFLD, non-alcoholic fatty liver disease.
Younossi Z et al. J *Hepatol.* 2019

La mortalità aumenta con il progredire della NALFD



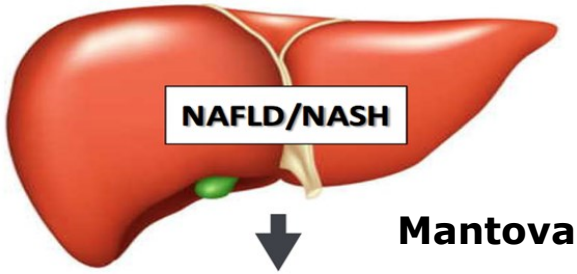
**Follow up time calculated as weighted mean; no NAFLD 14.5 years, isolated steatosis 13.3 years, NASH 13.0 years.*
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Bril and Cusi. Endocrinol Metab Clin North Am 2016;45:765–81.

La FIBROSI aumenta il rischio di mortalità



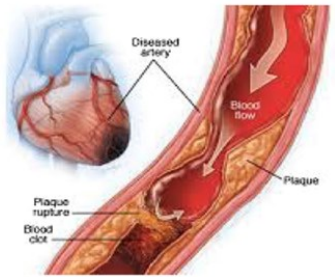
Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, Sebastiani G, Ekstedt M, Hagstrom H, Nasr P, Stal P, Wong VW, Kechagias S, Hultcrantz R, Loomba R. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017 May;65(5):1557-1565. doi: 10.1002/hep.29085. Epub 2017 Mar 31. PMID: 28130788; PMCID: PMC5397356.

CVD & NAFLD

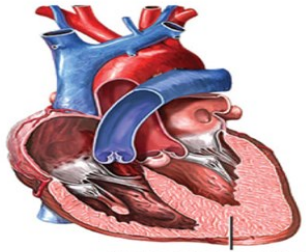


Mantovani A *et al.* Dig Dis Sci 2016

NAFLD-related cardiac complications



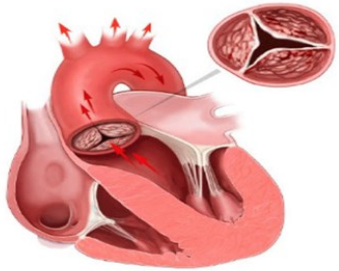
Coronary Heart Disease



Enlargement of heart muscle

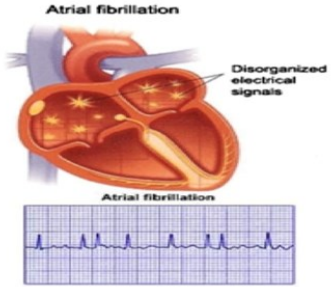
Cardiac Dysfunction
Cardiac Hypertrophy

Heart Failure



Aortic-Valve Sclerosis

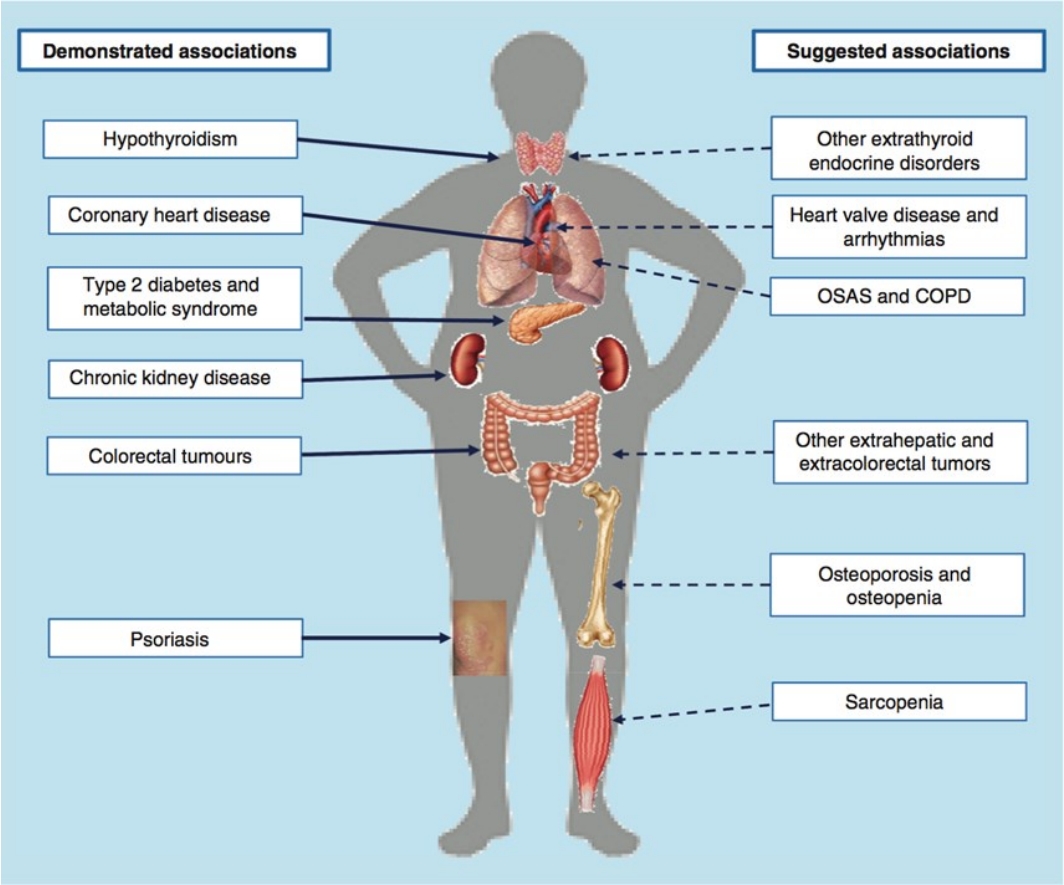
Mitral Annulus Calcification



Atrial Fibrillation

QTc Prolongation

Manifestazioni extra-epatiche associate a NAFLD



Ballestri S, Mantovani A, Nascimbeni F, Lugari S, Lonardo A. Extra-hepatic manifestations and complications of nonalcoholic fatty liver disease. Future Med Chem. 2019 Aug;11(16):2171-2192

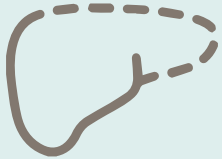
Diagnosi di NAFLD-NASH

Pochi sintomi

- Spesso asintomatica
- Sintomi aspecifici (ad esempio, malessere)

Enzimi epatici ed ecografia

- Lievemente elevati con prevalenza di ALT predominante nella maggior parte dei pazienti
- Steatosi all'ecografia



Esclusione di altre eziologie

- Nessun consumo significativo di alcol
- Nessuna eziologia concorrente per l'epatosteatosi
- Nessuna causa coesistente di malattia epatica cronica

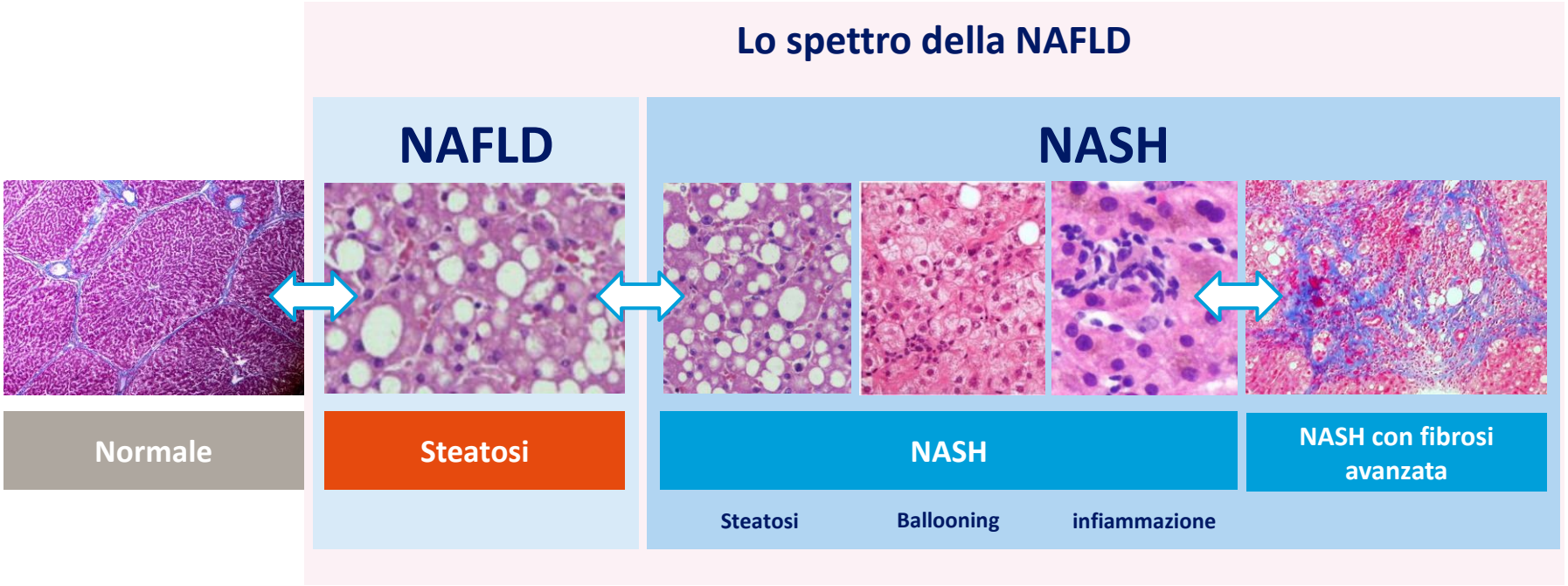
Richiede una biopsia epatica

- La diagnosi di NASH richiede la **presenza congiunta di steatosi, ballooning e infiammazione lobulare**
- Diagnostica gold standard

> 31 IU/L M
> 19 IU/L F

ALT, alanina aminotransferasi; NASH, steatoepatite non alcolica.
European Association for the Study of the Liver et al. J Hepatol. 2016;64:1388-1402;
Stengel JZ e Harrison SA. Gasteroenterol Hepatol 2006;2:440-9; Chalasani N et al. Hepatology 2018;67:328-57.

ASPETTI ISTOLOGICI DELLA NAFLD NASH



NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. Chalasani et al. Hepatology. 2018;67:328–335;

Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} = 2.25$$

Age (years): 55
AST Level (U/L): 55
Platelet Count (10^9/L): 200
ALT (U/L): 45

<1.30	Low Risk
1.30 – 2.67	Intemediate Risk
>2.67	High Risk

IL PRESENTE

DALLE LINEE GUIDA ALL'AMBULATORIO

Il pioglitazone e la vitamina E non sono approvati per il trattamento della NASH.

Sintesi delle linee guida di gestione dell'AASLD e dell'EASD-EASL-EASO

Stile di vita

- 7-10% di perdita di peso
- 500-1000 calorie giornaliere in meno
- Esercizio fisico

Farmacologia

- Pioglitazone
- Vitamina E

Chirurgia

- Chirurgia bariatrica
- Trapianto di fegato

AASLD, American Association for The Study of Liver Disease (Associazione americana per lo studio delle malattie del fegato); EASD, European Association for the study of Diabetes (Associazione europea per lo studio del diabete); EASL, European Association for The Study of The Liver (Associazione europea per lo studio dell'obesità).

European Associated for the Study of the Liver et al. J Hepatol 2016;64:1388-402; Chalasani N et al. Hepatology 2018;67;328-57.

Farmaci per il diabete ed effetto su NAFLD-NASH

Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Medication	Liver fat	Disease activity (steatohepatitis/NAS)
Metformin	Unchanged	Neutral
Pioglitazone	Decreased	Improved[a]
Insulin	Decreased	Effect unknown
GLP-1 RAs (semaglutide and liraglutide)	Decreased	Improved[a]
SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin)	Decreased	Effect unknown
DPP-IV inhibitors (sitagliptin and vildagliptin)	Unchanged (in RCTs)	Effect unknown

Cusi K et Al. Endocr Pract 2022 - https://doi.org/10.1016/j.eprac.2022.03.010

Diabetes Management in NAFLD

Fibrosis Risk Stratification

	 **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7	 **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	 **High Risk[1]** FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1 RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF.		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates.		
Individualize A1c target	≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise).		In advanced cirrhosis[1], caution with risk of hypoglycemia and avoid oral agents[2]
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i).	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No efficacy data in cirrhosis.
Metformin, sulfonylurea, DPP-4i, acarbose and insulin	May continue but limited benefit on liver histology in NAFLD.	May continue but limited benefit on liver histology in NAFLD.	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option

Abbreviations: CKD = Chronic kidney disease, CVD = Cardiovascular disease, DPP-4i = Dipeptidyl peptidase 4, GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HF = Heart failure, NASH = Nonalcoholic steatohepatitis, SGLT2i = Sodium-glucose cotransporter-2 inhibitors.

1. Advanced cirrhosis is defined as persons with cirrhosis based on biopsy and Child class B or C with clinical evidence of comorbidities (varices, portal hypertension, ascites, etc.).
2. Limited data on oral diabetes medications and GLP-1 RA in persons with cirrhosis. Avoid metformin, GLP-1 RA appear safe, insulin preferred. Avoid oral agents in advanced cirrhosis.
3. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

 https://doi.org/10.1016/j.eprac.2022.03.010

Algorithm Figure 4

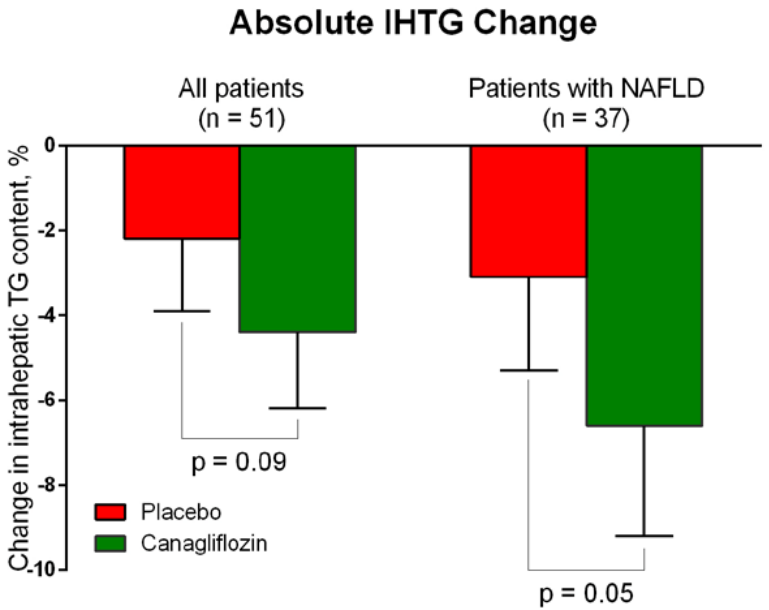
AACE.

Potenziali benefici di SLGT-2i e GLP-1 RA e co-morbilità associate alla NASH

Potenziale dei nuovi farmaci diabetologici come opzione di trattamento per la NASH

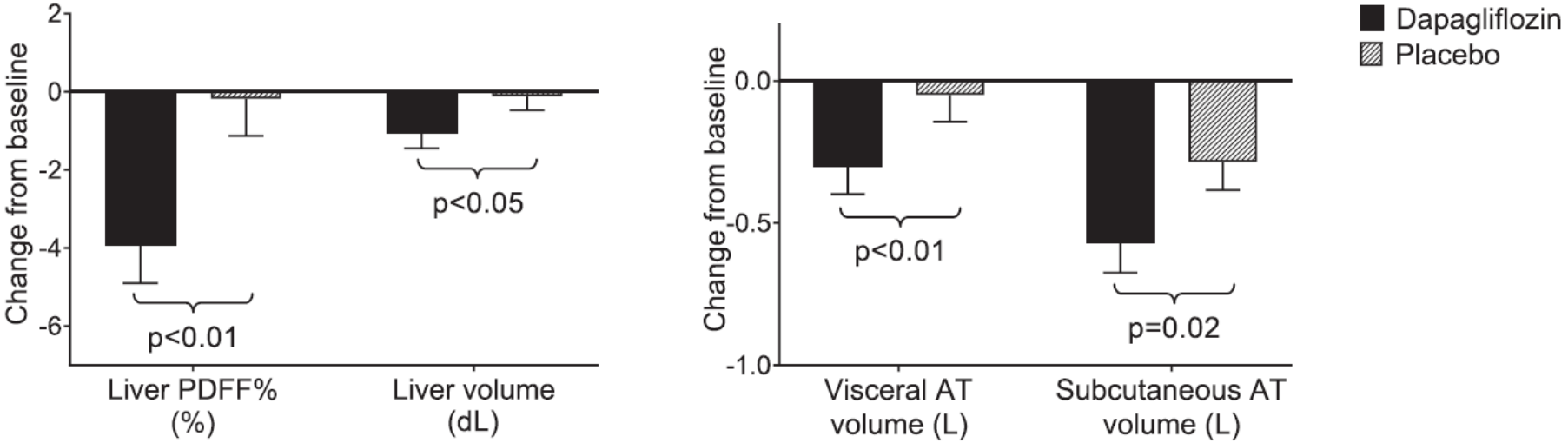
1. Younossi ZM et al. Hepatology 2016;64:73-84; 2. Sanyal AJ. Nat Rev Gastro Hepatol 2019;16:377-86; 3. Prasad-Reddy L, Drugs in Context 2015;4:212283; 4. Newsome P et al. Ailment Pharmacol Ther 2019;50:193-203.

Cana 300 vs placebo in DM2 non controllato, dopo 24 settimane



Cusi et Al, DOM 2019

Dapa+met vs Placebo per 8 settimane, migliorare NAFLD e AT senza modifiche alla sensibilità insulinica



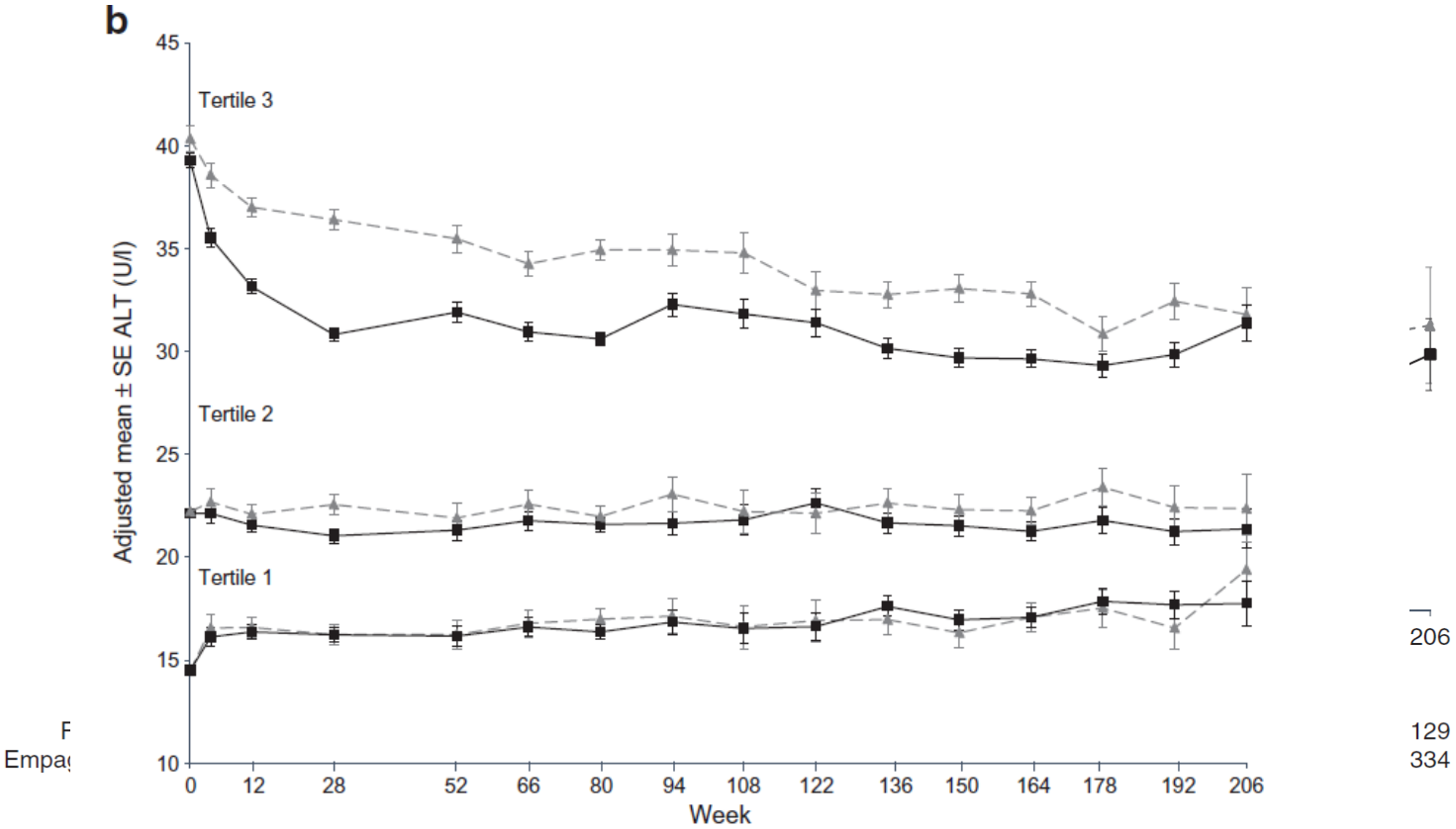
Rasku et Al, Diabetes Care 2019

Dapagliflozin 5mg vs terapia standard in soggetti con NAFLD

Masanori et al, DOM 2019

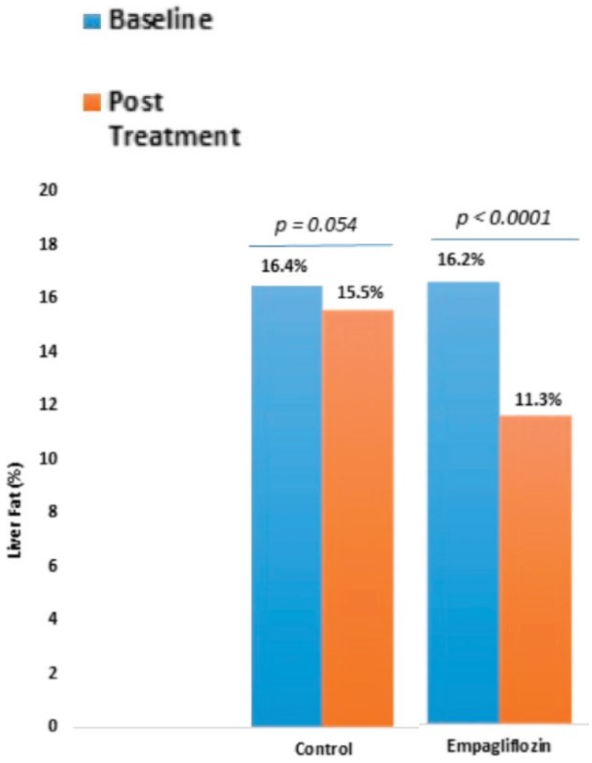
Yoshimasa et al, IJCP 2019

Andamento delle ALT in EMPAREG-OUTCOME



Sattar et Al, Diabetologia 2018

Empa 10 vs terapia standard in DM2 E-LIFT Trial



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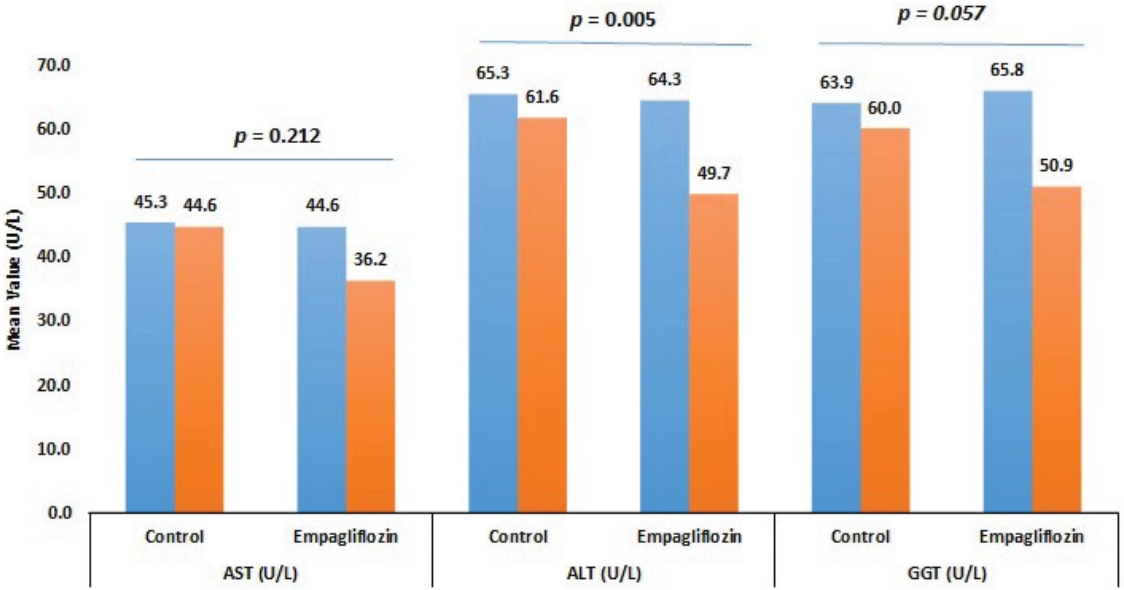
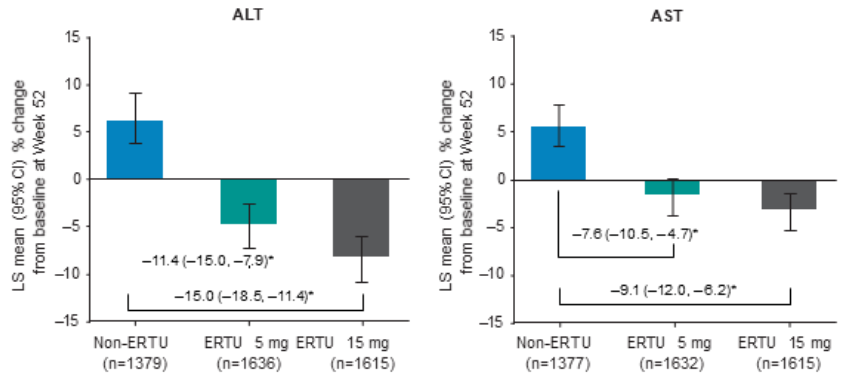


Kuchay et Al, Diabetes Care 2018

Ertugliflozin vs placebo negli studi VERTIS

Mean % change from baseline at Week 52 for ALT and AST



ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ERTU, ertugliflozin; LS, least squares.
*Difference in LS means (95% CI).

Mean change from baseline at Week 52 for FIB-4 index

	Treatment	Baseline Mean (SD)	Week 52 Mean (SD)	Change From Baseline at Week 52: Change in LS Mean (95% CI)	Change From Baseline at Week 52: Difference in LS Means Relative to Non-ERTU (95% CI)
FIB-4 index	Non-ERTU	1.12 (0.56)	1.16 (0.52)	0.01 (–0.02, 0.03)	
	ERTU 5 mg	1.11 (0.57)	1.11 (0.51)	0.02 (0.00, 0.04)	0.01 (–0.02, 0.04)
	ERTU 15 mg	1.10 (0.53)	1.09 (0.55)	0.01 (–0.01, 0.03)	0.00 (–0.03, 0.03)

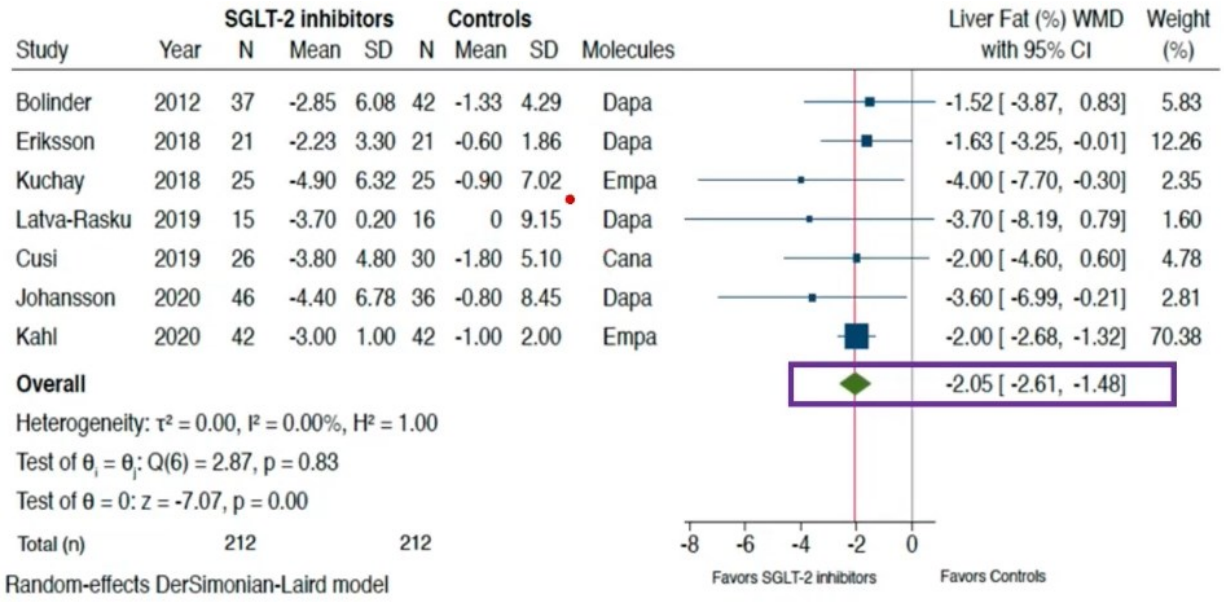
CI, confidence interval; ERTU, ertugliflozin; FIB-4, Fibrosis-4; LS, least squares; SD, standard deviation.

Gallo et Al, EASD Liver poster 2019

Effetto di SGLT-2i su NAFLD-NASH

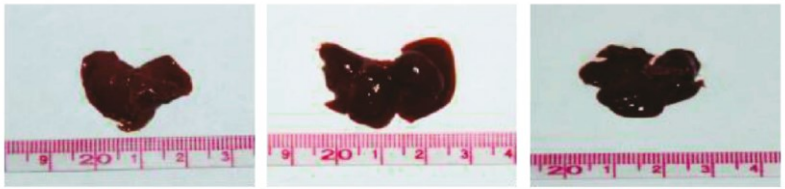
Meta-analisi di 12 RCT su soggetti 850 soggetti (90% con DM2) con NAFLD, trattati con dapagliflozin (6 RCT), empagliflozin (3 RCT)
ipragliflozin (2 RCT) o canagliflozin (1 RCT) studiati per una mediana di 24 settimane

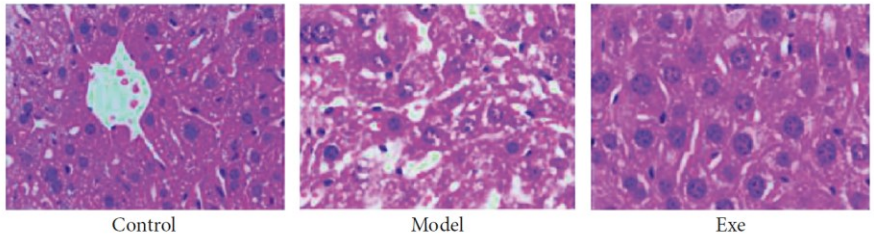
Riduzione assoluta della LFC con RMI

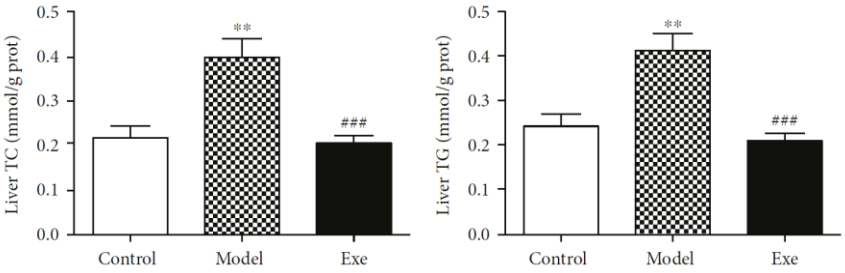


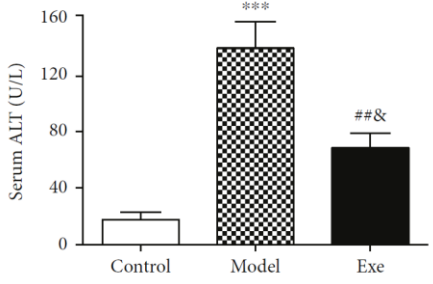
Mantovani et Al, Metabolites 2021

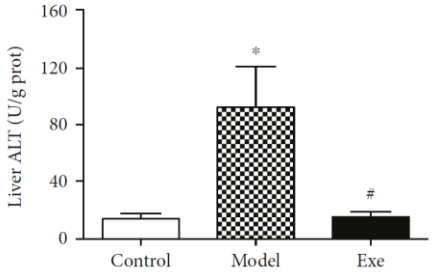
Exenatide dopo 4 settimane in topi C57BL/6







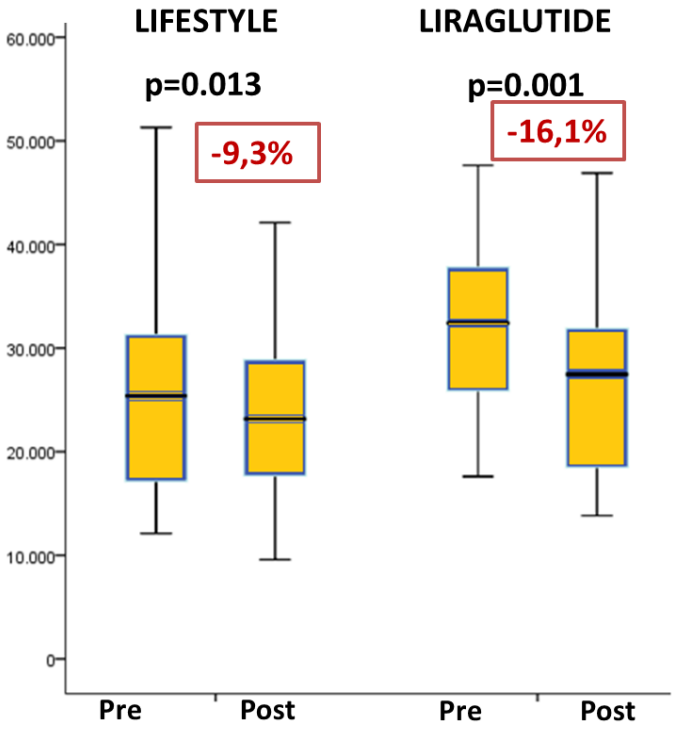


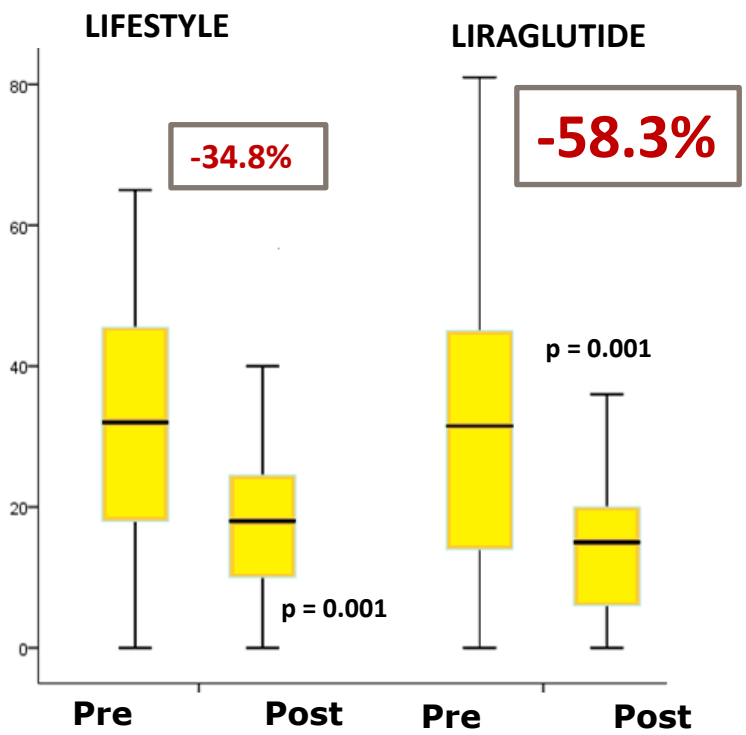


Shao et Al, Gast Res and Prac 2018

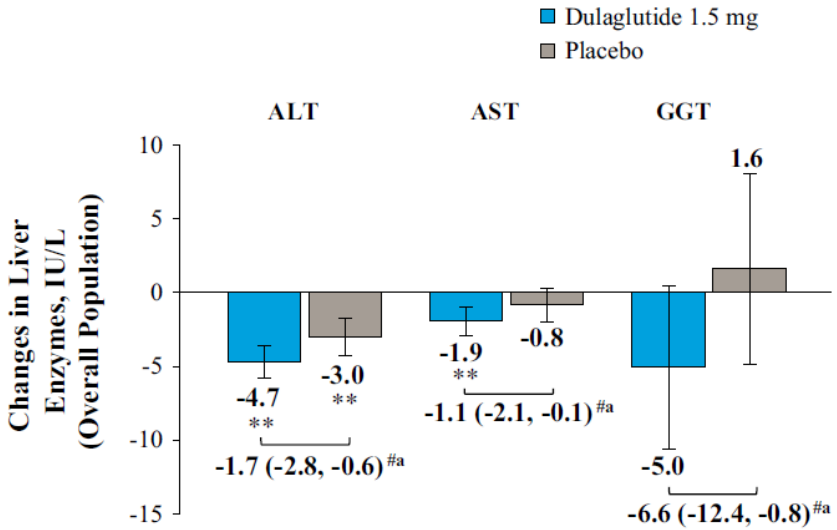
Effects of Liraglutide or Lifestyle Modification induced weight loss on VAT & NAFLD Grade in Obese Patients

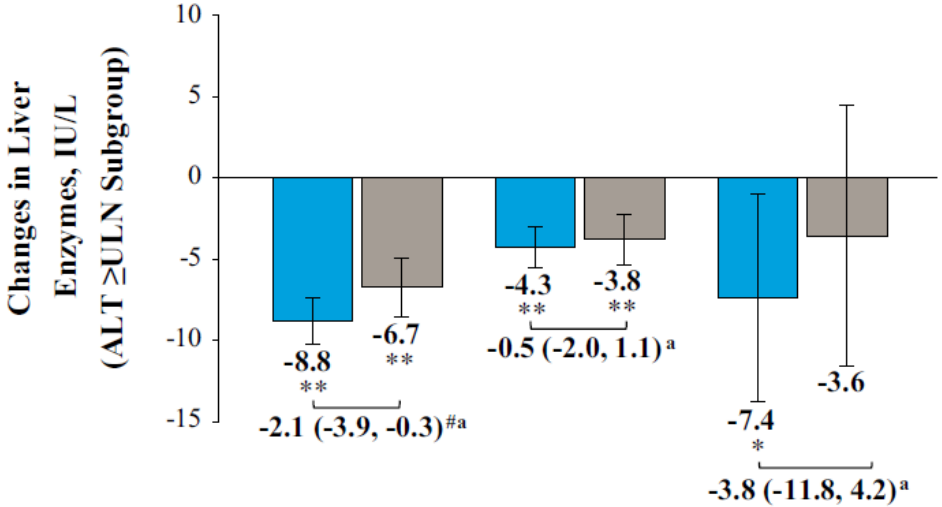
Santilli et al





Dulaglutide e NAFLD nel programma AWARD





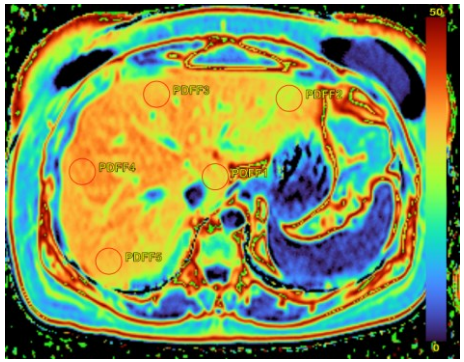
Cusi et Al, Diab Med 2018

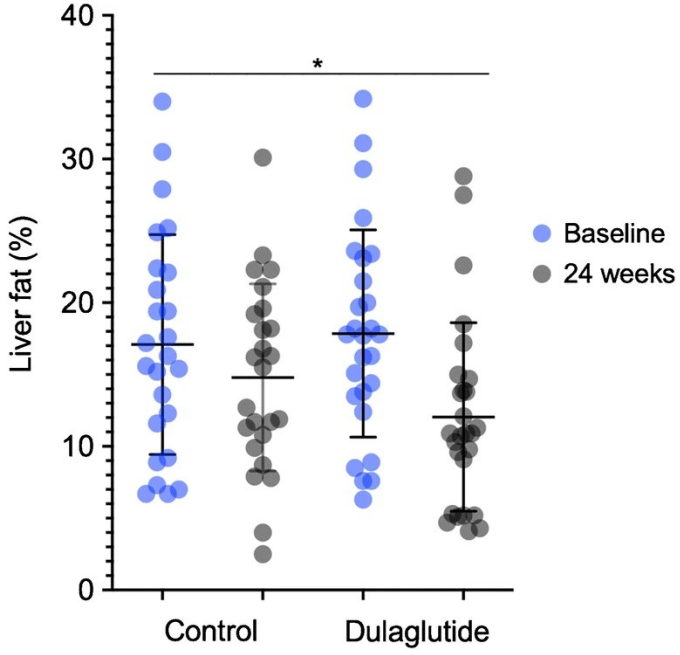
Diabetologia
https://doi.org/10.1007/s00125-020-05265-7

ARTICLE

Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial)

Mohammad S. Kuchay[1] · Sonal Krishan[2] · Sunil K. Mishra[1] · Narendra S. Choudhary[3] · Manish K. Singh[4] · Jasjeet S. Wasir[1] · Parjeet Kaur[1] · Harmandeep K. Gill[1] · Tarannum Bano[1] · Khalid J. Farooqui[1] · Ambrish Mithal[1]

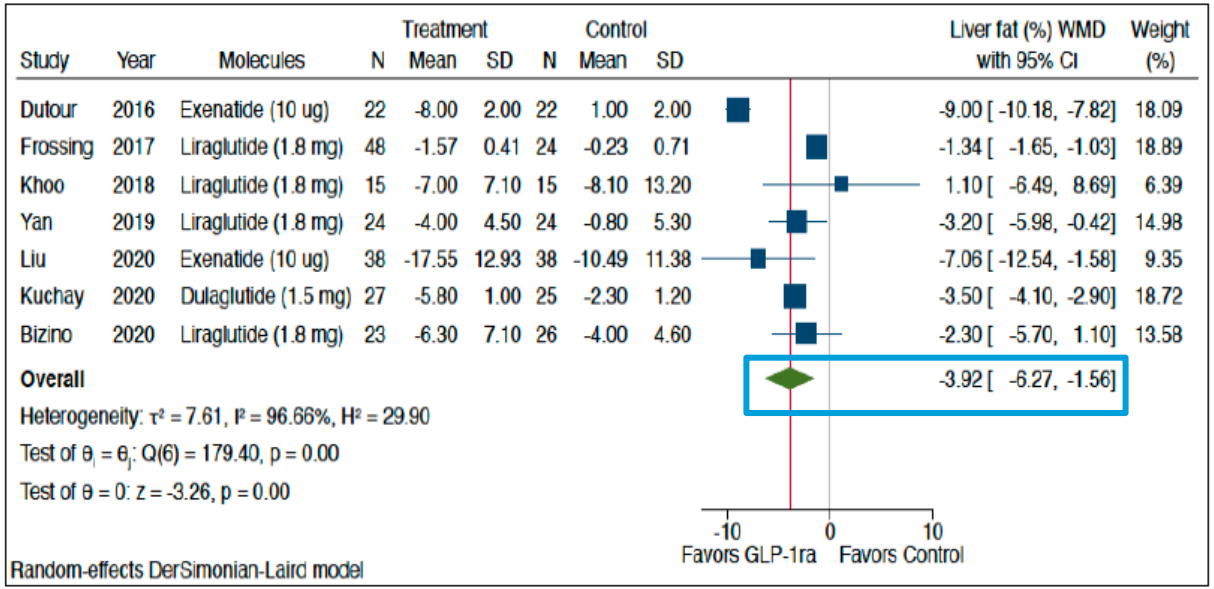




Riduzione LFC e dei livelli di GGT.
Miglioramento di AST e ALT.

Effetto di GLP-1 su NAFLD-NASH

Meta-analisi di 11 RCT (936 soggetti) con NAFLD/NASH, trattati con Liraglutide (6 RCT), exenatide (3 RCT) Dulaglutide (1 RCT) o semaglutide (1 RCT) studiati con biopsia (2 RCT) o imaging (9 RCT di cui 7 con RMN)



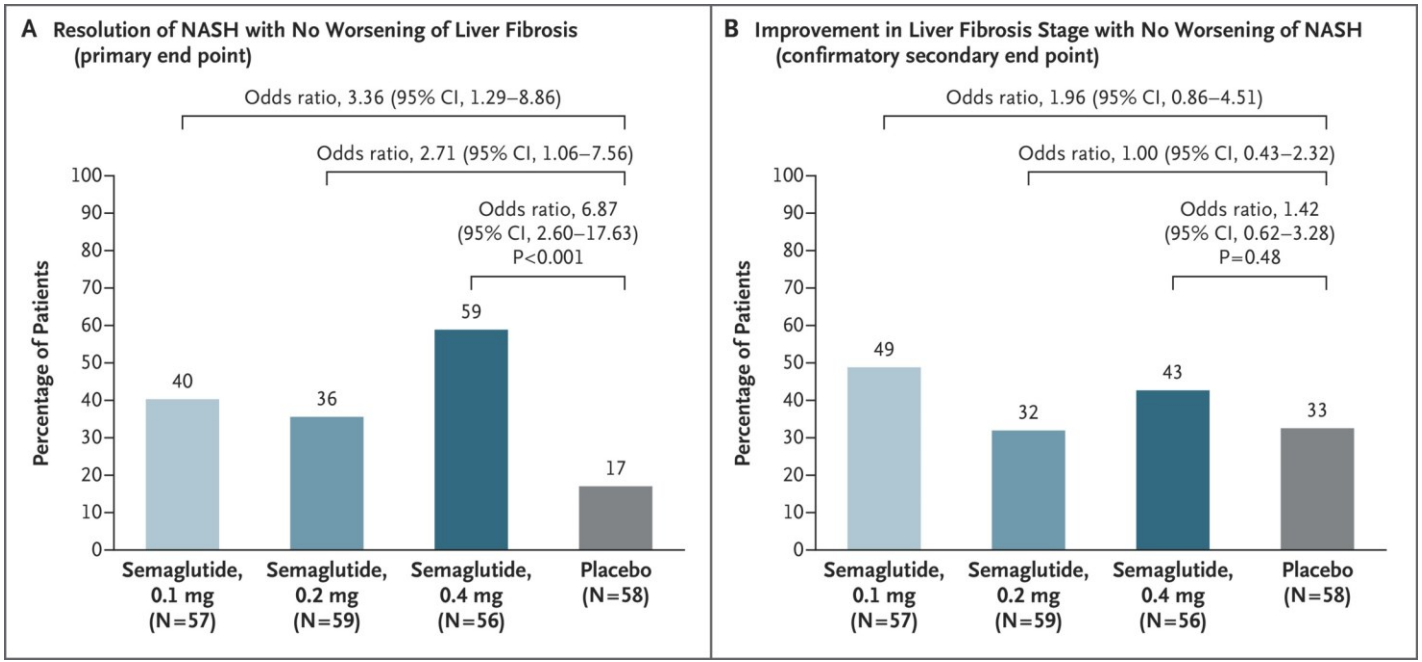
Mantovani et Al, Metabolites 2021

IL FUTURO


STEVEN SPIELBERG PRESENTS
BACK TO THE FUTURE
PG
A ROBERT ZEMECKIS FILM
OUTATIME

SEMAGLUTIDE VS PLACEBO in soggetti con NASH

Trial di fase 2 su 320 soggetti con NASH confermata alla biopsia e stadio di fibrosi epatica F1-F3 (età media 55 anni, BMI 36 kg/m2, 60% con DM2). Randomizzati a ricevere semaglutide iniettiva qd 0.1, 0.2, 0.4 mg o placebo, follow-up di 72 settimane.



Newsome PN e altri. N Engl J Med 2021;384:1113-1124

CO-AGONISTI

Two is meglio che One

Effetti combinati di GLP-1R e GIPR

GLP-1 Receptor Agonism

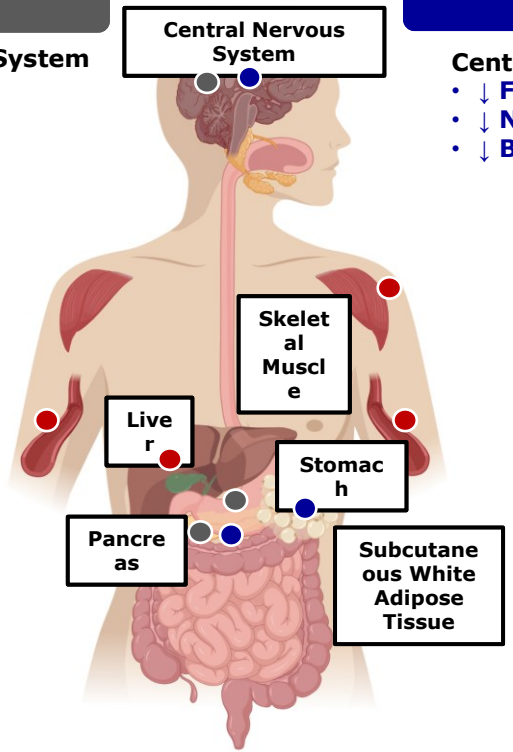
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



GIP Receptor Agonism

Central Nervous System
- ↓ Food intake
- ↓ Nausea
- ↓ Body weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

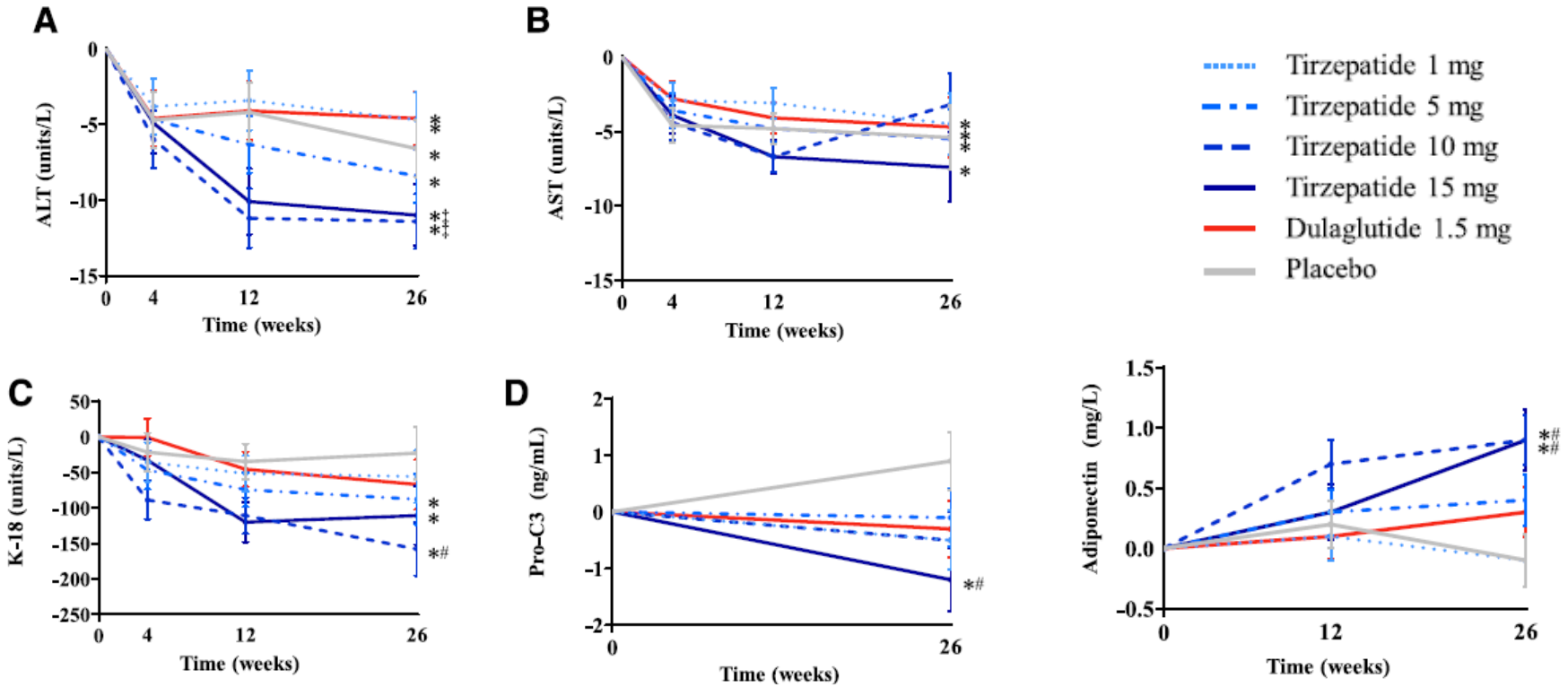
Systemic
- ↓ Hyperglycemia, Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

GLP-1 Receptor Agonism
GIP Receptor Agonism
Indirect Action

Adapted from: Samms RJ, et al. Trends Endocrinol Metab. 2020;31(6):410-421

TIRZEPATIDE su marker epatici in 316 soggetti DM2

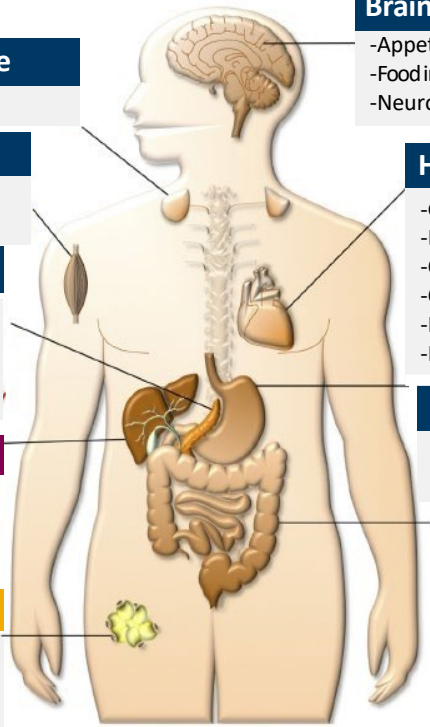


Diabetes Care 2020;43:1352–1355 | https://doi.org/10.2337/dc19-1892

Effetti combinati di GLP-1 e Glucagone:

GLP-1 effects: ↑

Glucagon effects: ↑ ↓



Brain
- -Appetite ↓↓
- -Food intake ↓↓
- -Neuroprotection ↑

Brown adipose tissue
- -Thermogenesis ↑

Muscle
- -Insulin sensitivity ↑
- -Glucose uptake ↑↓

Heart
- -Glucose utilization ↑
- -Lipid metabolism ↓
- -Cardiac function ↑
- -Cardioprotection ↑
- -Inflammation ↓
- -Heart rate ↑
- -Cardiomyocyte survival ↑

Pancreas
- - Insulin production ↑↑ ↓
- -β-cell proliferation ↑
- -β-cell apoptosis ↓
- -Secretion of glucagon

Stomach
- -Peristalsis ↓↓
- -Gastric emptying ↓

Liver
- -Gluconeogenesis ↓ ↑
- -Glycogenolysis ↓ ↑
- -Hepatic steatosis ↓
- -Bile acid production ↑
- -Lipid oxidation ↑
- -Lipid synthesis ↓

Intestine
- -Lipoprotein secretion ↓
- -Peristalsis ↓

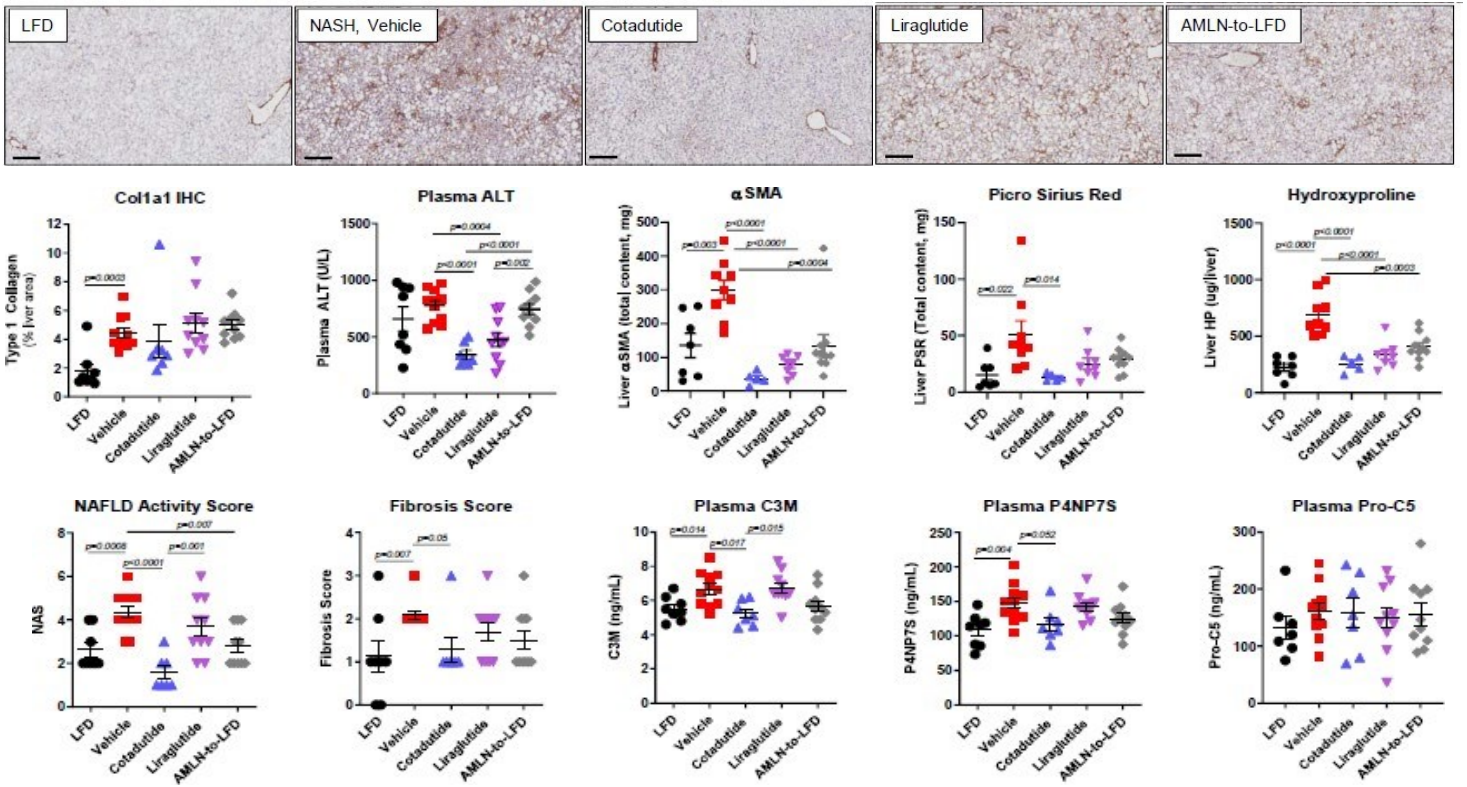
Adipose tissue
- -Lipogenesis ↓
- -Lipolysis ↑↑
- -Fat mass ↓↓

Müller et al. Physiol Rev 2017;97:721-766.

GLP-1, glucagon-like peptide-1.

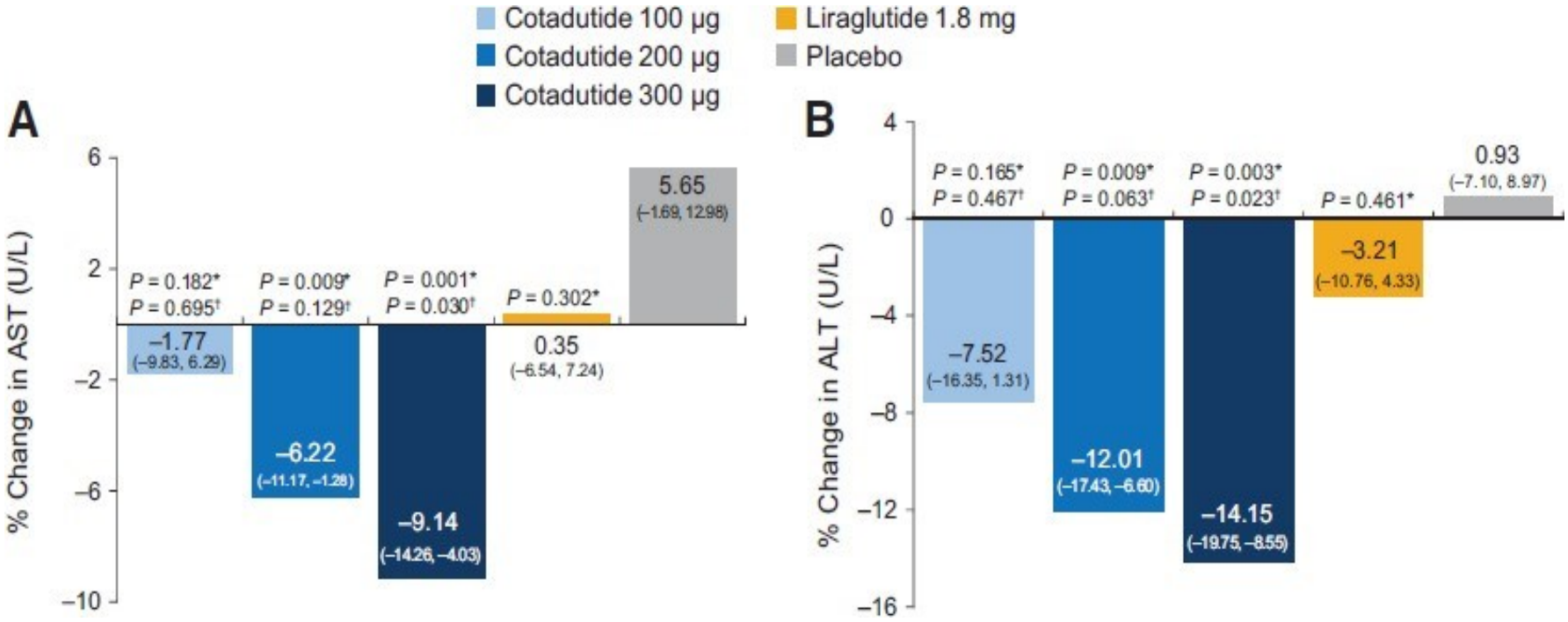
Dati preclinici con cotadutide in un modello di NASH

- Modello animale di NASH con fibrosi -> miglioramento di steatosi, infiammazione e fibrosi
- Fast Track FDA



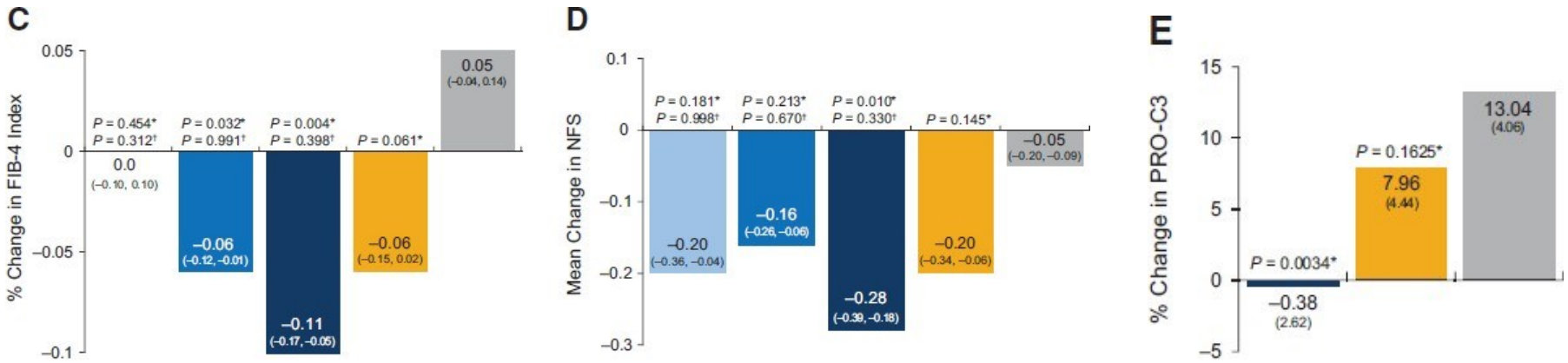
Boland et al. Resolution of NASH and Hepatic Fibrosis by the GL-1R/GcGR dual agonist Cotadutide via Modulation of Mitochondrial Function and Lipogenesis. Nature Metabolism. 2020 May: 2(5): 413-431

Cotadutide migliora AST/ALT in DM2



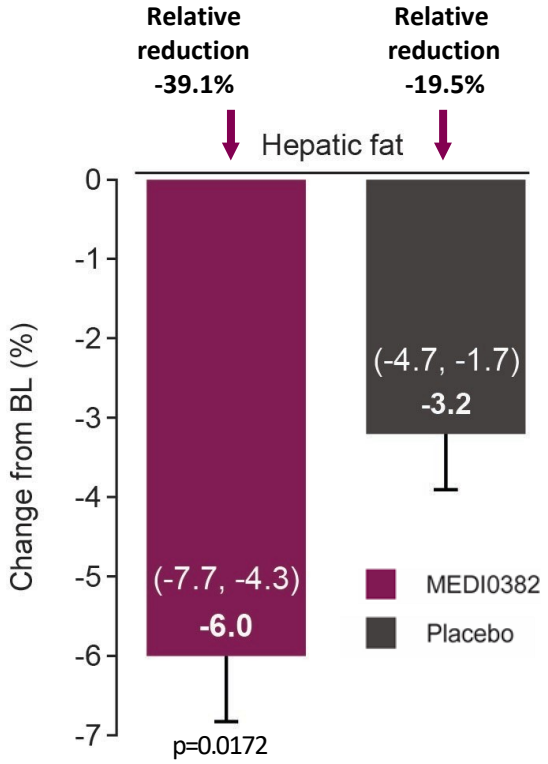
Nahra et al. Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults with Overweight or Obesity and Type 2 Diabetes: a 54-week Randomized Phase 2b Study. Diabetes Care 2021: 44 (1-10).

Cotadutide migliora indici di infiammazione epatica

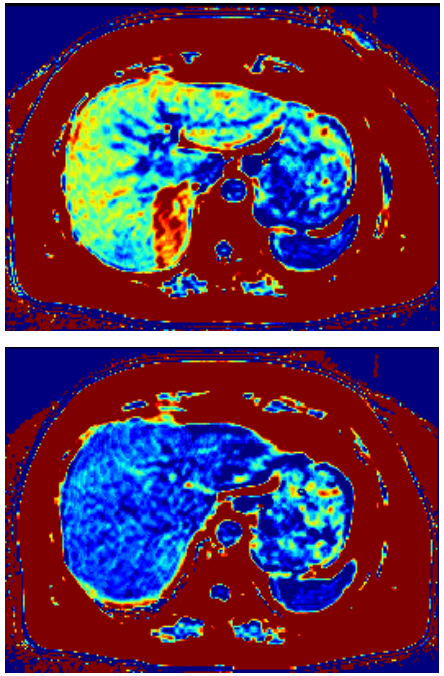


Nahra et al. Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults with Overweight or Obesity and Type 2 Diabetes: a 54-week Randomized Phase 2b Study. Diabetes Care 2021: 44 (1-10).

Cotadutide migliora steatosi epatica



MEDI0382-treated subject



Baseline
Hepatic fat: 10.1%

Day 41
Hepatic fat: 3.6%

0% 5% 10% 15% 20%

Results are least square means (90% confidence interval) ± standard error BL, baseline.

Ambery Pet al. Lancet.2018.

CONCLUSIONI

- La NAFLD è una patologia diffusa e sottodiagnosticata
- Utile screening e stratificazione del rischio
- Perdita di peso come PRIMO approccio terapeutico
- Necessaria una terapia sempre più sartoriale
- Conoscere le molecole per sfruttarne gli effetti pleiotropici


THE
DIABEATLES
GREATEST HITS


Grazie!