Management of NAFLD/NASH Most common Liver disease of present and Future IAGH Aban 1402

Reza Malekzadeh M.D AGAF

Professor of Medicine

TUMS/DDRI

NAFLD Most Global common Liver Disease

- The continuously increasing prevalence of excessive bodyweight in the world's population, combined with a sustained rise in life expectancy, has led nonalcoholic fatty liver disease (NAFLD) pathology to become the **number one burden of liver disease.**
- Indeed, an astonishing 20%–30% of the global adult population is affected by NAFLD, which frequently progresses to NASH in which excessive fat accumulation is accompanied by inflammation, hepatocyte ballooning, and even fibrosis.

NAFLD Epidemic

- The incidence of fatty liver disease is reaching epidemic levels in the world , with more than 30% of adults in US having NAFLD (non-alcoholic fatty liver disease).

- NAFLD can progress to more severe non-alcoholic steatohepatitis (NASH).

Definition of NAFLD

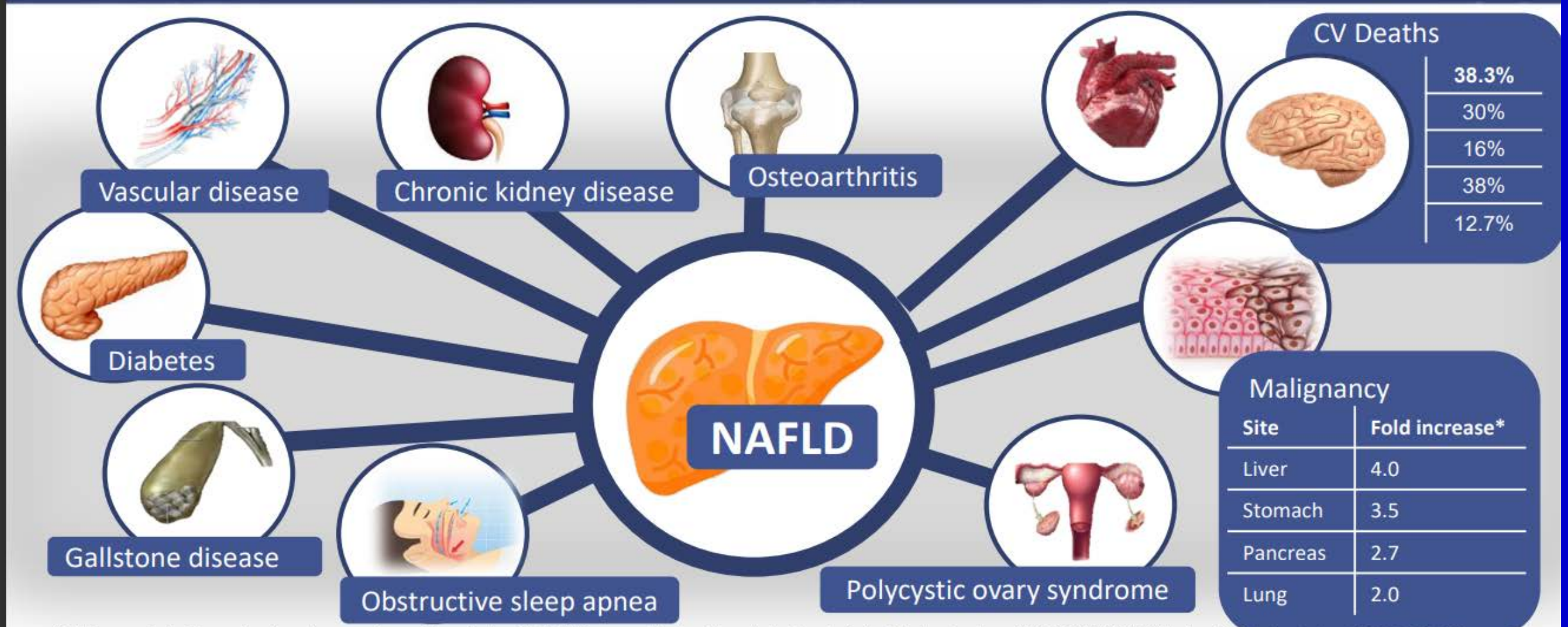
- **A cut-off of 5.5% hepatic steatosis has been accepted as the threshold to diagnose fatty liver, based upon the 95th centile of hepatic fat content in low risk subjects.**

- **NAFLD may begin in childhood in some individuals, with a prevalence of 10% found in an autopsy study of 2-19 year olds from the United States .**

- **The prevalence of NAFLD increases with advancing age with a peak between 40 and 69 years of age**

NAFLD is Part of A Multisystem Disorder

Non-Liver Related Outcomes of NAFLD



*Fold increase in incidence of malignant cancer diagnosis in patients with NAFLD compared to healthy controls. Angulo P et al. *Gastroenterology*. 2015;149:389–397; Söderberg C et al. *Hepatology*. 2010;51:595–602; Ekstedt M et al. *Hepatology*. 2006;44:865–873; Dam-Larsen S et al. *Scand J Gastroenterol*. 2009;44:1236–1243; Rafiq N et al. *Clin Gastroenterol Hepatol*. 2009;7:234–238; Hicks SB et al. Oral abstract presented at the AASLD Liver Meeting; 31; 11 November 2018; San Francisco, USA.

عوارض مهم و خطرناک بیماری کبد چرب متابو لیک که علل اصلی مرگهای زودرس در ایران محسوب میشوند

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- فیبروز کبدی (سیروز کبدی جبران شده)، سیروز کبدی پیشرفته (جبران نشده)
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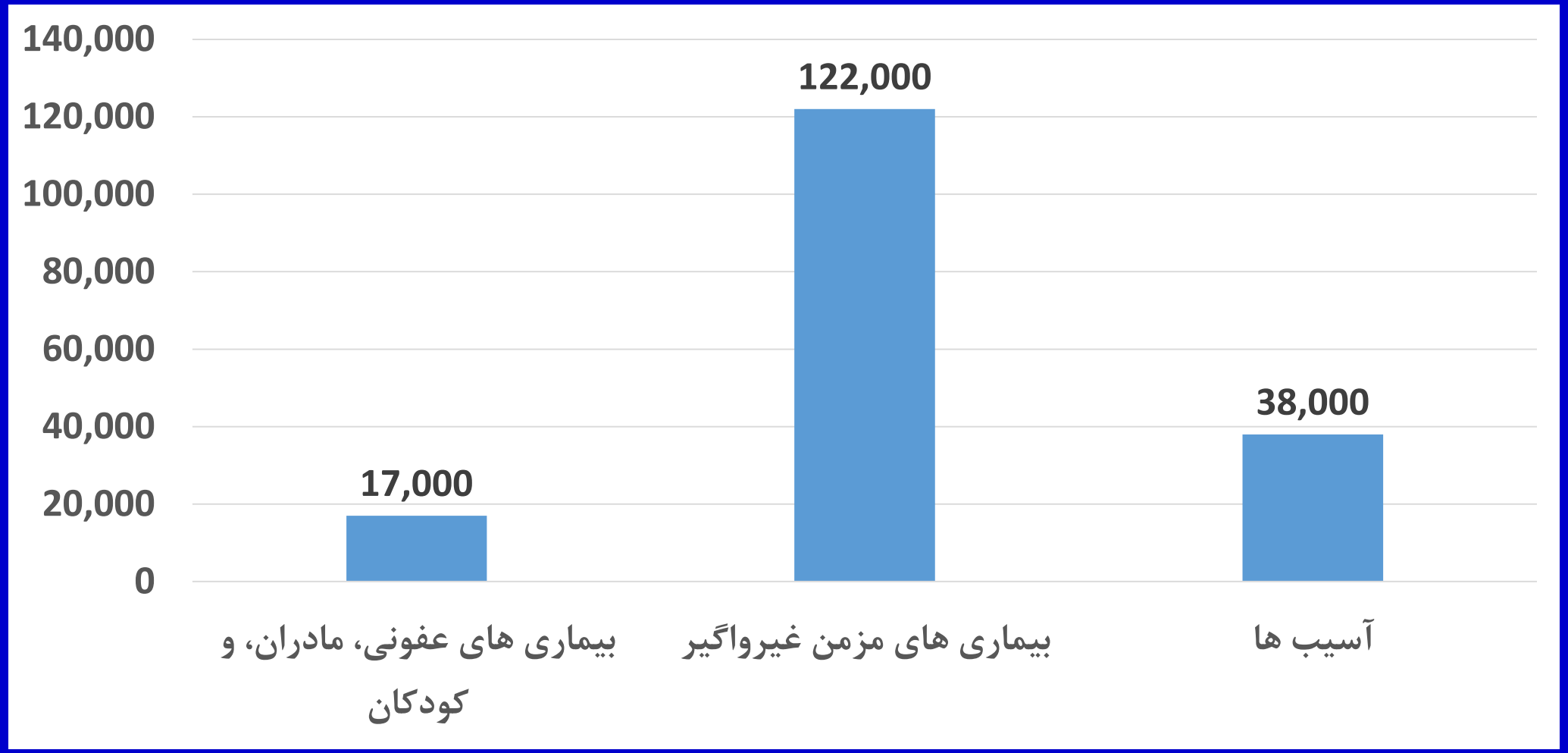

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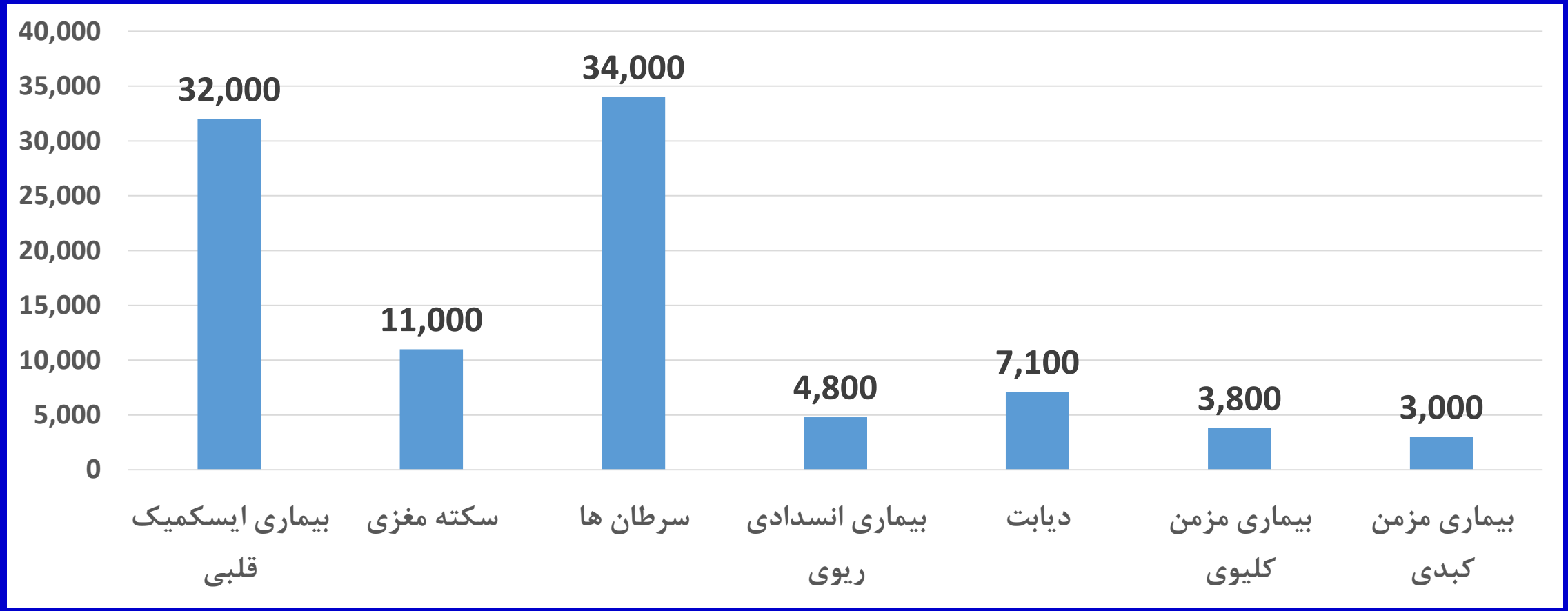


NAFLD Clinical Presentation

- Symptoms
  - **Usually asymptomatic**, majority discovered by chance
  - Fatigue frequently present
- Often an "incidental finding"
  - Incidental abnormal liver enzymes
  - Incidental "bright liver" on imaging
  - Incidental hepatomegaly
- Common scenarios
  - Statin monitoring
  - "Annual reviews" in T2DM/ lipid/hypertension clinics
  - Medical insurance/occupational health checks

de Alwis. Dig Dis. 2016;34:19.

To Screen or Not to Screen for NAFLD?

AASLD Guidance[1]

- **Type 2 diabetes**
  - Have high index of suspicion for NAFLD and NASH; risk stratify with NFS, FIB-4, VCTE
- **Other risk factors for NAFLD**
  - Uncertain long-term benefits, cost-effectiveness of routine screening for NAFLD

EASL-EASD-EASO Guidelines[2]

- **High CV risk**
  - Screening for NAFLD recommended

❑ **Low Platelate count may be an indication for live fibrosis secondary to NAFLD/NASH**

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.

Evaluation: NAFLD is a Diagnosis of Exclusion

Alternative causes of steatosis[1]

- Alcohol
- Hepatitis B,C virus.
- Lipodystrophy
- Medications
- Malnutrition
- Hereditary disorders
  - Wilson disease (check 24-hr urine copper[2])
  - Hypobetalipoproteinemia (check ApoB)
  - Lysosomal acid lipase deficiency

Also exclude other causes of liver disease as coexisting etiologies

1. Chalasani. Hepatology. 2018;67:328. 2. Roberts. Hepatology. 2008;47:2089.

Normal Liver Enzymes Do Not Rule Out NASH

- **NAFLD is the most common diagnosis in patients with "incidental" abnormal liver enzymes such as ALT, AST**[1-3]

However:

- **Liver enzymes may be normal in ~ 80% of NAFLD patients**[4,5]
  - ALT and AST not sensitive for NAFLD/NASH
  - Poor correlation between ALT and histology
    - ALT typically decreases with advanced fibrosis
    - As NASH progresses, AST/ALT ratio may increase (ie, ALT < AST)
- Histology severity similar in NAFLD patients with normal vs abnormal liver enzymes[6-8]

1. Daniel. Am J Gastroenterol. 1999;94:3010. 2. Skelly. J Hepatol. 2001;35:195. 3. Pendino. Hepatology. 2005;41:1151.
4. Browning. Hepatology. 2004;40:1387. 5. Dyson. Frontline Gastroenterol. 2014;5:211. 6. Mofrad. Hepatology. 2003;37:1286.
7. Sorrentino. J Hepatol. 2004;41:751. 8. Fracanzani. Hepatology. 2008;48:792.

Main Challenge in NAFLD Care

- **The most challenging part is the lack of awareness about this liver disease.**
- **There is a tremendous lack of awareness about NAFLD and NASH amongst all Physician and public .**

- **The most common and important liver disease that impacts not only clinical outcomes, but also quality of life and we need to make sure that we address that.”**

Lack of awareness among Physician

- There is a urgent need to identify patients at risk for significant liver disease to give them proper care.

- A recent global survey of over 3,000 providers like primary care, endocrinologists, gastroenterologists and hepatologists suggested a lack of awareness among front line providers who see most of these patients .
- A lot of these patients are not getting identified in clinical practices

Global Delphi study, a multidisciplinary group of 218 experts developed consensus statements

CONSENSUS STATEMENT

Check for updates

Advancing the global public health agenda for NAFLD: a consensus statement

Abstract | Non-alcoholic fatty liver disease (NAFLD) is a potentially serious liver disease that affects approximately one-quarter of the global adult population, causing a substantial burden of ill health with wide-ranging social and economic implications. It is a multisystem disease and is considered the hepatic component of metabolic syndrome. Unlike other highly prevalent conditions, NAFLD has received little attention from the global public health community. Health system and public health responses to NAFLD have been weak and fragmented, and, despite its pervasiveness, NAFLD is largely unknown outside hepatology and gastroenterology. There is only a nascent global public health movement addressing NAFLD, and the disease is absent from nearly all national and international strategies and policies for non-communicable diseases, including obesity. In this global Delphi study, a multidisciplinary group of experts developed consensus statements and recommendations, which a larger group of collaborators reviewed over three rounds until consensus was achieved. The resulting consensus statements and recommendations address a broad range of topics — from epidemiology, awareness, care and treatment to public health policies and leadership — that have general relevance for policy-makers, health-care practitioners, civil society groups, research institutions and affected populations. These recommendations should provide a strong foundation for a comprehensive public health response to NAFLD.

NATURE REVIEWS | October 2021

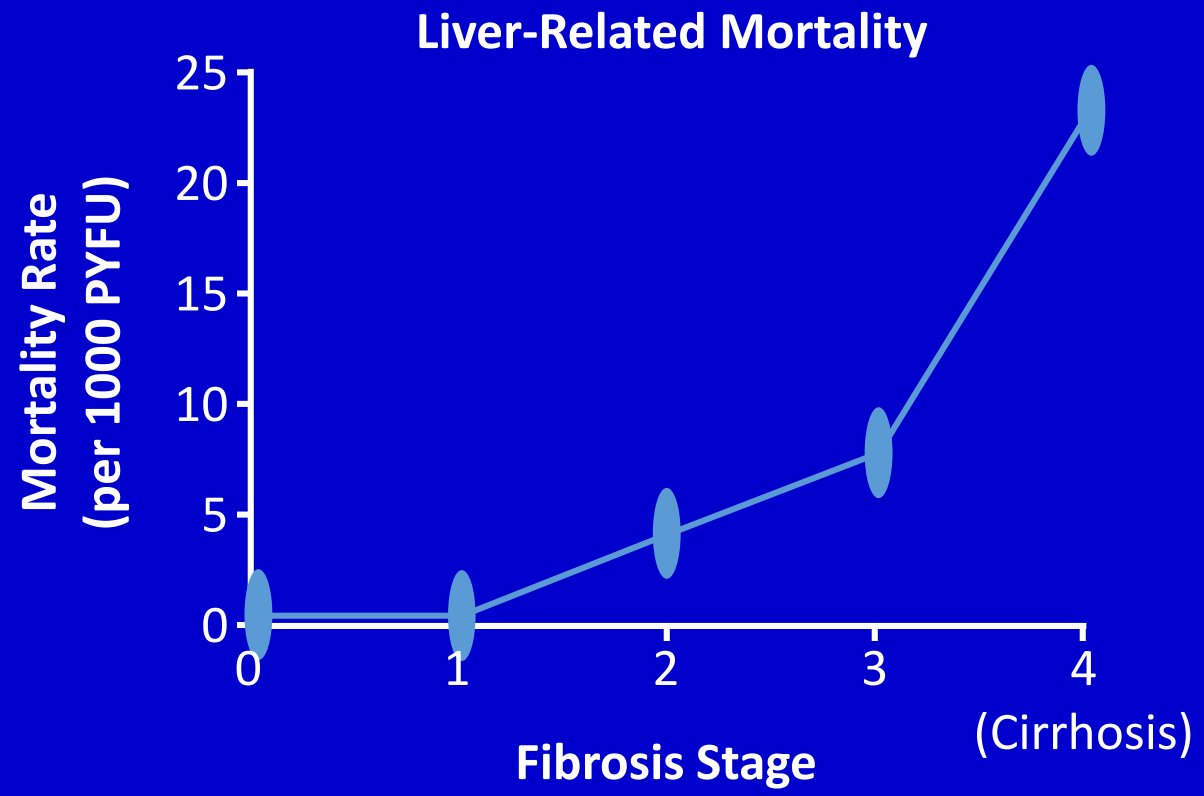
Another challenge is conducting risk stratification for NAFLD patients

- Using noninvasive tests and linking patients at high risk to gastrointestinal and hepatology care.

- COVID-19 seems more aggressive in patients with visceral obesity, especially morbid obesity, and these poor outcomes may be seen in patients with NAFLD and NASH.
- .

NAFLD: Quantitative Risk of Liver Mortality by Fibrosis Stage

- Meta-analysis of 5 cohort studies with N = 149 patients with NAFLD followed for 17,452 patient-yrs
- Liver-related mortality exponentially increased with fibrosis stage



Dulai. Hepatology. 2017;65:1557.

Liver biopsy is not the ideal way for NFLD diagnosis and risk stratification

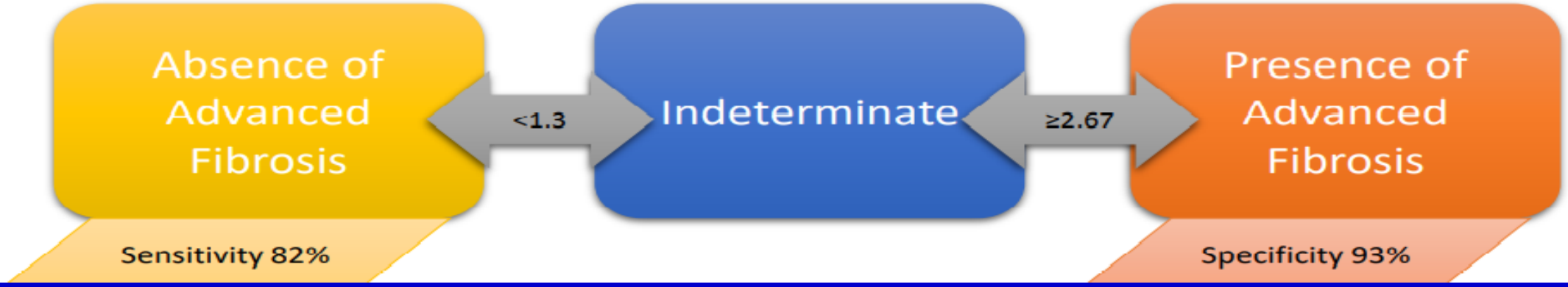
- Liver biopsy was relied on the most for diagnosing and staging NASH but it is not practical to perform biopsy on every patient.
- Biopsies may be expensive, have modest risk and patients may not accept them.
- Therefore, it is not the ideal way to diagnose patients, according to Fried.

Non-invasive markers are acceptable for long-term outcomes related to liver disease, cardiovascular disease, liver cancer and mortality

- Age, diabetes, AST, ALT, Platelet count, and Albumin create a reliable risk score for likelihood of advanced fibrosis.
- liver ultrasounds combined with transient elastography equipment such as FibroScan can assess liver elasticity as well as fatty liver disease.
- T1 weighted MRI elastography, the stiffness test for measuring potential correlation with fibrosis.

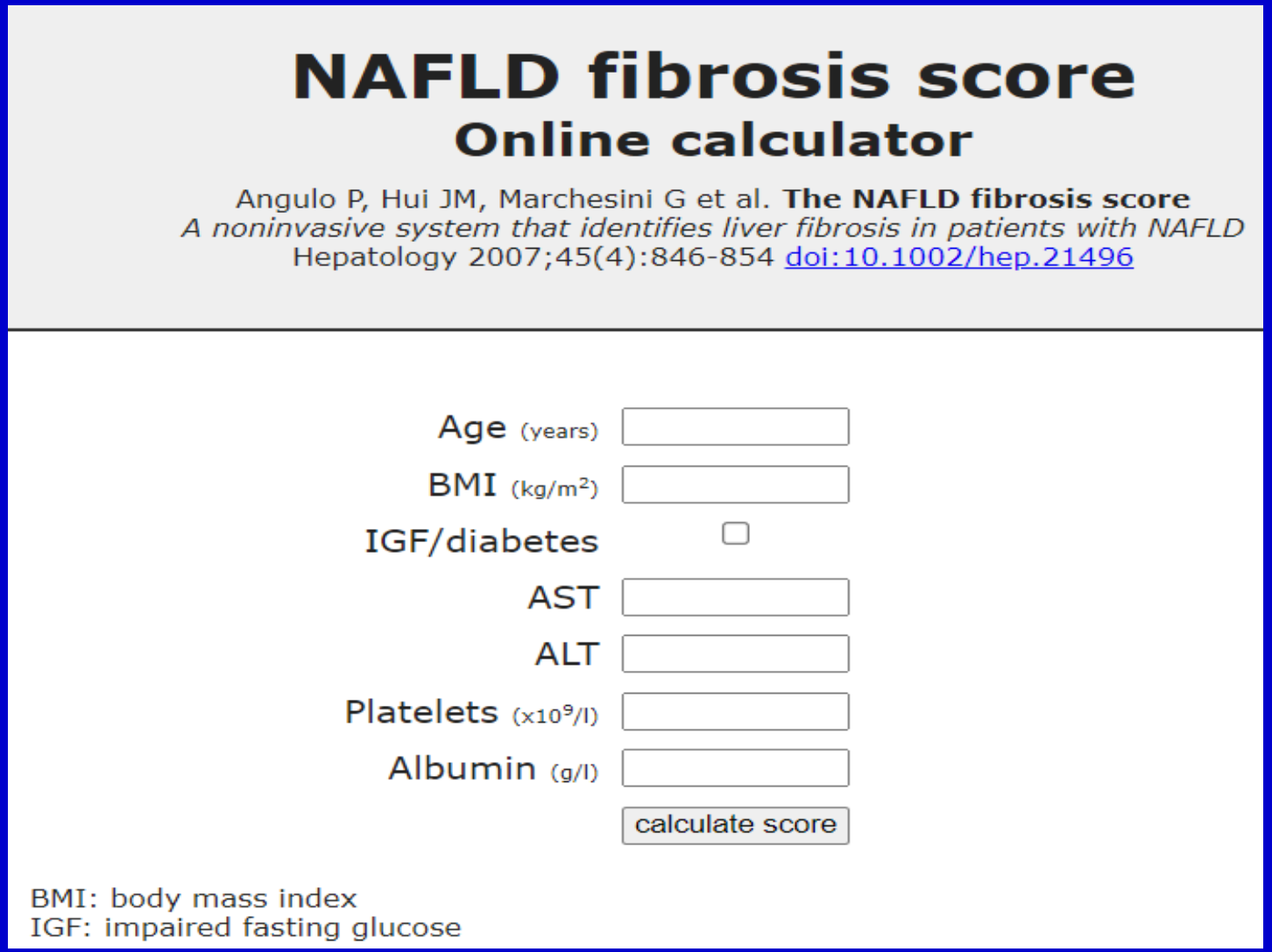
FIB-4

- Can be calculated in the office with easily available variables
  - Age, platelet count, ALT, AST
- Useful in identifying patients with a higher likelihood of F3 or F4
- AUROC 0.78 (95% CI: 0.78-0.78)



Anstee QM, Lawitz EJ, Alkhouri N, et al. Noninvasive Tests Accurately Identify Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials. Hepatology. 2019;70(5):1521-1530.

https://nafldscore.com/



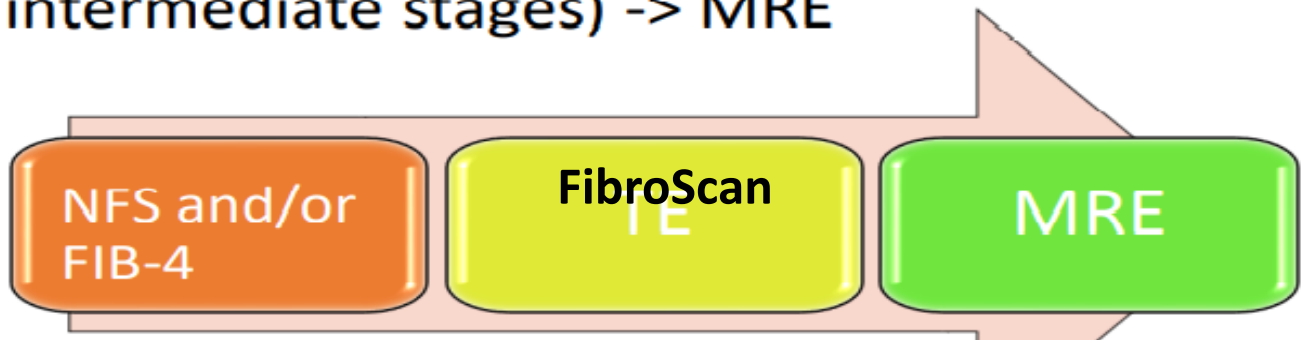
Other Scoring Systems

- FibroSure/FibroTest
  - Proprietary serum
    - Haptoglobin, α2-macroglobin, apoplipoprotien A1, total bilirubin, and GGT
- Enhanced Liver Fibrosis (ELF) Score
  - Combines three biomarkers: hyaluronic acid, tissue inhibitor of metalloproteinase 1, amino-terminal peptide of procollagen III
- Aspartate aminotransferase/Platelet Ratio Index (APRI)
  - Higher sensitivity than specificity
- BARD Score
  - BMI, AST, ALT, Diabetes
  - Strong negative predictive value to rule out fibrosis

Anstee QM, Lawitz EJ, Alkhouri N, et al. Noninvasive Tests Accurately Identify Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials. Hepatology. 2019;70(5):1521-1530

Sequential Use of NIT

- NFS and FIB-4
  - Better than other indices
  - As good as MRE
- Sequential use can improve diagnosis
  - Rule in/out with NFS and/or FIB-4
  - If intermediate to high risk -> TE
    - If failure (obesity, intermediate stages) -> MRE



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Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019;156(5):1264-1281.e4. doi:10.1053/j.gastro.2018.12.036

New and more powerful Test in future

- Detecting new proteins that may reflect the disease state , this technology that measures many proteins in blood may help NASH disease state and fibrosis grading.
- Measurement of nanoparticles in the urine that are cleaved in a very selective way and excreted.
- Artificial intelligence-based digital pathology methods to quantify the different features of a liver biopsy.

Point of care Test for NAFLD

- In addition to blood test Ultrasonography and transient elastography (TE), can serve as t a point of care test that can be used in a clinical setting.
- TE is much more practical in the clinical setting although MR elastography is the most accurate technology, it is less available and more expensive than TE.
- We are moving toward a future where we will not need a liver biopsy.

Best therapy for NAFLD/NASH

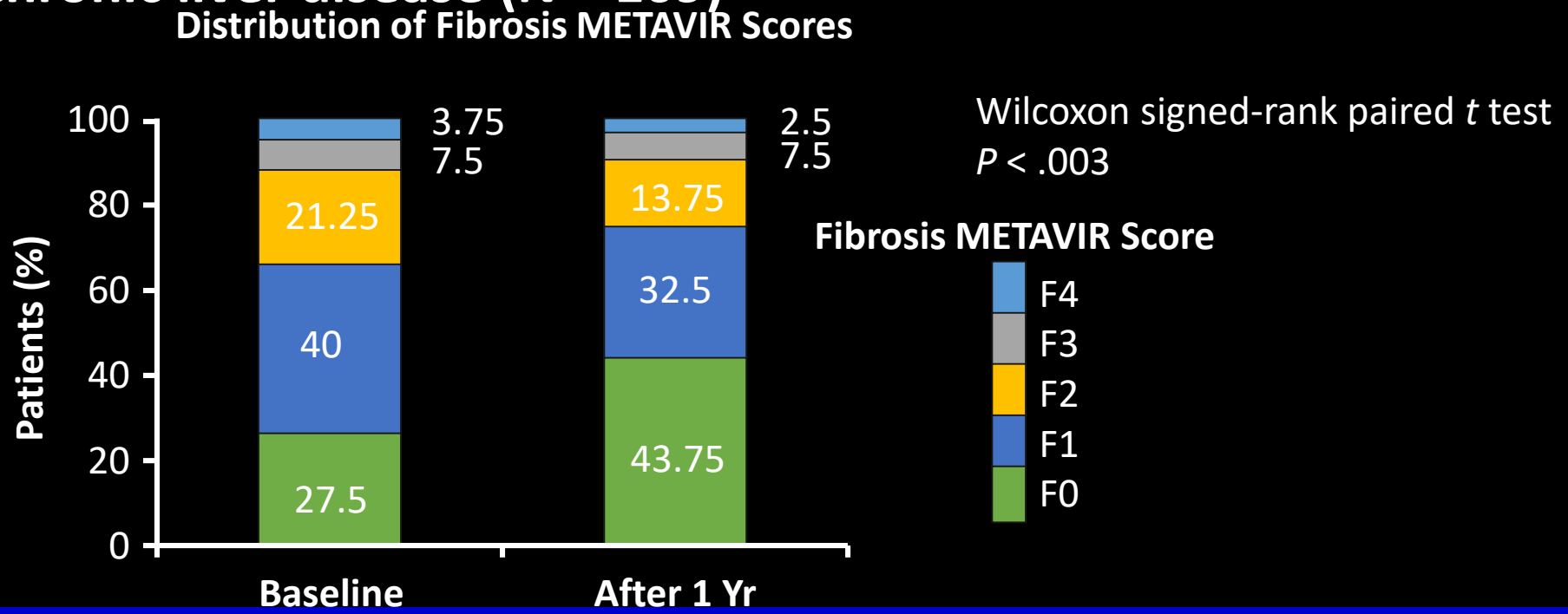
- Lifestyle modification and 10% weight loss is the best treatment option available for NAFLD and NASH.

- 10% weight loss, emphasizing dietary changes, steady weight loss, physical activity most effective therapy

- Patients would have to lose 10% of their baseline weight, which is both difficult to achieve and maintain in the long term.

Bariatric Surgery Improves Fibrosis in Patients With NASH

- **Prospective study of bariatric surgery in patients who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)**



Lassailly G, et al. Gastroenterology. 2015;149:379-388.

Pharmacotherapy

- No pharmacological agent is FDA-approved for the treatment of NASH.
- Patients with T2DM may benefit from some diabetes medications, such as pioglitazone and some GLP-1 RAs that have reported histological improvement in RCTs in patients with NASH, either with or without diabetes.
- Among GLP-1 RAs, semaglutide has the strongest evidence of liver histological benefit .
- Pharmacotherapy in patients with NASH cirrhosis is very limited and should be avoided until more data become available.

SGLT2 inhibitor in Iran

- **Empagliflozin (Gloripa** (Abidi):First SGLT2 inhibitor drug manufactured inside Iran.
- Effective for T2DM,prevention of CVD,CHF and CKD
- Gloripa" should be taken just once every 24 hours , and 10 milligram and 25 milligram capsules are available.
- **Dapagliflozin**:

Statin is Safe in NASH and fibrosis

- Vitamin E improves steatohepatitis in patients with NASH without diabetes , with less evidence in patients with T2D 81.

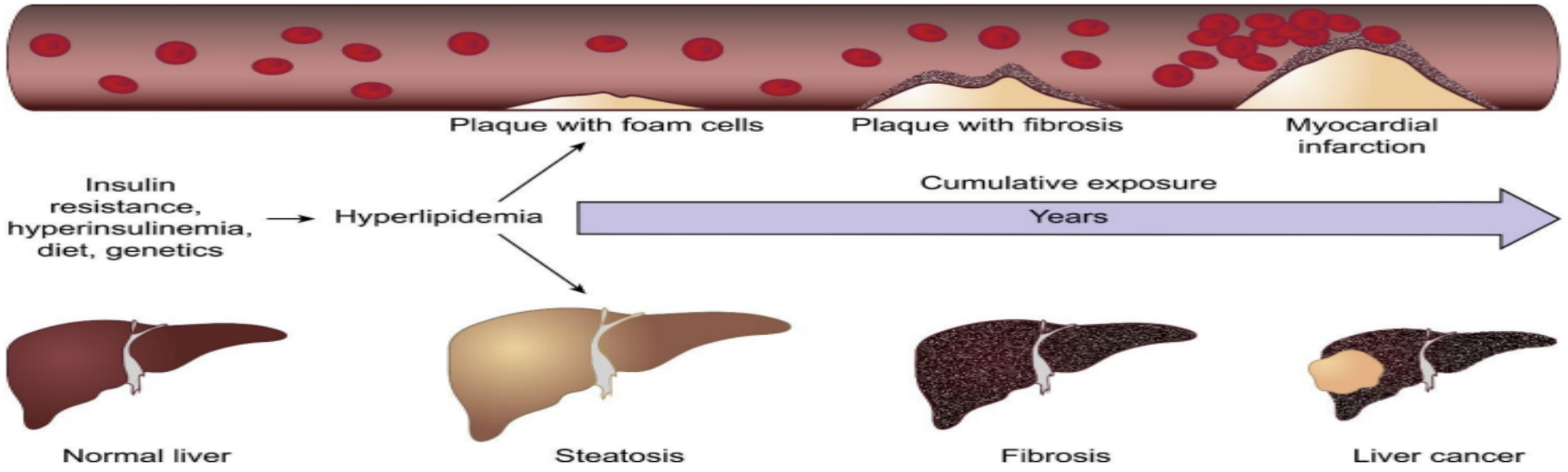
- Statins can be used safely in patients with steatohepatitis and liver fibrosis; to be avoided in decompensated cirrhosis.

What is target LDL-Cholesterol level in NAFKD/NASH

The target level of LDL cholesterol is **50**

CVD the most common cause of death in NASH

Parallel between the Development and Progression of Atherosclerosis and NAFLD



- NASH, atherosclerosis and T2DM share many common pathogenic features which are expected to drive common diagnostic tools
- Therapies that will beneficially affect all of these end- organ diseases will emerge as the first- line treatments

Romeo et al Cell Metab 2020

Liver and overall mortality among NAFLD and NASH

- **Liver-specific mortality** among NAFLD and NASH were 0.77 per 1,000 (range, 0.33- 1.77) and 11.77 per 1,000 person-years (range, 7.10-19.53)

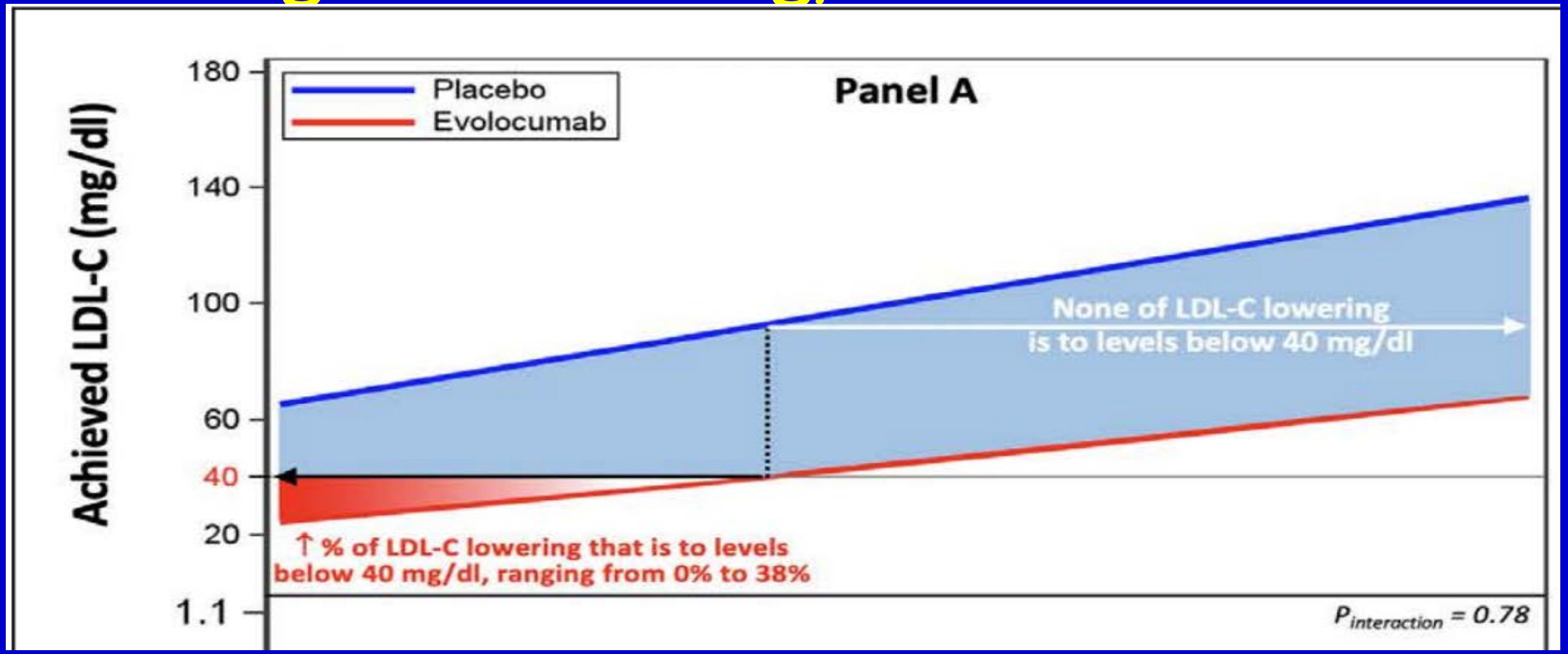
- **Overall mortality** among NAFLD and NASH were **15.44 per 1,000** (range, 11.72-20.34) and 25.56 per 1,000 person-years (range, 6.29-103.80).

HEPATOLOGY, VOL. 64, NO. 1, 2016

LDL Target level target of <55 mg/dL in patients with high risk CVD

- The 2019 **European** Society of Cardiology/ European Atherosclerosis Society Dyslipidemia Guidelines go further and recommend an LDL-C goal of <55 mg/dL for patients with very high-risk ASCVD and to consider an even lower goal of <40 mg/dL for patients with multiple cardiovascular events within 2 years despite optimal statin therapy.2

Cardiovascular benefit of continued LDL-C lowering below 40 mg/dl



Standard expected years of life lost due to premature death

Causes of premature death	SEYLL (SE)	%
Ischaemic heart diseases	32 466 (218)	33.74
Stroke	13 004 (135)	13.52
Road injury	5160 (89)	5.36
Oesophageal cancer	4301 (78)	4.47
Stomach cancer	4220 (71)	4.39
Chronic obstructive pulmonary diseases	2972 (59)	3.09
Kidney diseases	2295 (58)	2.39
Cirrhosis of the liver	1866 (55)	1.94
Trachea, bronchus, lung cancers	1711 (47)	1.78
Pancreas cancer	1483 (42)	1.54
All*	96 219 (376)	100

PolyIran trial with Editorial, Commentary and Press release

Articles

Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial

Gholamreza Roshandel, Masoud Khoshnia*, Hossein Poustchi*, Karla Hemming, Farin Kamangar, Abdolsamad Gharavi, Mohammad Reza Ostovaneh, Alireza Nateghi, Masoud Majed, Behrooz Navabakhsh, Shahin Merat, Akram Pourshams, Mahdi Nalini, Fatemeh Malekzadeh, Masoumeh Sadeghi, Noushin Mohammadifard, Nizal Sarrafzadegan, Mohammad Naemi-Tabiei, Abdolreza Fazel, Paul Brennan, Arash Etemadi, Paolo Boffetta, Neil Thomas, Tom Marshall, Kar Keung Cheng, Reza Malekzadeh*

Lancet 2019; 394: 672–83

See Editorial page 611

See Comment page 617

*Contributed equally as joint lead authors

Digestive Disease Research Center (G Roshandel PhD, M Khoshnia MD, H Poustchi PhD, A Gharavi MD, M R Ostovaneh MD, A Nateghi PhD, M Majed MD, B Navabakhsh MD, Prof A Pourshams MD, M Nalini PhD, F Malekzadeh MD

Summary

Background A fixed-dose combination therapy (polypill strategy) has been proposed as an approach to reduce the burden of cardiovascular disease, especially in low-income and middle-income countries (LMICs). The PolyIran study aimed to assess the effectiveness and safety of a four-component polypill including aspirin, atorvastatin, hydrochlorothiazide, and either enalapril or valsartan for primary and secondary prevention of cardiovascular disease.

Methods The PolyIran study was a two-group, pragmatic, cluster-randomised trial nested within the Golestan Cohort Study (GCS), a cohort study with 50 045 participants aged 40–75 years from the Golestan province in Iran. Clusters (villages) were randomly allocated (1:1) to either a package of non-pharmacological preventive interventions alone (minimal care group) or together with a once-daily polypill tablet (polypill group). Randomisation was stratified by three districts (Gonbad, Aq-Qala, and Kalaleh), with the village as the unit of randomisation. We used a balanced randomisation algorithm, considering block sizes of 20 and balancing for cluster size or natural log of the cluster size (depending on the skewness within strata). Randomisation was done at a fixed point in time (Jan 18, 2011) by

PolyPill Liver Study Nested in GCS

ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–11
https://doi.org/10.1093/eurheartj/ehab919

CLINICAL RESEARCH
Clinical trials

Polypill for prevention of cardiovascular diseases with focus on non-alcoholic steatohepatitis: the PolyIran-Liver trial

Shahin Merat [1,2†], Elham Jafari [1,3†], Amir Reza Radmard [4], Masoud Khoshnia [5], Maryam Sharafkhah [1], Alireza Nateghi Baygi [6], Tom Marshall [7], Abolfazl Shiravi Khuzani [4], Kar Keung Cheng [7], Hossein Poustchi [1,2*], and Reza Malekzadeh [1,2,3*]

[1]Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran; [2]Digestive Disease Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Shariati Hospital, Tehran 1411713135, Iran; [3]Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran; [4]Department of Radiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran; [5]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran; [6]Research and Development Department, Alborz-Darou Pharmaceutical Co., Ghazvin, Iran; and [7]School of Health and Population Sciences, University of Birmingham, Birmingham, UK

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Aims Individuals with non-alcoholic steatohepatitis or elevated liver enzymes have increased cardiovascular mortality but are often excluded from prevention trials. We investigated the effectiveness of fixed-dose combination therapy for the prevention of major cardiovascular events (MCVE) among individuals with and without presumed non-alcoholic steatohepatitis (pNASH).

Methods and results Two thousand four hundred participants over 50 were randomized into the intervention and control groups. Consent was obtained post-randomization. Consenting participants in the intervention group were given a pill containing aspirin, atorvastatin, hydrochlorothiazide, and valsartan (polypill). Participants were followed for 5 years. Presumed non-alcoholic steatohepatitis was diagnosed by ultrasonography and elevated liver enzymes. The primary outcome was MCVE. ClinicalTrials.gov: NCT01245608. Among the originally randomized population, 138 of 1249 in the intervention group (11.0%) and 137 of 1017 controls (13.5%) had MCVE during the 5-year follow-up [unadjusted risk ratio (RR) 0.83, 95% confidence interval (CI) 0.66–1.03]. Of the 1508 participants who consented to additional measurements and treatment, 63 of 787 (8.0%) intervention group participants and 86 of 721 (11.9%) controls had MCVE (adjusted RR 0.61, 95% CI 0.44–0.83). Although the adjusted relative risk of MCVE in participants with pNASH (0.35, 95% CI 0.17–0.74) was under half that for participants without pNASH (0.73, 95% CI 0.49–1.00), the difference did not reach statistical significance. There was no change in liver enzymes in participants taking polypill but among those with pNASH, there was a significant decrease after 60 months of follow-up (intragroup −12.0 IU/L, 95% CI −14.2 to −9.6).

Conclusion Among patients consenting to receive fixed-dose combination therapy, polypill is safe and effective for the prevention of MCVE, even among participants with fatty liver and increased liver enzymes.

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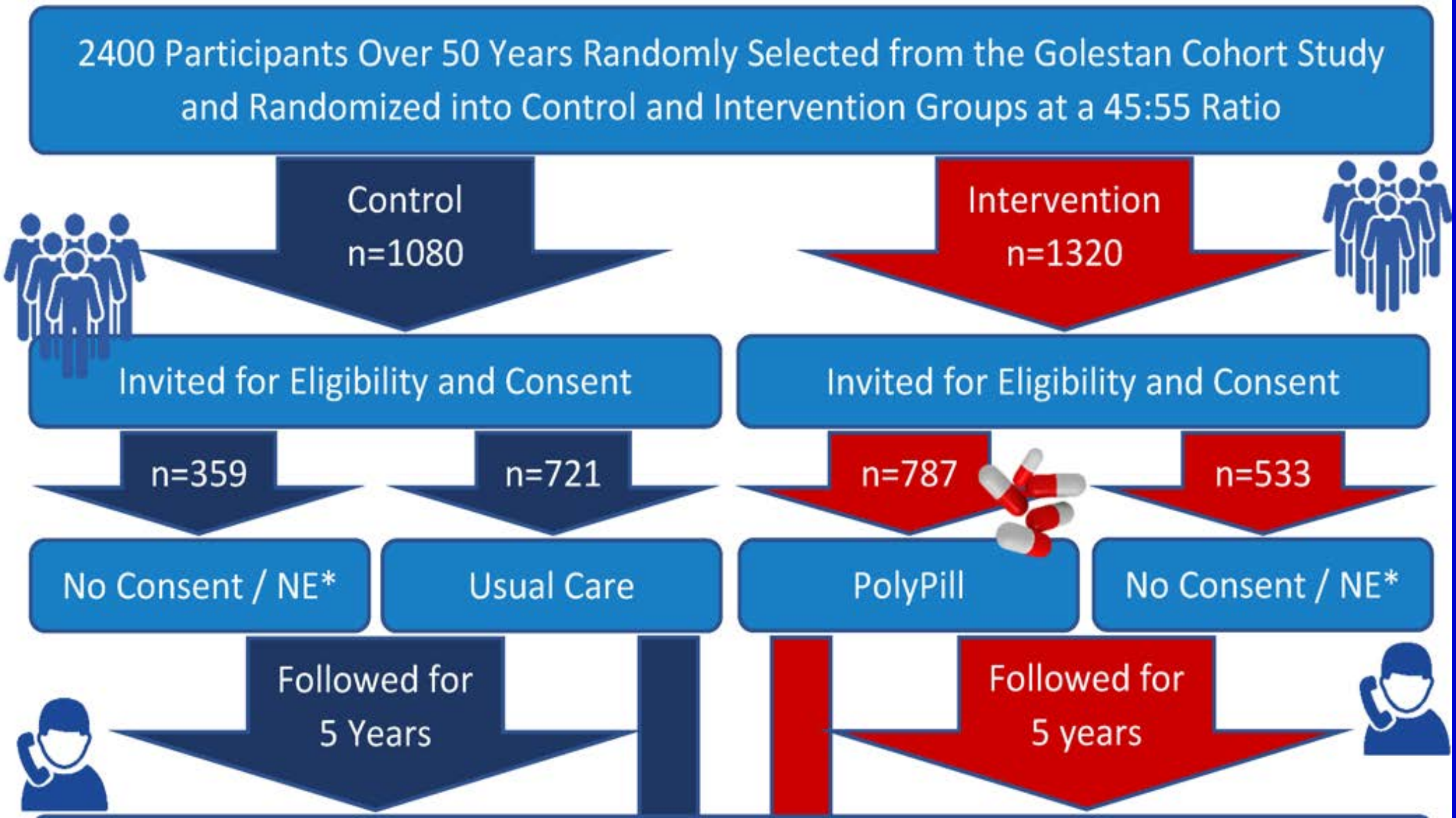
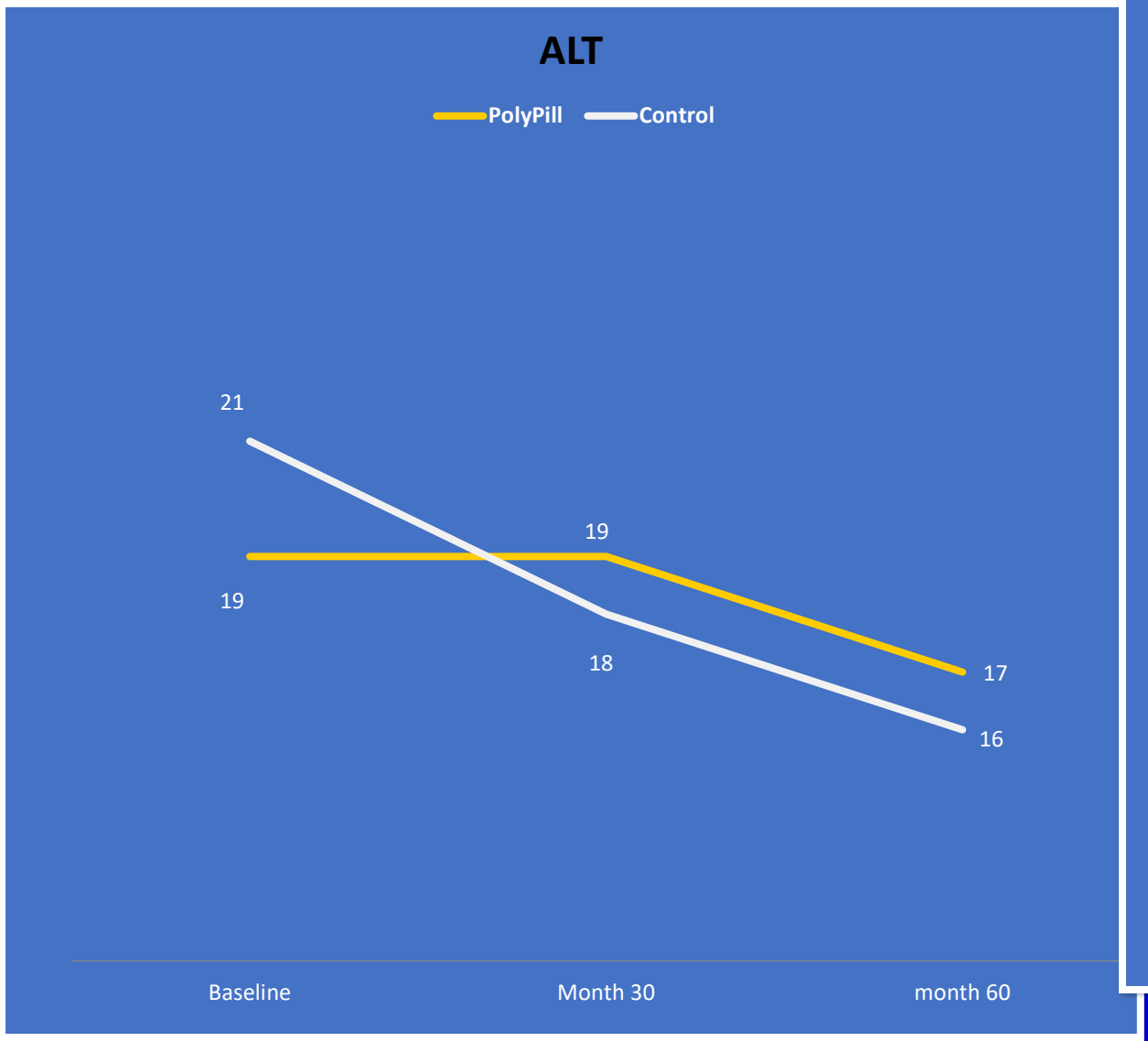
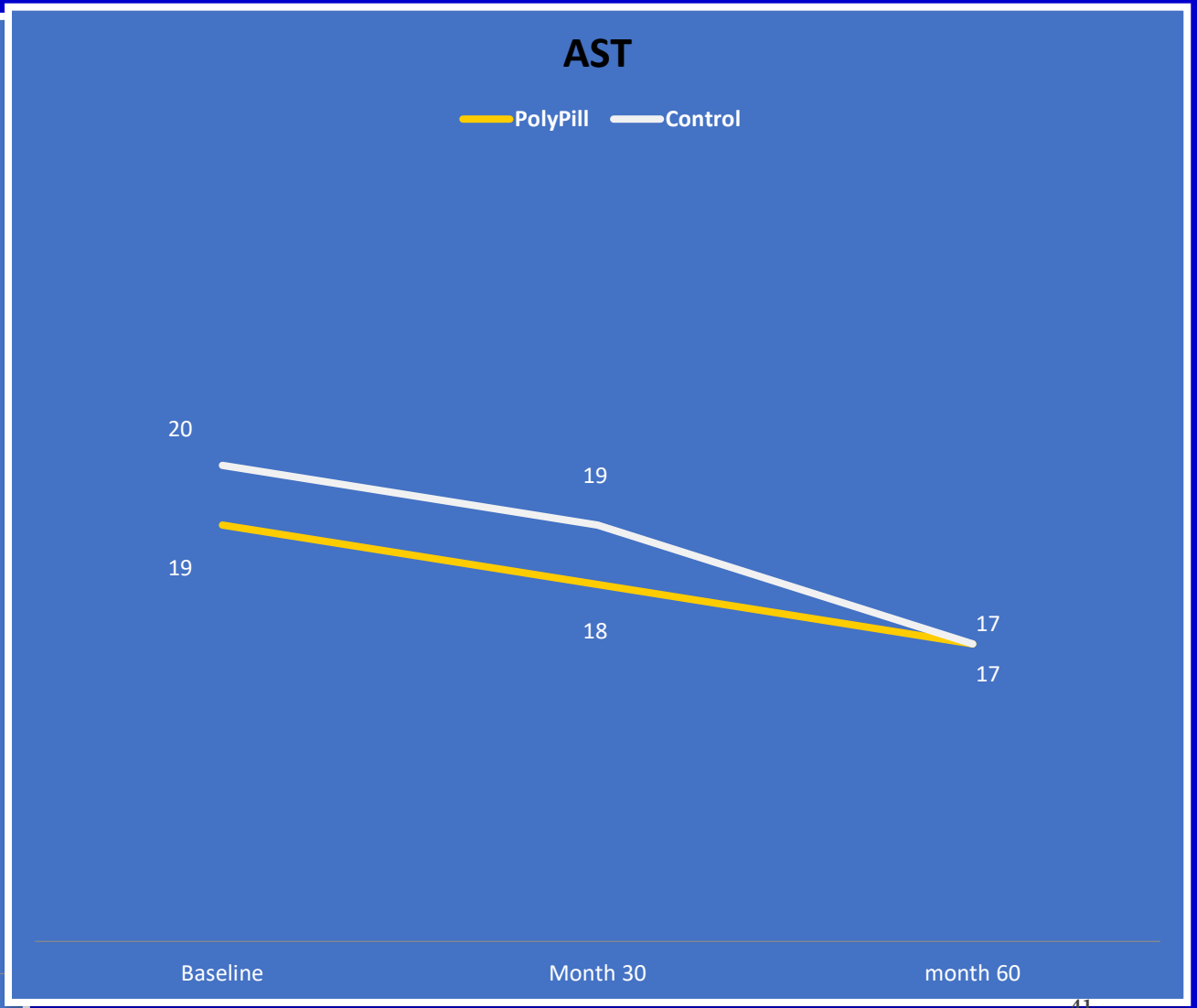

2400 Participants Over 50 Years Randomly Selected from the Golestan Cohort Study and Randomized into Control and Intervention Groups at a 45:55 Ratio
Control n=1080
Intervention n=1320
Invited for Eligibility and Consent
Invited for Eligibility and Consent
n=359
n=721
n=787
n=533
No Consent / NE*
Usual Care
PolyPill
No Consent / NE*
Followed for 5 Years
Followed for 5 years

The adjusted relative risk of MCVE In Participants with pNASH

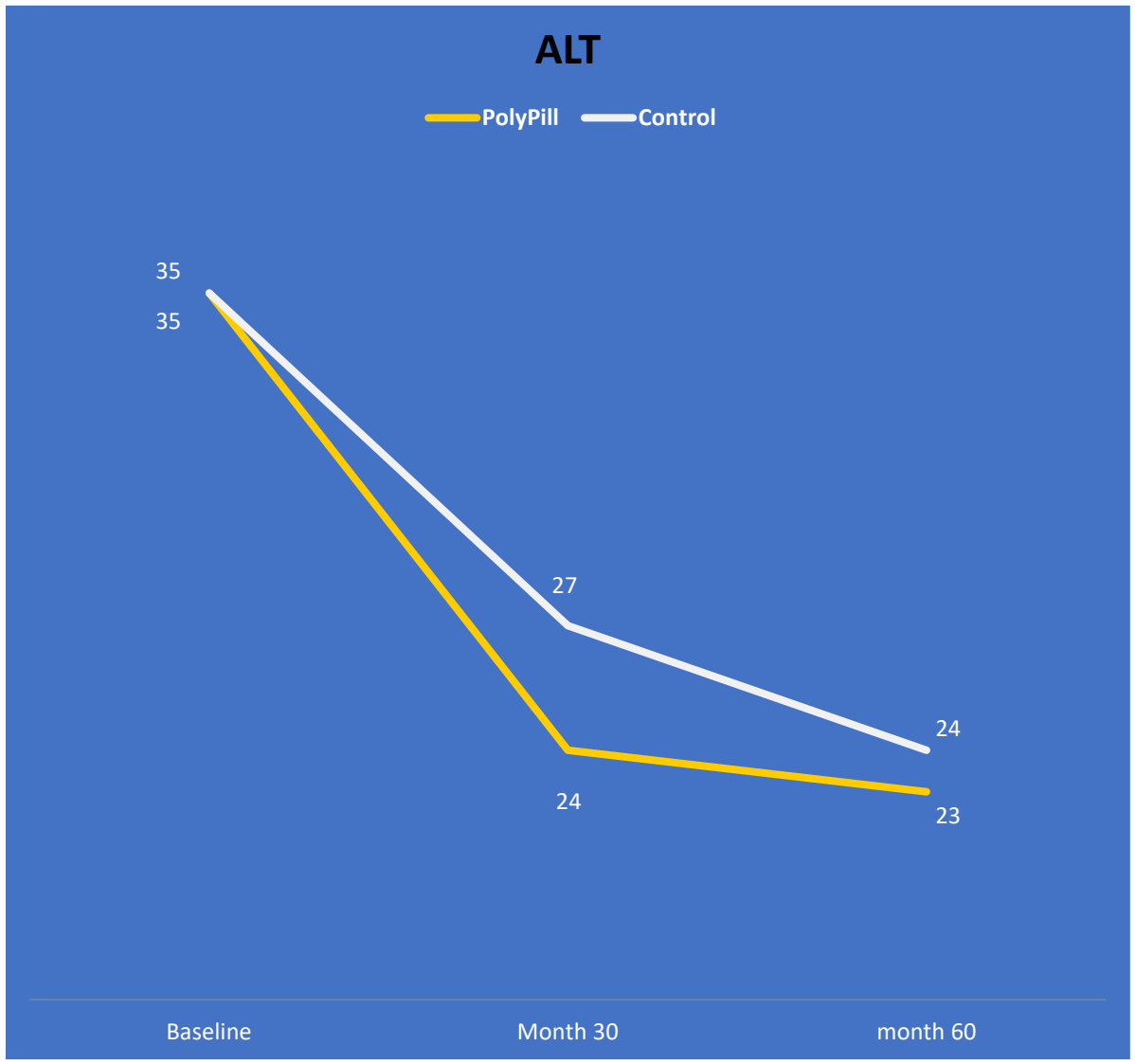
	Adjusted Relative Risk	95% CI
Major Cardiovascular Events	0.61	0.44-0.83
Non-fatal Cardiovascular Disease	0.68	0.48-0.97
Fatal Cardiovascular Disease	0.42	0.19-0.92
All-Cause Mortality:	0.55	0.34-0.88

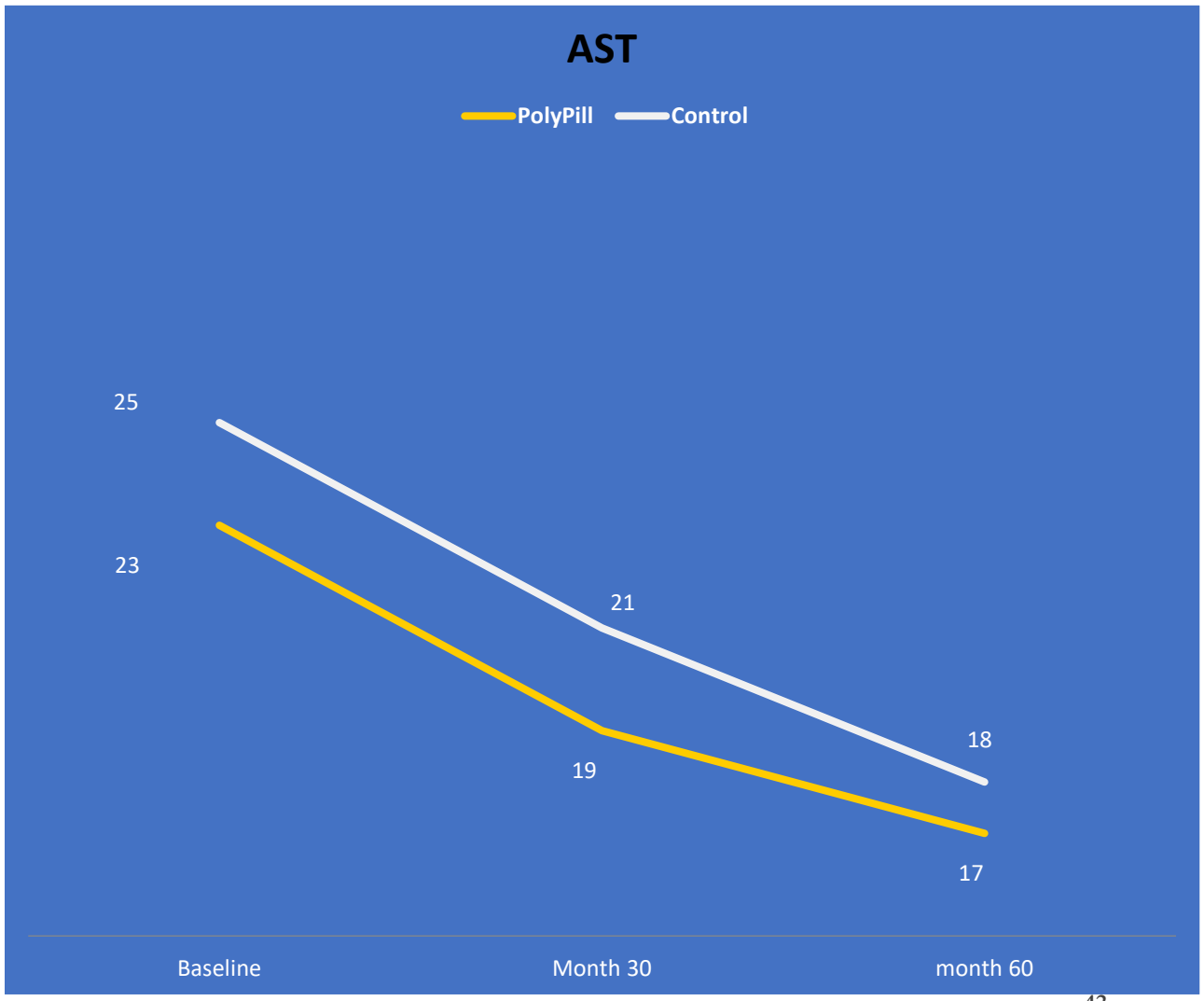
All followed participants





Patients with NASH





What is the new drug option for NASH

- Glucagon-like peptide-1 (GLP-1) receptor antagonist that produces weight loss and there are improvements in liver enzymes.
- Metformin and sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes
- Empagliflozin (Gloripa (Abidi):First SGLT2 inhibitor drug manufactured inside Iran. Effective for T2DM,prevention of CVD,CHF and CKD

Incretin Hormones

- Are gut peptides that are secreted after nutrient intake and stimulate insulin secretion together with hyperglycemia.
- known incretin hormones are :

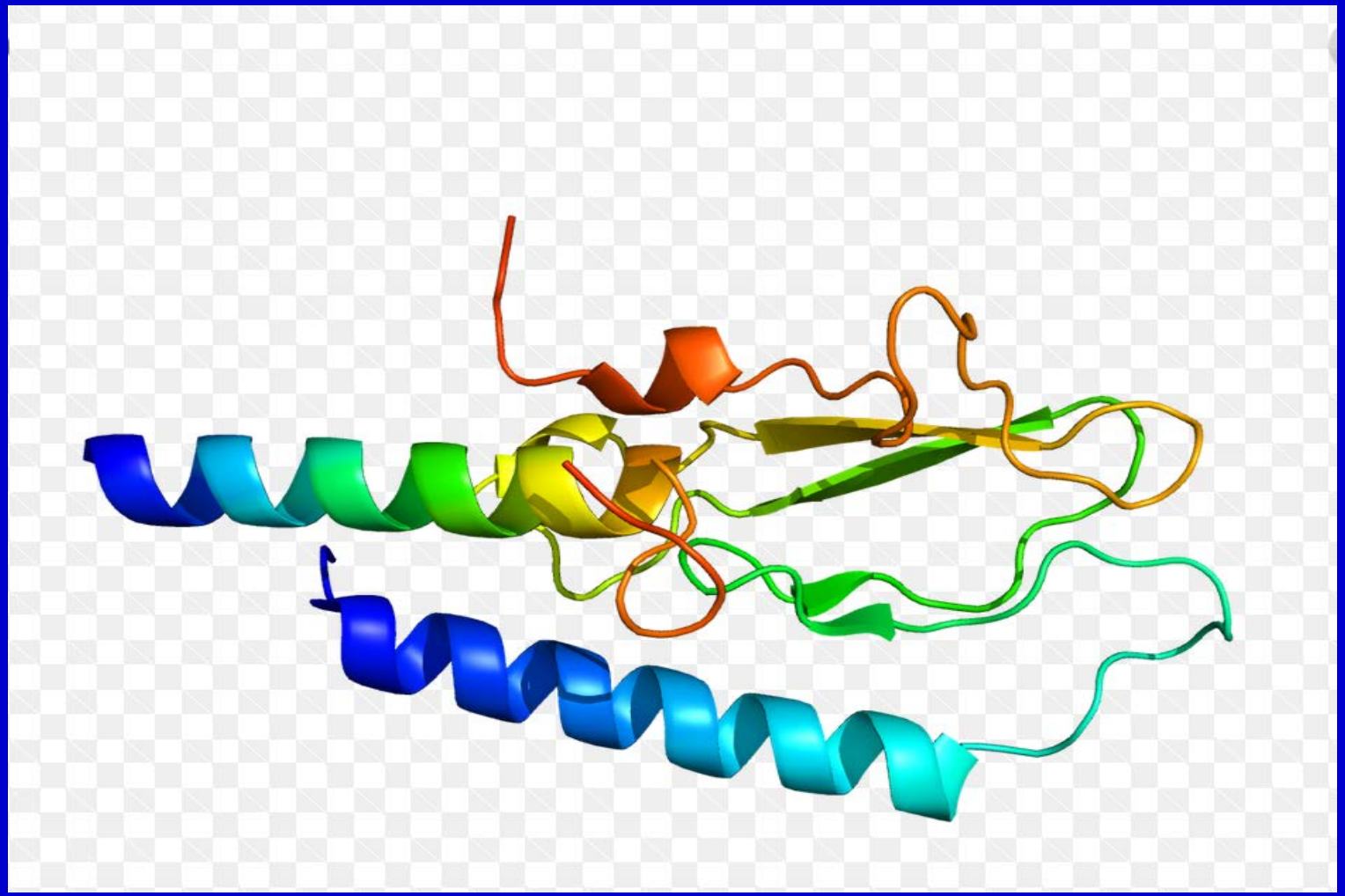
➢ **GIP** (glucose-dependent insulinotropic polypeptide) secreted by

K cells from upper GI trat

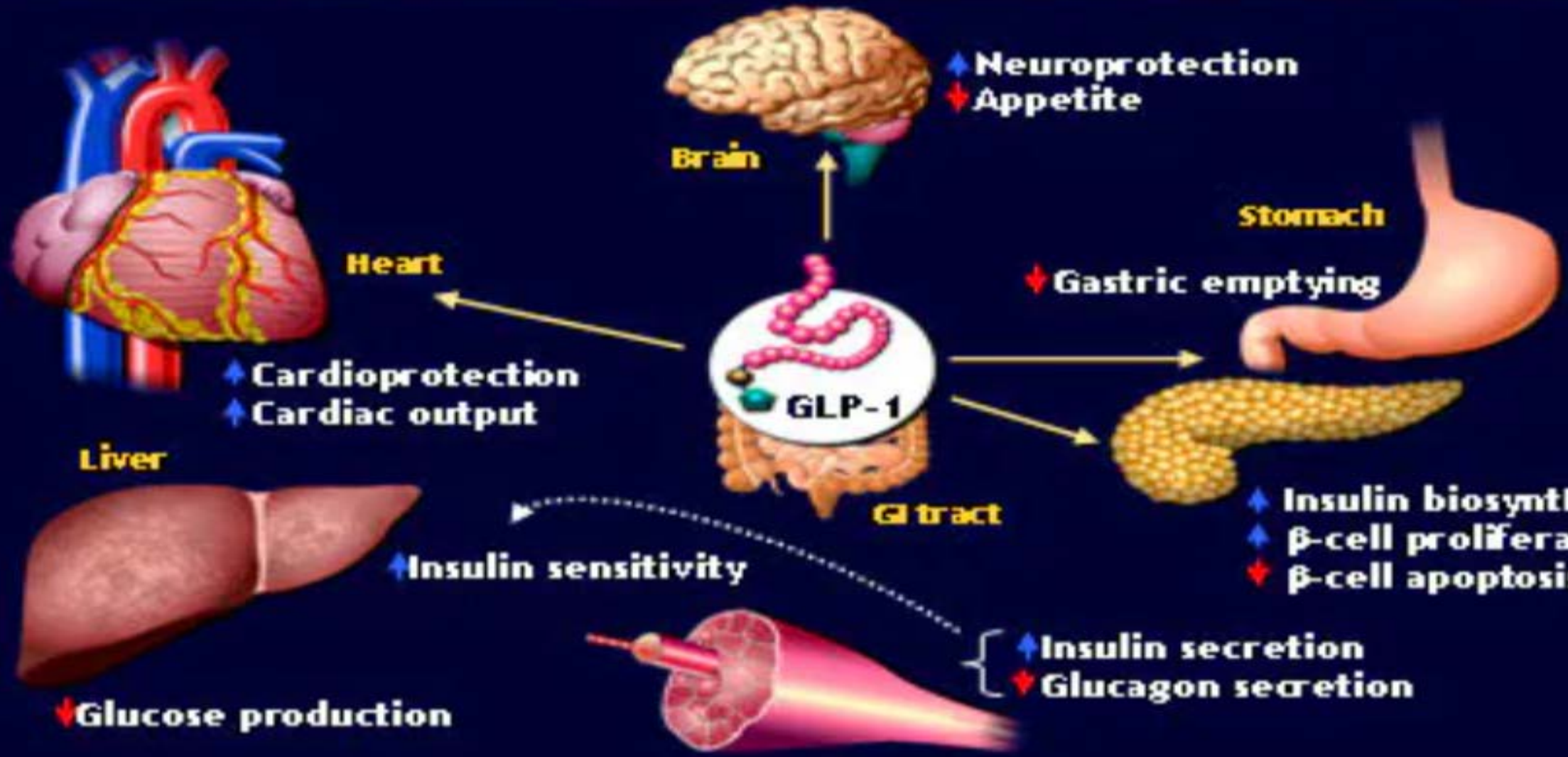
➢ **GLP-1** (glucagon-like peptide-1)) secreted by L cells from lower GI tract

Glucagon-like peptide-1 (glp-1) receptor

Is a receptor protein found on beta cells of the pancreas and on neurons of the brain. It is involved in the control of blood sugar level by enhancing insulin secretion. In humans it is synthesized by the gene GLP1R, which is present on chromosome 6.



Summary of Incretin Actions on Different Target Tissues



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 18, 2021 VOL. 384 NO. 11

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

ABSTRACT

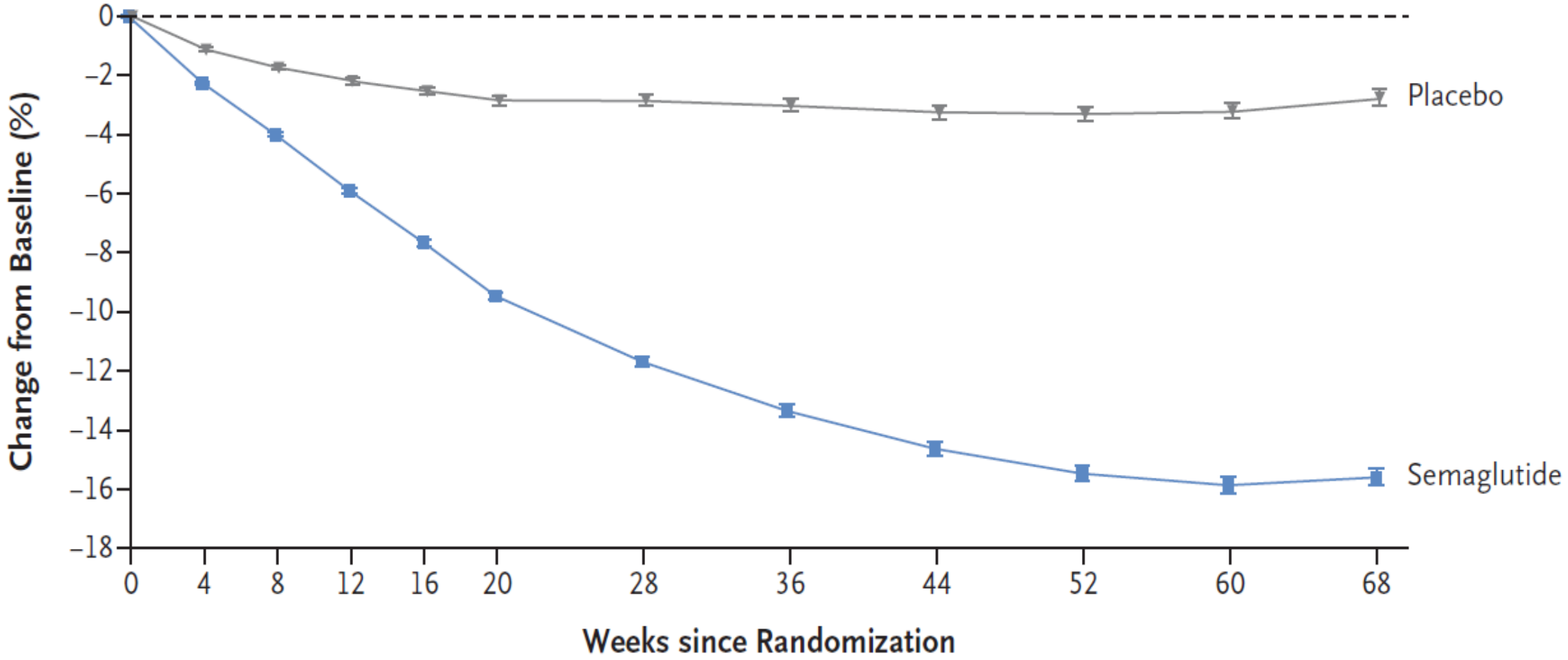
BACKGROUND

Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.

METHODS

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kushner at Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave., Suite 530, Chicago, IL

A Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at Risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

Glucagon-like peptide-1 (GLP-1) receptor agonist (Semaglutide) trial for NASH

- To date, there are no approved pharmacotherapies for the treatment of nonalcoholic steatohepatitis (NASH).
- Newsome et al. conducted a randomized, placebo-controlled, phase 2 trial to investigate the effect of semaglutide on histologic resolution of NASH in patients with biopsy-confirmed NASH and fibrosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ABSTRACT

BACKGROUND

Nonalcoholic steatohepatitis (NASH) is a common disease that is associated with increased morbidity and mortality, but treatment options are limited. The efficacy and safety of the glucagon-like peptide-1 receptor agonist semaglutide in patients with NASH is not known.

METHODS

We conducted a 72-week, double-blind phase 2 trial involving patients with biopsy-confirmed NASH and liver fibrosis of stage F1, F2, or F3. Patients were randomly assigned, in a 3:3:3:1:1:1 ratio, to receive once-daily subcutaneous semaglutide at a dose of 0.1, 0.2, or 0.4 mg or corresponding placebo. The primary end point was resolution of NASH with no worsening of fibrosis. The confirmatory secondary end point was an improvement of at least one fibrosis stage with no worsening of NASH. The analyses of these end points were performed only in patients with stage F2 or F3 fibrosis; other analyses were performed in all the patients.

RESULTS

In total, 320 patients (of whom 230 had stage F2 or F3 fibrosis) were randomly assigned to receive semaglutide at a dose of 0.1 mg (80 patients), 0.2 mg (78 patients), or 0.4 mg (82 patients) or to receive placebo (80 patients). The percentage of patients in whom NASH resolution was achieved with no worsening of fibrosis was 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group ($P<0.001$ for semaglutide 0.4 mg vs. placebo). An improvement in fibrosis stage occurred in 43% of the patients in the 0.4-mg group and in 33% of the patients in the placebo group ($P=0.48$). The mean percent weight loss was 13% in the 0.4-mg group and 1% in the placebo group. The incidence of nausea, constipation, and vomiting was higher in the 0.4-mg group than in the placebo group (nausea, 42% vs. 11%; constipation, 22% vs. 12%; and vomiting, 15% vs. 2%). Malignant neoplasms were reported in 3 patients who received semaglutide (1%) and in no patients who received placebo. Overall, neoplasms (benign, malignant, or unspecified) were reported in 15% of the patients in the semaglutide groups and in 8% in the placebo group; no pattern of occurrence in

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Newsome at the Centre for Liver and Gastrointestinal Research, 5th Flr., Institute of Biomedical Research, Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom, or at p.n.newsome@bham.ac.uk.

*A complete list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 13, 2020, at NEJM.org.

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Therapeutic Approaches to NAFLD/NASH

- Targeting weight Loss
- Targeting more specific aspects of the lipotoxicity–fibro-inflammatory cascade.

Agents in Phase III Clinical Trials for Treatment of NASH

Agent	MoA	Trial	N	Study Population
Cenicriviroc	CCR2/5 antagonist	AURORA[1]	2000	NASH with fibrosis
Elafibranor	PPARα/σ agonist	RESOLVE-IT[2]	2000	NASH with fibrosis
Obeticholic acid	FXR agonist	REGENERATE[3]	2370	NASH with fibrosis
		REVERSE[4]	540	NASH with compensated cirrhosis
Selonsertib	ASK1 inhibitor	STELLAR 3[5]	800	NASH with fibrosis
		STELLAR 4[6]	883	NASH with compensated cirrhosis

References in slidenotes.

Slide credit: clinicaloptions.com

Phase II Data on Investigational NASH Therapies Presented at EASL 2018

Agent	Mechanism of Action
Cenicriviroc[1,2]	CCR2/5 antagonist
GR-MD-02[3,4]	Galectin-3 inhibitor
GS-0976*[5-7]	ACC inhibitor
(GS-0976 or GS-9674) ± selonsertib[8,9]	(ACC inhibitor or FXR agonist) ± ASK1 inhibitor
JKB-121[10,11]	TLR-4 antagonist
MGL-3196[12,13]	THR-β agonist
NGM282*[14]	FGF19 analogue
Semaglutide†[15,16]	GLP-1 receptor agonist

*Includes single-arm exploratory or proof-of-concept studies; all others phase II.
†FDA approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM.

References in slidenotes.

Pegozafermin Trial published in NEJM this week

Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH

Rohit Loomba, M.D., M.H.Sc., Arun J. Sanyal, M.D., Kris V. Kowdley, M.D., Deepak L. Bhatt, M.D., M.P.H., Naim Alkhouri, M.D., Juan P. Frias, M.D., Pierre Bedossa, M.D., Ph.D., Stephen A. Harrison, M.D., Donald Lazas, M.D., Robert Barish, M.D., Mildred D. Gottwald, Pharm.D., Shibao Feng, Ph.D., et al.

September 14, 2023
N Engl J Med 2023; 389:998-1008
DOI: 10.1056/NEJMoa2304286

Print Subscriber? Activate your online access.

Abstract

BACKGROUND Pegozafermin is a long-acting glycopegylated (pegylated with the use of site-specific glycosyltransferases) fibroblast growth factor 21 (FGF21) analogue in development for the treatment of nonalcoholic steatohepatitis (NASH) and severe hypertriglyceridemia. The efficacy and safety of pegozafermin in patients with biopsy-proven noncirrhotic NASH are not well established.

METHODS In this phase 2b, multicenter, double-blind, 24-week, randomized, placebo-controlled trial, we randomly assigned patients with biopsy-confirmed NASH and stage F2 or F3 (moderate or severe) fibrosis to receive subcutaneous pegozafermin at a dose of 15



Related Articles

EDITORIAL SEP 14, 2023

Pegozafermin for NASH — A Sprint to Start

M.E. Rinella

Pegozafermin for NASH — A Sprint to Start a Marathon

Mary E. Rinella, M.D.

Pharmacotherapy in patients with nonalcoholic steatohepatitis (NASH) has been a frustrating endeavor, with failures outnumbering successes by some margin, even in late-phase clinical trials. The complex pathobiologic features of NASH, the slow and variable natural history of the disease, and the nefarious nature of assessing histologic end points have contributed to the difficulty of attaining efficacy with pharmacotherapy that is meaningfully distinct from that seen with placebo. In this context, studies that have shown even moderately compelling histologic efficacy are understandably heralded. Therapeutic approaches have broadly dichotomized into those targeting weight loss and those targeting more specific aspects of the lipotoxicity–fibroinflammatory cascade. Fibroblast growth factor 21 (FGF21) has pleiotropic metabolic effects, mediated in part by adiponectin, that improve insulin sensitivity and reduce inflammation, improve vascular function,

N ENGL J MED 389;11 NEJM.ORG SEPTEMBER 14, 2023

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Fibroblast growth factor 21 (FGF21)

- Has pleiotropic metabolic effects, mediated in part by adiponectin, that improve insulin sensitivity and reduce inflammation, improve vascular function and act directly on various tissues, including the liver, adipose tissue, and the pancreas.
- These effects modulate lipogenesis, ketogenesis, and energy expenditure.

FGF21 analogues

- Several FGF21 analogues — such as pegozafermin, a long-acting glycopegylated FGF21 analogue — are under development for the treatment of NASH, with the metabolic effects in humans differing across compounds


Thank you