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HEPATITIS

Current Management of NASH

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Faculty Disclosures

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NASH Management: Outline

- Definition
  - NAFLD: NAFL vs NASH
  - Metabolic syndrome
- Key clinical questions
  - Presence of NASH
  - Presence of advanced fibrosis
  - Risk of complications and mortality
- Indications for treatment
- Pharmacologic treatment

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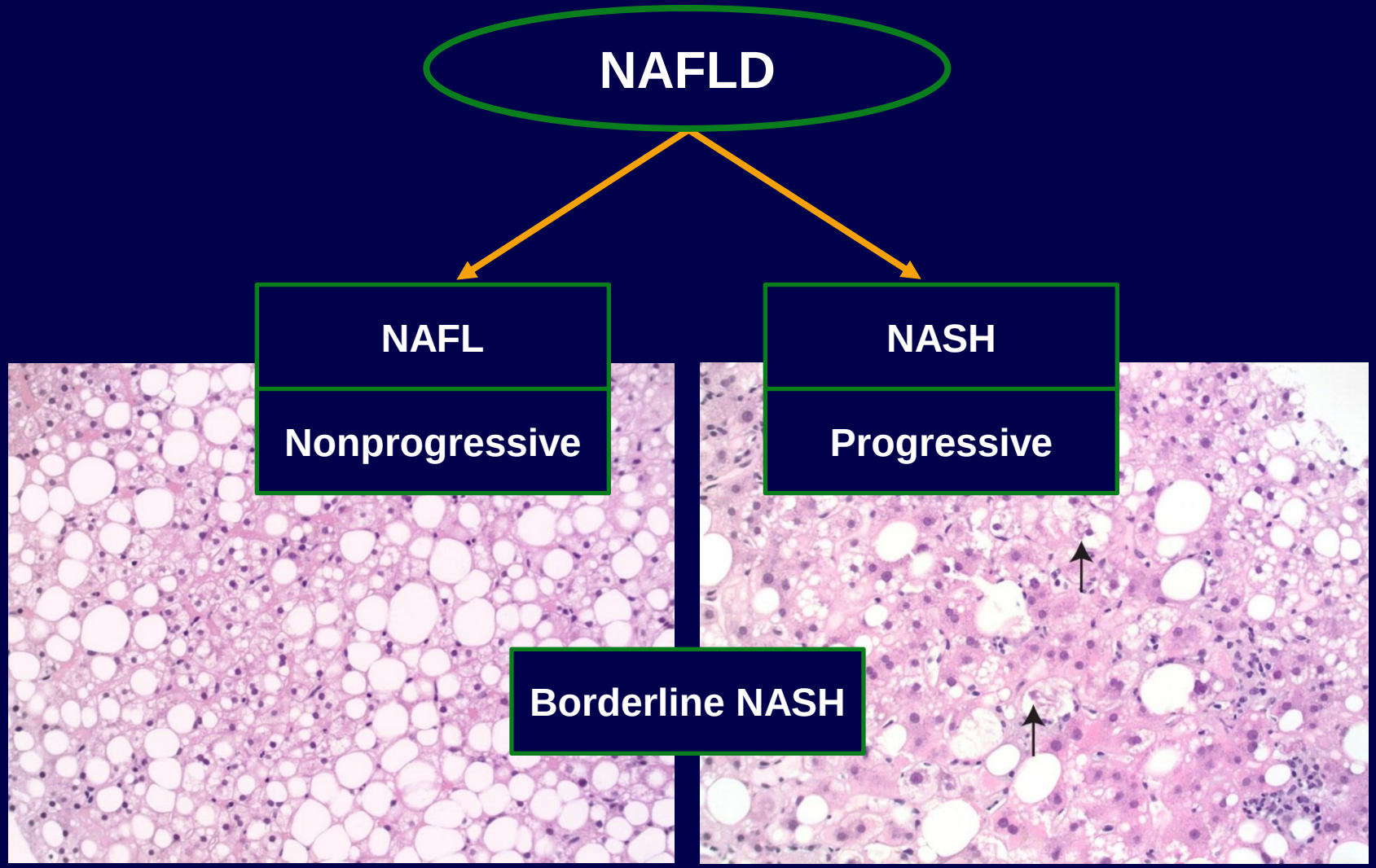
Subtypes of NAFLD

Caveats

- Steatosis in ≥ 5% hepatocytes
- Minimal alcohol use
- Biopsy consistent with NAFLD
- No other etiology for liver disease
- No secondary causes of NAFLD
  - Medications
  - HIV
  - Lipodystrophy



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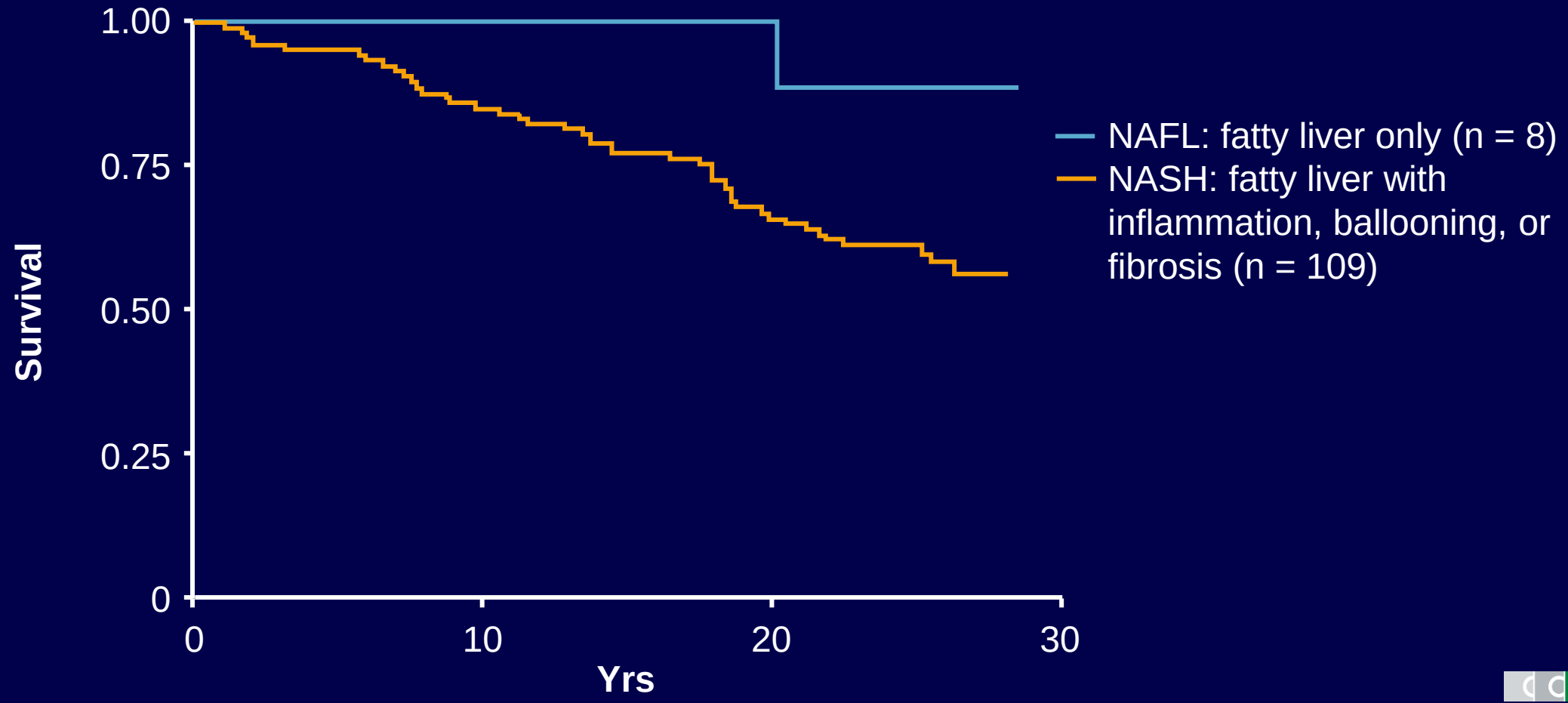
Is It Important to Determine if Your Patient Has NASH vs NAFL?

NAFLD: Mortality

- Long-term follow-up of pts with biopsy-confirmed NAFLD



Söderberg C, et al. Hepatology. 2010;51:595-602.

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A 50-Yr-Old Man With Fatty Liver on Ultrasound May be Considered for Biopsy if He Has…

- Near normal ALT, AST > ALT suggests advanced fibrosis

Indications for Liver Biopsy in Pts With NAFLD

Perform liver biopsy

- More features of metabolic syndrome
  - Obesity, hypertension, increased TG, low HDL, impaired glucose tolerance
- Diabetes
  - Family history of diabetes
- Older age
- High AST/ALT
- Low platelets/albumin

Consider liver biopsy

- Cholecystectomy
- Bariatric surgery

Chalasani N, et al. Hepatology. 2012;55:2005-2023. Noureddin M, et al. Clin Liver Dis. 2012;1:104-107.

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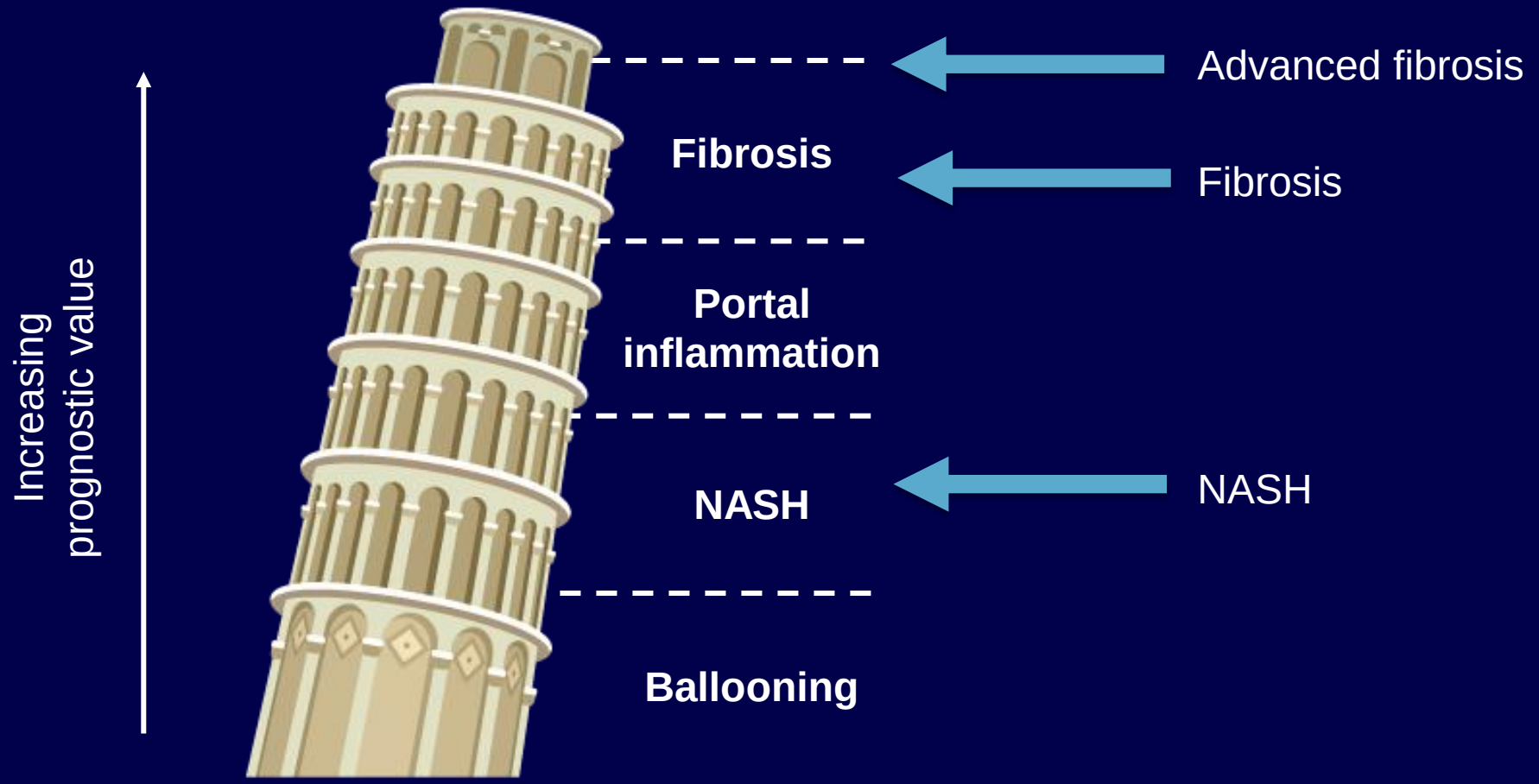
What Is the Significance of Fibrosis?

Key Histologic Predictors of Mortality in NAFLD

Fibrosis is the single most important predictor of mortality in NASH



Angulo P, et al. Gastroenterology. 2015;149:389-397. Loomba R, et al. Gastroenterology. 2015;149:278-281.

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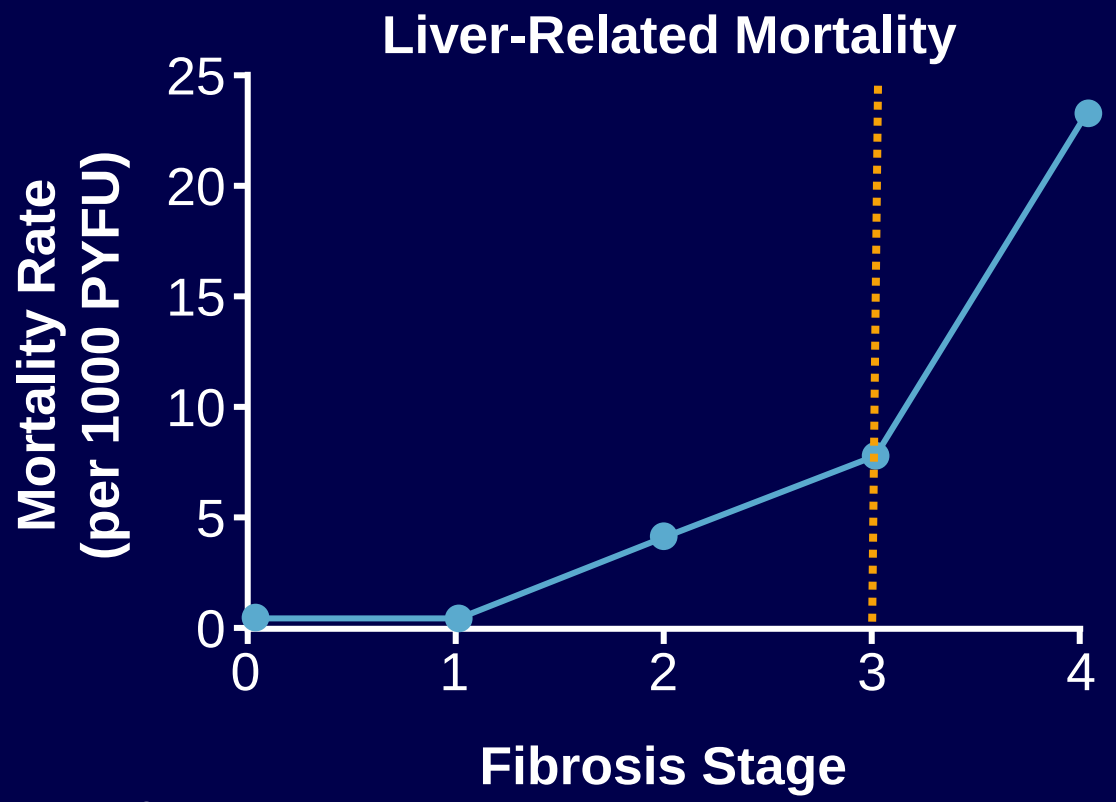
Quantitative Risk of Liver Mortality by Fibrosis Stage

- Meta-analysis of 5 cohort studies with N = 1495 pts with NAFLD followed for 17,452 pt-yrs
- Liver-related mortality exponentially increased with fibrosis stage



Dulai PS, et al. Hepatology. 2017;65:1557-1565.

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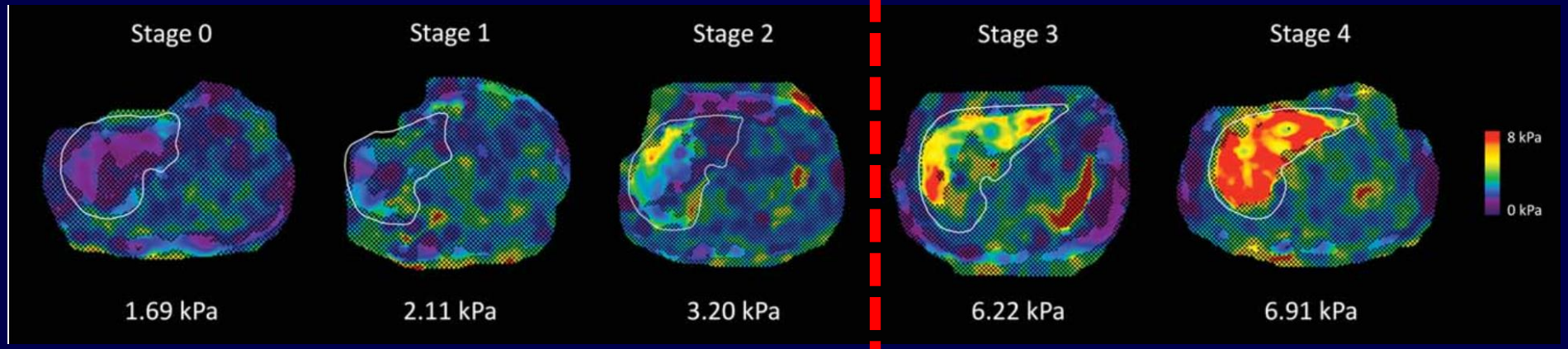
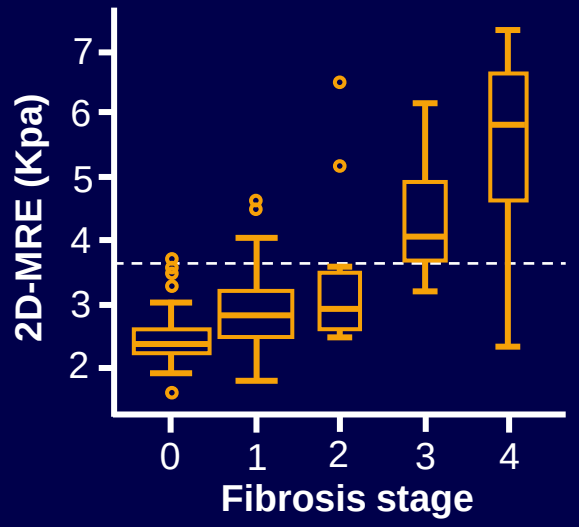
MR-Based Fibrosis Assessment in NASH: Innovations in Fibrosis Assessment

MRE: Advanced Fibrosis Diagnosis





Cutoff for Detecting Advanced Fibrosis	Sensitivity	Specificity
MRE stiffness > 3.63 kPa	.86	.91

AUC for diagnosis of advanced fibrosis: 0.924

Dulai PS, et al. Hepatology. 2017;65:1557-1565.

Slide credit: clinicaloptions.com

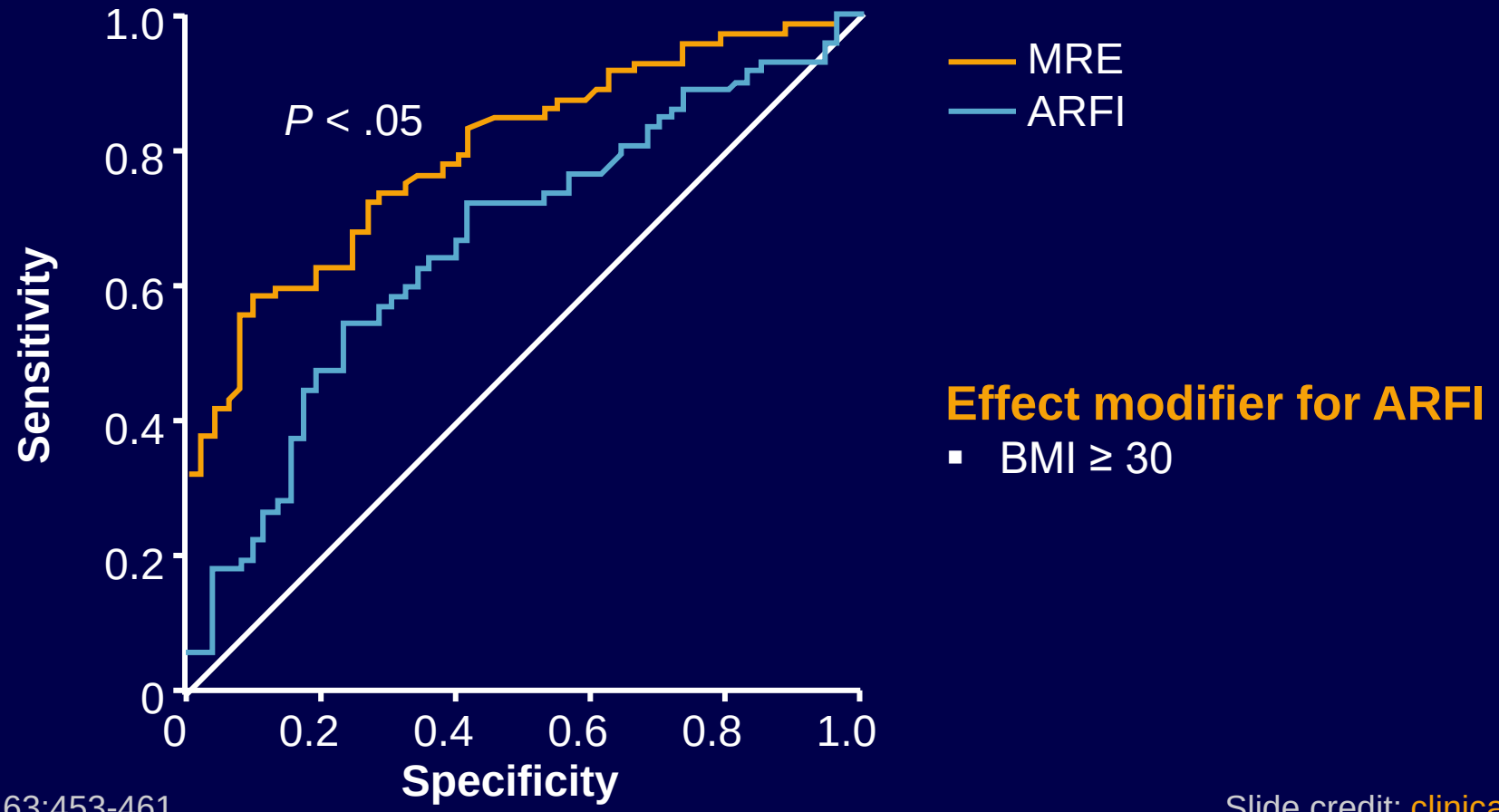
Which Modality Is More Accurate?

MRE vs VCTE/ARFI

MRI-PDFF vs CAP

MRE Better Than ARFI for Detection of Fibrosis in NAFLD: Prospective Study

- Head-to-head comparison in N = 125 consecutive pts with biopsy-proven NAFLD and contemporaneous MRE and ARFI



Effect modifier for ARFI

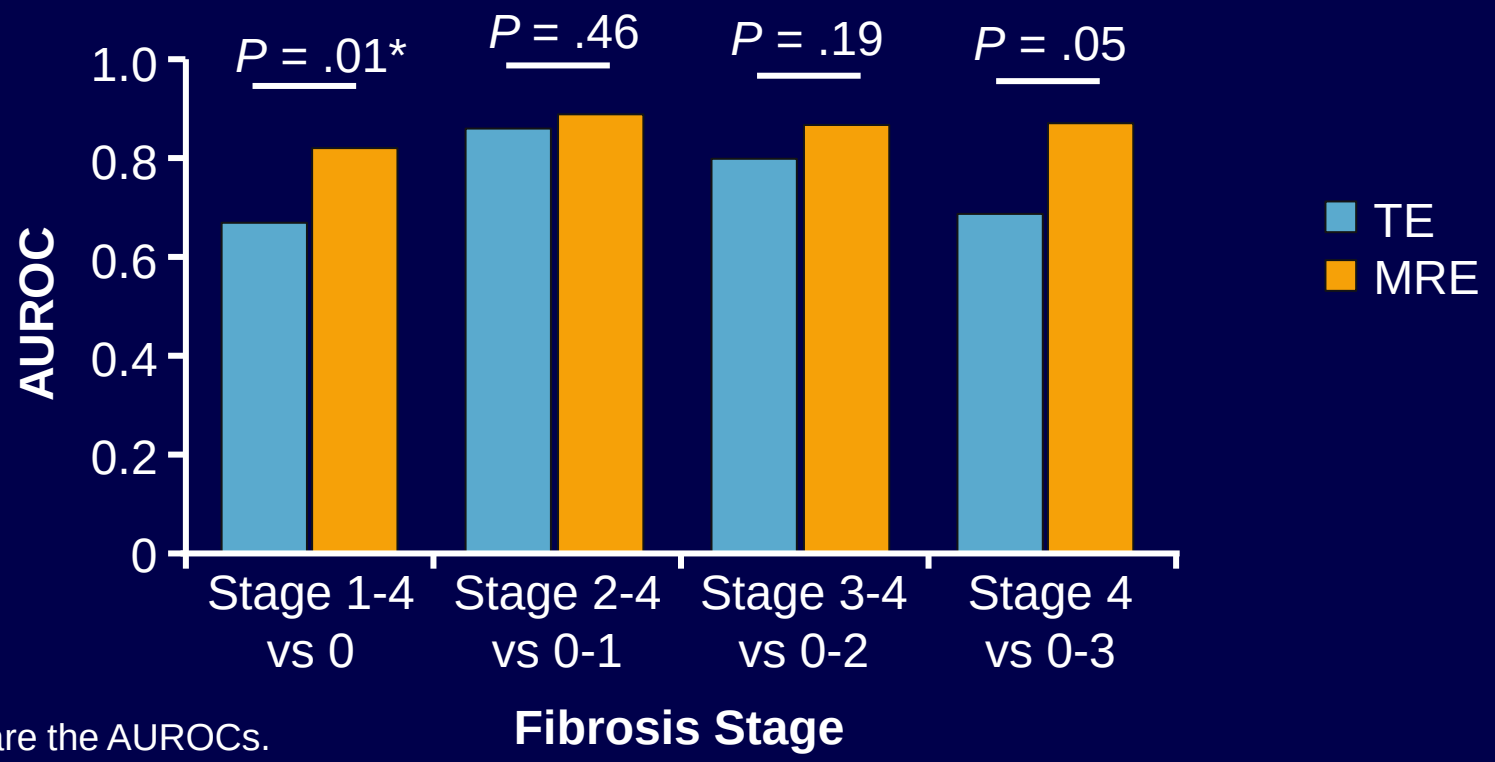
- BMI ≥ 30

Cui J, et al. Hepatology. 2016;63:453-461.

Slide credit: clinicaloptions.com

MRE Better Than TE for Detection of Fibrosis in NAFLD

- Head-to-head prospective comparison
- N = 104 pts with biopsy-proven NAFLD from UCSD NAFLD Research Center

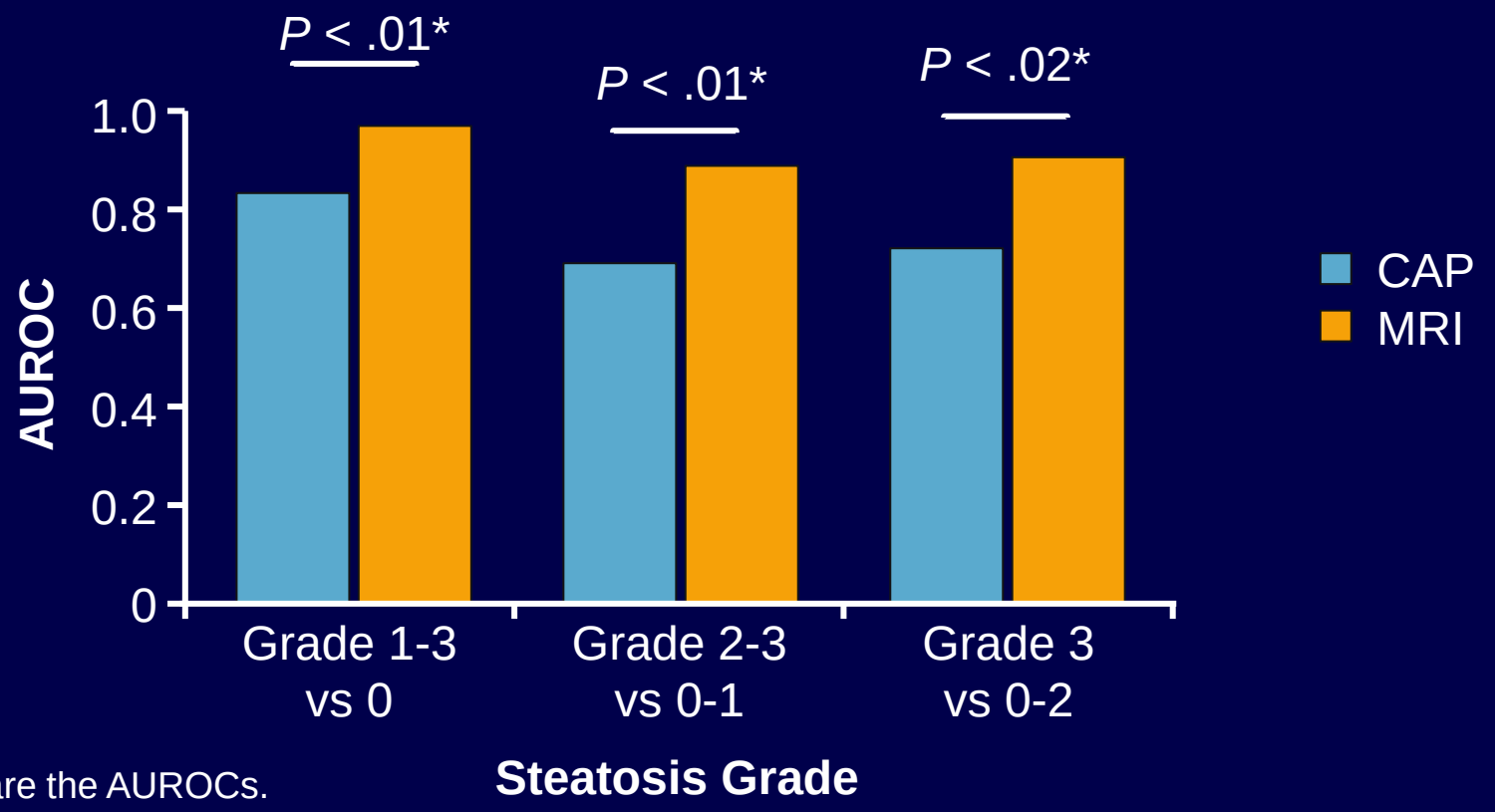


*Delong test used to compare the AUROCs.

Park CC, et al. Gastroenterology. 2017;152:598-607.

Slide credit: clinicaloptions.com

MRI-PDFF Better Than CAP for Quantification of Steatosis Grade in NAFLD



*Delong test used to compare the AUROCs.

Park CC, et al. Gastroenterology. 2017;152:598-607.

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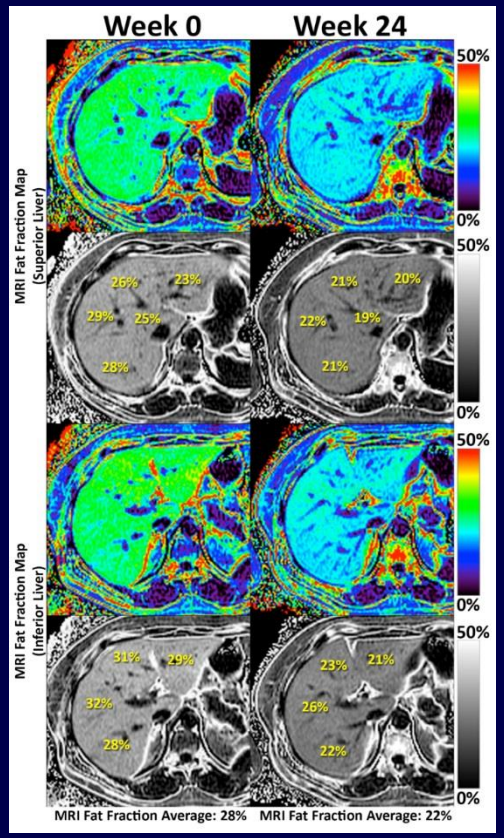
Innovations in Clinical Trial Design:
How Will Future Clinical Trials Assess NASH?

Phase II MOZART Trial: Fat and Stiffness Mapping Before and After Treatment

- Randomized, double-blind, allocation-concealed, placebo-controlled phase II study
- First study to assess 2D and 3D MRE in NASH

Whole-liver fat mapping



Why do we need to colocalize?

Heterogeneity in distribution

More comprehensive assessment

↓

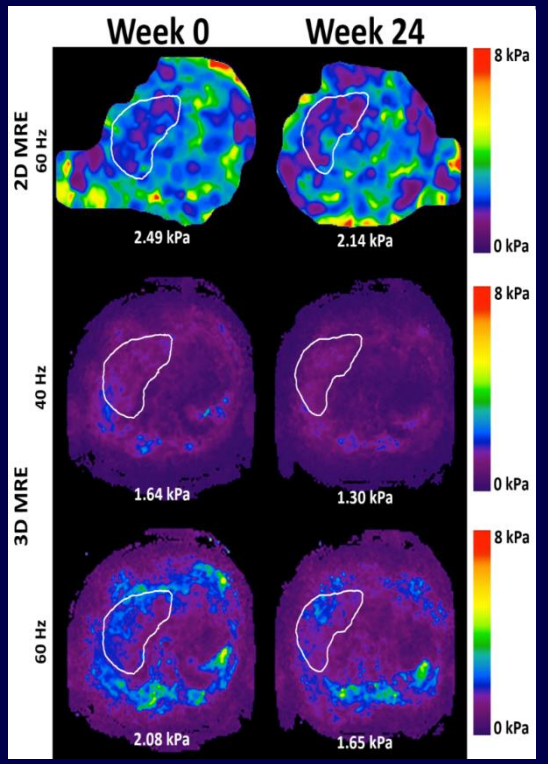
Higher precision and accuracy

↓

Enhanced responsiveness

↓

Efficiency in clinical trial



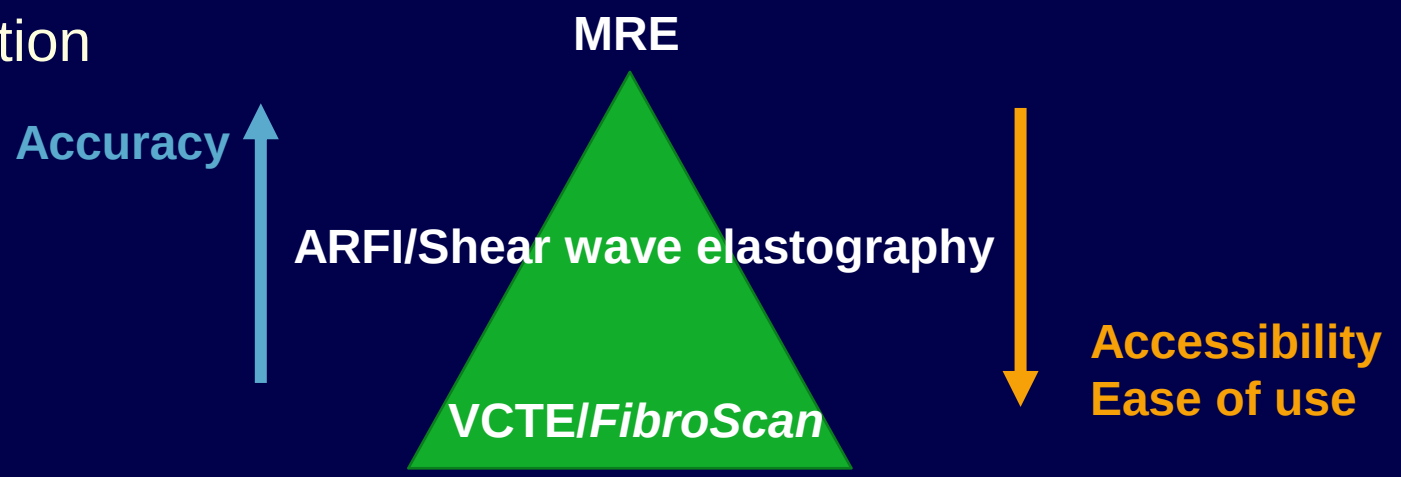
Liver stiffness

Loomba R, et al. Hepatology. 2015;61:1239-1250.

Slide credit: clinicaloptions.com

Summary: Caveats Associated With Available Modalities for Diagnosing and Staging NAFLD

- Transient elastography or ARFI or other ultrasound-based test have following limitations:
  - Obesity
  - Ascites
  - Acute inflammation
  - Cirrhosis
- MRE improves upon all except
  - Iron overload
  - Acute inflammation



Park CC, et al. Gastroenterology. 2017;152:598-607. Cui J, et al. Hepatology. 2016;63:453-461.

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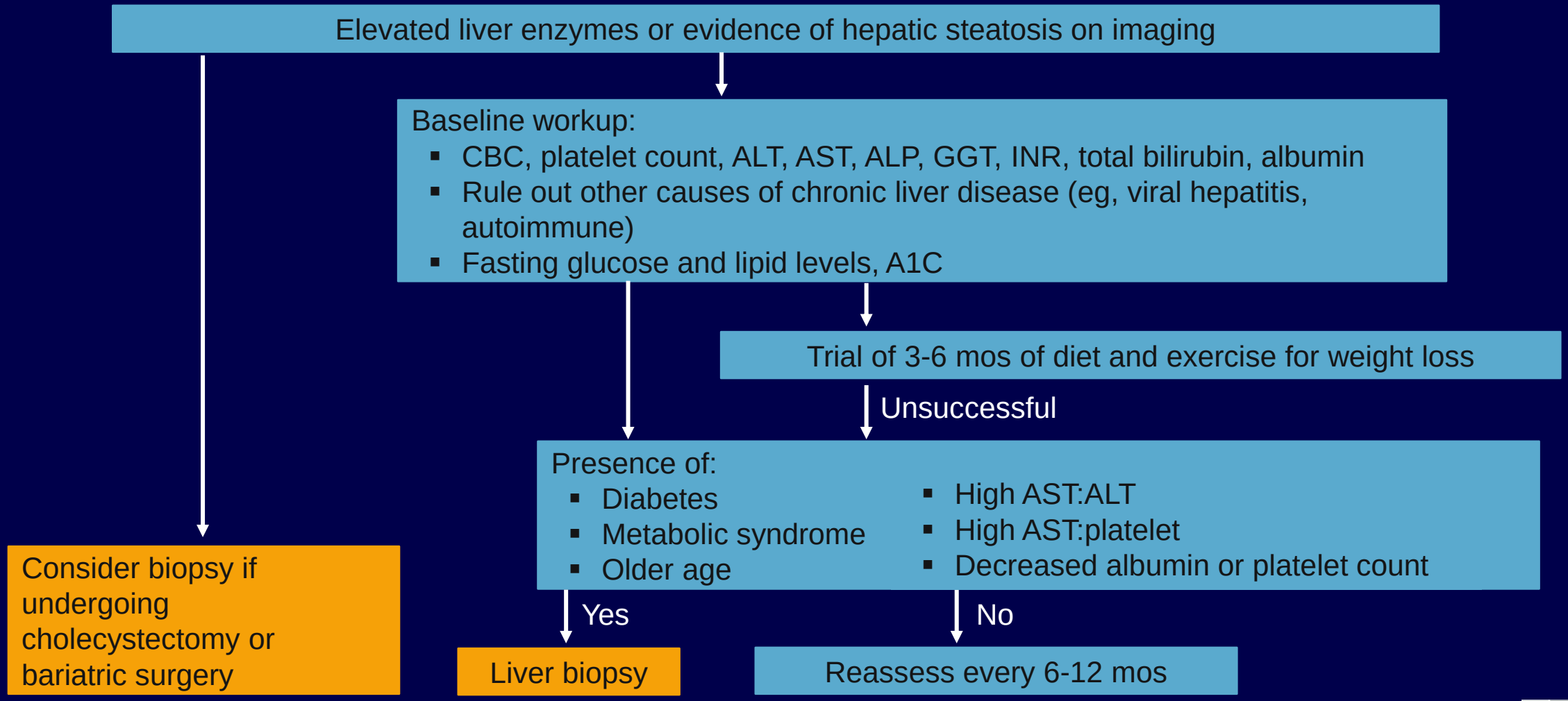
Approach to Initial Assessment and Consideration for a Liver Biopsy



Noureddin M, et al. Clin Liver Dis. 2012;1:104-107.

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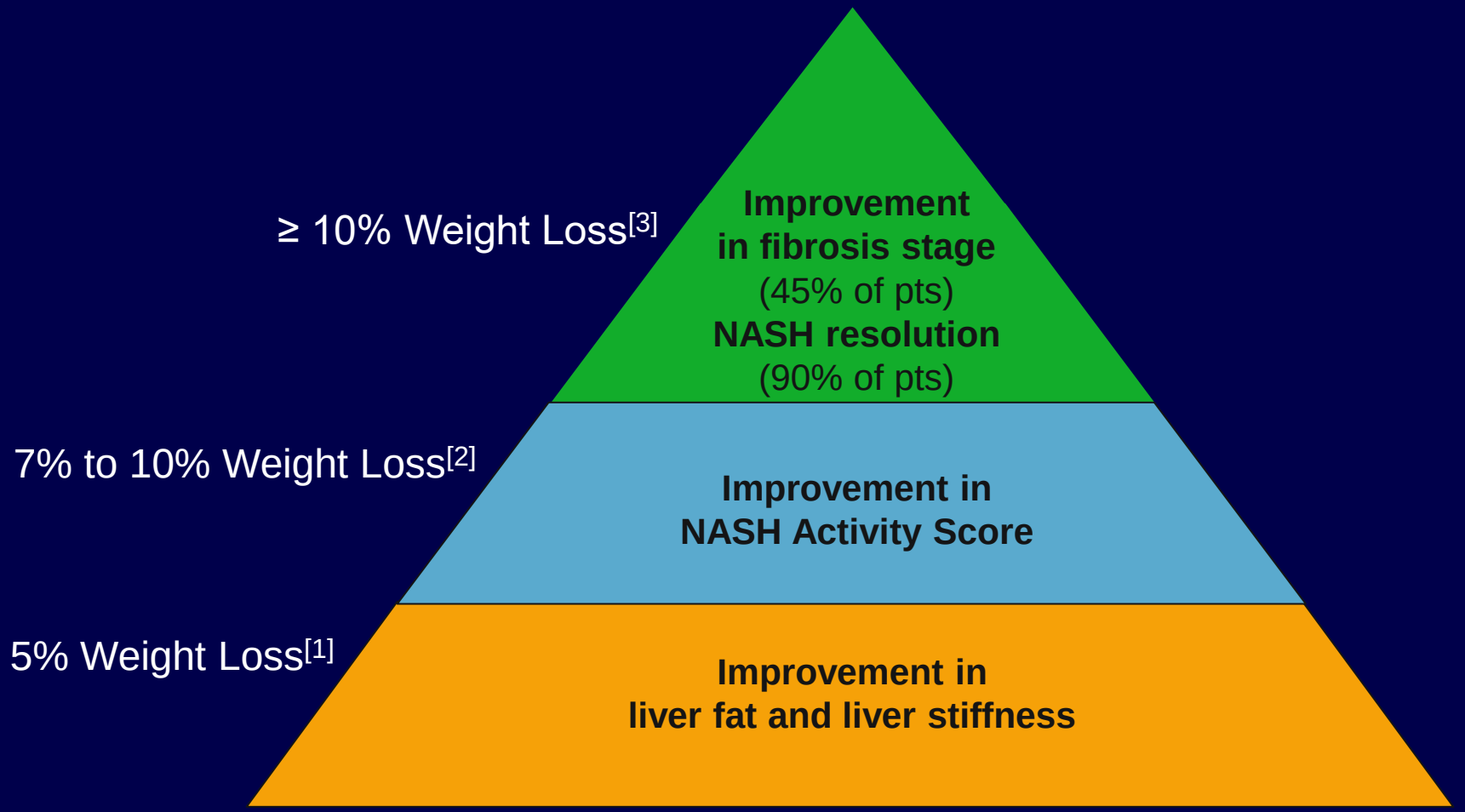
Population of Interest for Treatment

- **Treat**
  - NASH
  - NASH with fibrosis
  - Advanced fibrosis
  - NASH-related cirrhosis
- **Do Not Treat**
  - NAFL
  - Pt without biopsy-confirmed NASH
  - Steatosis alone
    - Focus on CVD risk factor modification in primary care; no need for liver clinic

Slide credit: clinicaloptions.com

How Much Weight Loss Is Needed for Improvement in NASH?



1. Patel NS, et al. Clin Gastroenterol Hepatol. 2017;15:463-464. 2. Promrat K, et al. Hepatology. 2010;51:121-129. 3. Vilar-Gomez E, et al. Gastronterol. 2015;149:367-378.

Slide credit: clinicaloptions.com

Summary: NASH and Weight Loss

- Weight loss in obese pts leads to improvement in liver histology
- Lifestyle modification leads to improvement in NASH

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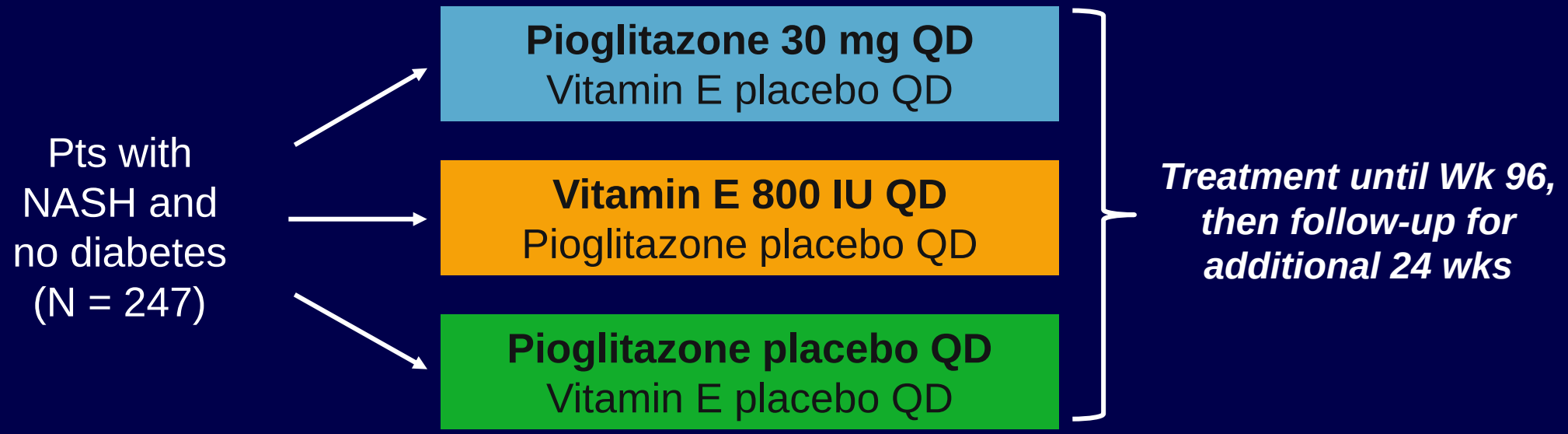
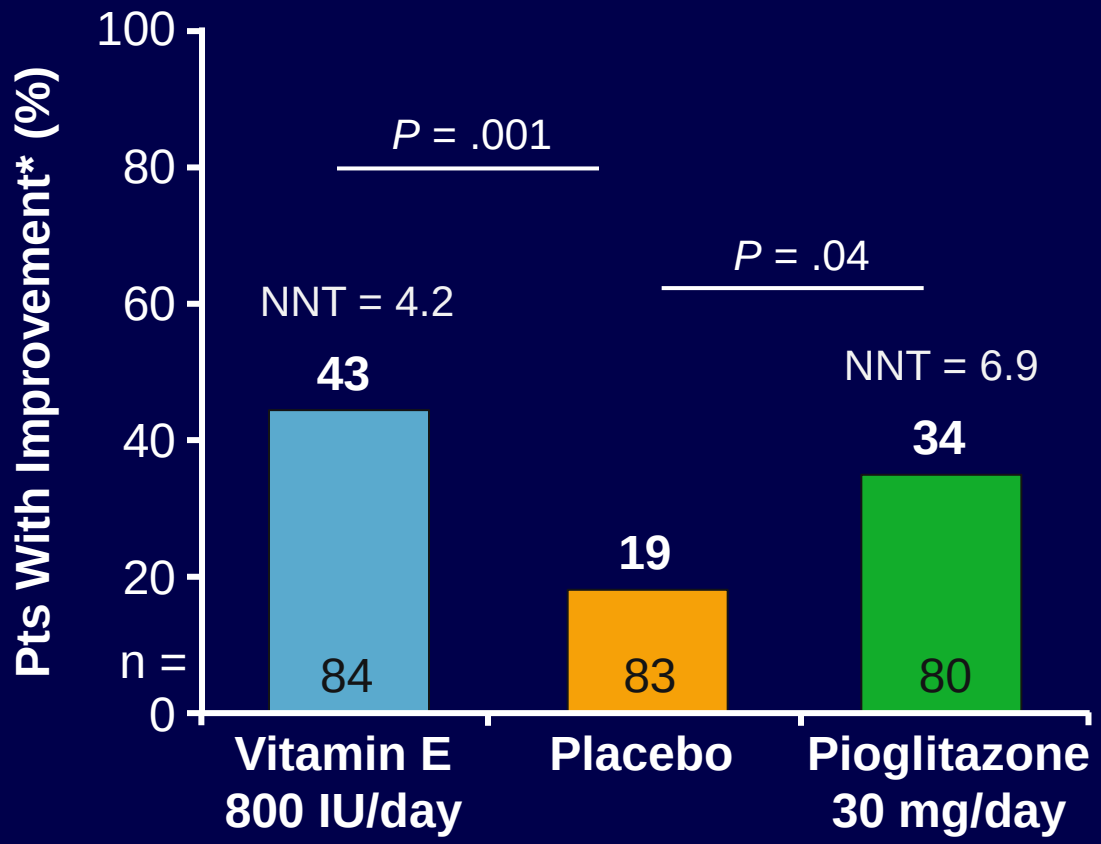
PIVENS Trial: Pioglitazone vs Vitamin E vs Placebo in NASH

- Randomized, double-masked, double-dummy, placebo-controlled study



Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.
Chalasani NP, et al. Contemp Clin Trials. 2009;30:88-96.

PIVENS Primary Endpoint: Histologic Improvement With Vitamin E or Pioglitazone

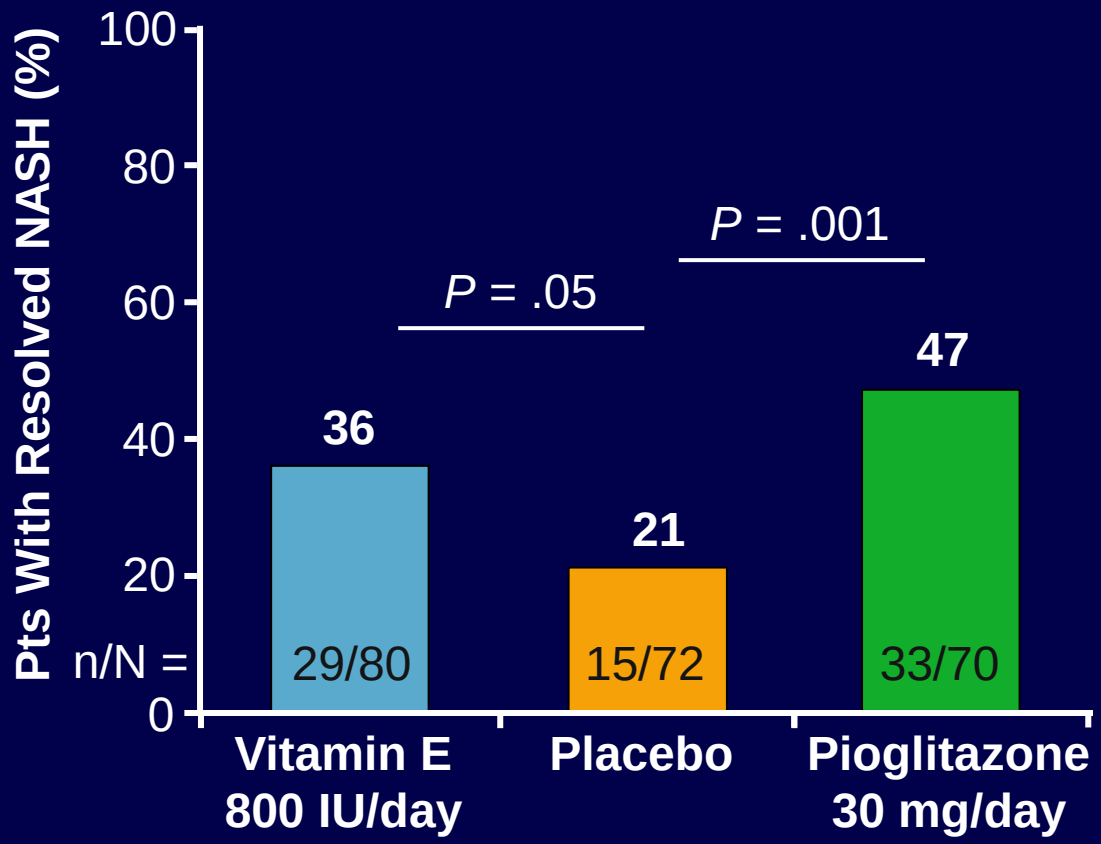


*Histologic improvement: ≥ 1-point improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in NAS to ≤ 3 or a ≤ 2-point decrease in NAS plus ≥ 1-point decrease in either the lobular inflammation or steatosis score.

Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.

Slide credit: clinicaloptions.com

PIVENS: Histologic Resolution of NASH at Wk 96 With Vitamin E or Pioglitazone



Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.

Slide credit: clinicaloptions.com

Vitamin E: The Glass Is Half Full

- Does vitamin E:
  - Improve NASH?
    Yes
  - Reverse NASH?
    Yes
  - Improve fibrosis?
    No (based on RCTs)
  - Improve long-term outcomes?
    No data

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Vitamin E: Risks

- Increases risk of bleeding in a dose-dependent manner
  - Especially ≥ 400 units daily[1]
- Increases risk of prostate cancer in older men [2]
- Increases risk of hemorrhagic stroke[3]
  - May be preventive in reducing the risk of ischemic stroke[3]

1. Miller ER III, et al. Ann Intern Med. 2005;142:37-46. 2. Klein EA, et al. JAMA. 2011;306:1549-1556. 3. Schürks M, et al. BMJ. 2010;341:c5702.

Pragmatic Approach for Using Vitamin E: Balancing Risks vs Benefits

Vitamin E: Treatment Considerations

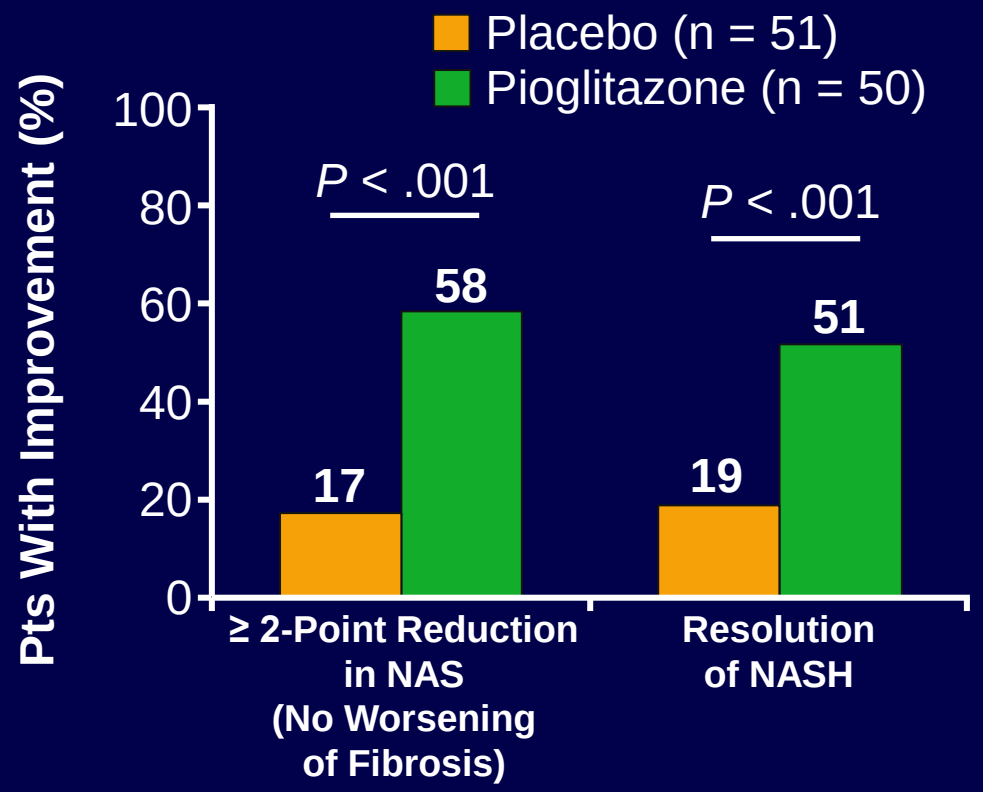
- Consider in nondiabetic pts with biopsy-proven NASH[1]
  - Not recommended in elevated ALT/AST with suspected NAFLD without a liver biopsy
  - Not recommended in mild NAFL with no evidence of NASH on biopsy
- No efficacy data in:
  - Diabetes
  - Cirrhosis
  - Post liver transplantation
- Risks may outweigh benefits in:
  - Older men
  - Uncontrolled hypertension (risk factors for hemorrhagic stroke)
  - Family history of prostate cancer
  - Personal history of stroke or prostate cancer

Chalasani N, et al. Hepatology. 2017;[Epub ahead of print].

Pioglitazone:
Balancing Risks vs Benefits

Pioglitazone in Diabetes: Improvement or Resolution of NASH at 18 Mos

- Randomized, placebo-controlled, double-blind clinical trial of pts with NASH and prediabetes or type 2 diabetes mellitus (N = 101)

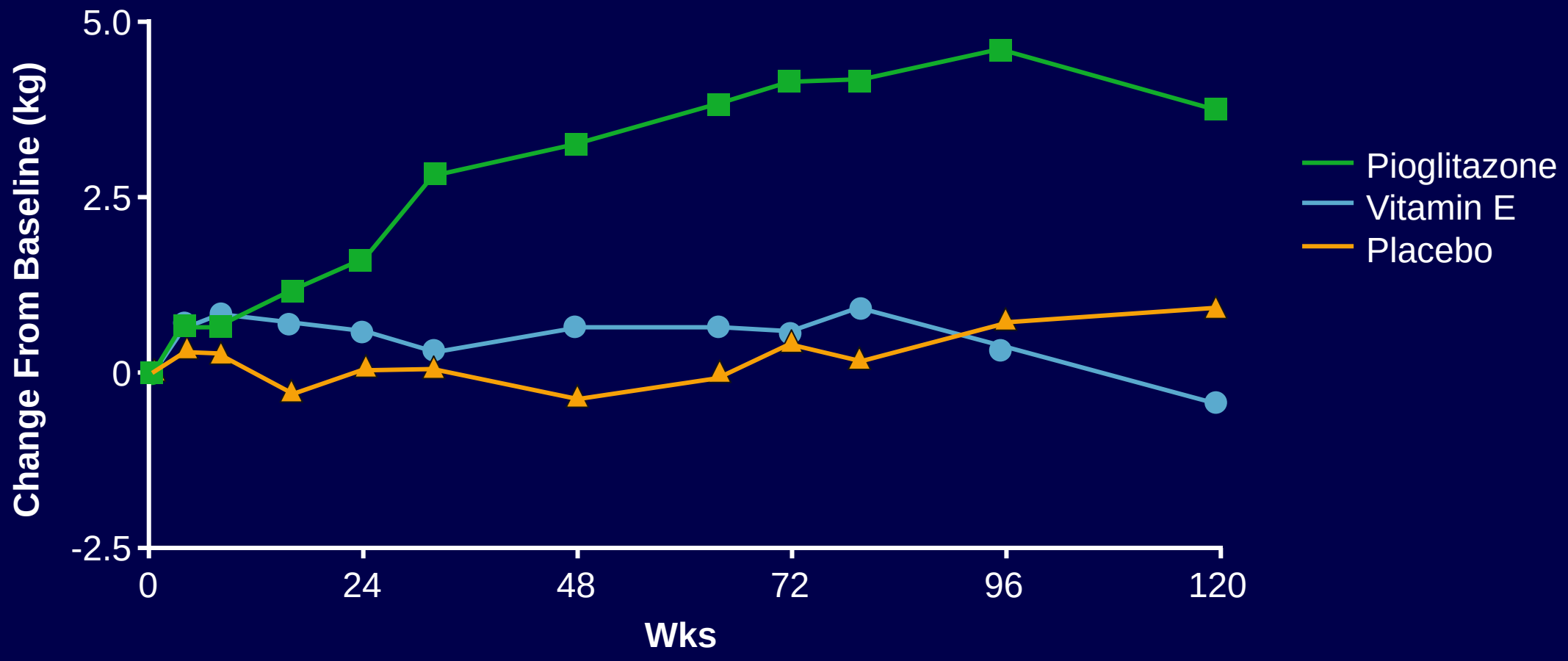


- Other pioglitazone outcomes:
  - Improved fibrosis score (treatment difference: -0.5; CI: -0.9 to 0; *P* = .039)
  - Greater weight gain (2.5 kg vs placebo)

Cusi K, et al. Ann Intern Med. 2016;165:305-315.

Slide credit: clinicaloptions.com

PIVENS: Change in Weight by Treatment



Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.

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Pioglitazone in NASH: When and How

- Biopsy-proven NASH with diabetes or prediabetes[1]
- Monitor:
  - Body weight (and address with lifestyle interventions such as exercise and diet)
  - ALT and AST response
  - DEXA scan

1. Chalasani N, et al. Hepatology. 2017;[Epub ahead of print].

Conclusions: Current Management of NASH

- NASH can lead to cirrhosis and HCC
  - Initial assessment
  - Natural history
- Indications for liver biopsy
  - Metabolic traits
- Current and future status of elastography-based noninvasive assessment
  - Innovations in clinical trial endpoints: MRI/MRE
- Treatment of NASH
  - Lifestyle, vitamin E, pioglitazone

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