

Pharmacotherapy: Expanding Care Beyond Diet and Exercise in NASH Management: Who should get it?

Naga Chalasani, MD, AGAF, FAASLD
Indiana University School of Medicine
Indianapolis, IN

American Gastroenterology Association
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Disclosures

- Paid consulting activities in last 12 months – Abbvie (Allergan), Madrigal, Foresite Labs, La Jolla, Zydus, Galectin, and Axcella
- Research support – Exact Sciences, DSM and Intercept
- Speaker's bureau – None
- Off label use - Vitamin E, Pioglitazone, Metformin

Major causes of morbidity and mortality of NAFLD sub-phenotypes

NAFL	NASH w/ F0 & F1	NASH with F2 & F3	NASH Cirrhosis
Cardiovascular	Cardiovascular	Liver disease	Liver disease
Non-hepatic malignancies	Non-hepatic malignancies	Cardiovascular disease	Cardiovascular disease
?Renal disease	Liver disease	Hepatic & non-hepatic malignancies	Hepatic & non-hepatic malignancies
?Cerebrovascular disease	?Renal disease	?Renal	?Renal

Liver directed pharmacotherapy

	Liver directed pharmacotherapy	Management of co-morbidities¥
NAFL	No	Yes
NASH w/F0 & F1	Probably Not	Yes
NASH w/F2&F3	Yes	Yes
NASH Cirrhosis	Yes	Yes

¥Aggressive management of dyslipidemia, diabetes, hypertension, and weight. Alcohol consumption should be avoided or limited to 2-3 drinks per week in women and 4-5 drinks per week in men. Smoking should be discouraged. Coffee drinking may offer some benefit.

Options for liver directed pharmacotherapy

- No therapies are approved in the Western world to treat NASH
- Several medications have been studied as **off-label** indications

	Histological efficacy
Pioglitazone	Yes
Vitamin E	Yes
Liraglutide	Possibly
Ursodeoxycholic acid	No
Metformin	No
Omega-3 polyunsaturated fatty acid	No
Milk thistle	Probably Not
Angiotensin converting enzyme inhibitors	Probably Not

Pioglitazone improves liver histology in NASH

- Multiple studies showed pioglitazone (30 mg/d or 45 mg/d) improves aminotransferases, steatosis and necroinflammation in both diabetics and non-diabetics with NASH
- May improve fibrosis but definitive evidence is lacking
- No evidence to date to show that improves long term outcomes such as development of cirrhosis or liver cancer
- Pioglitazone has not been tested in patients with NASH cirrhosis
- Weight gain is a concern

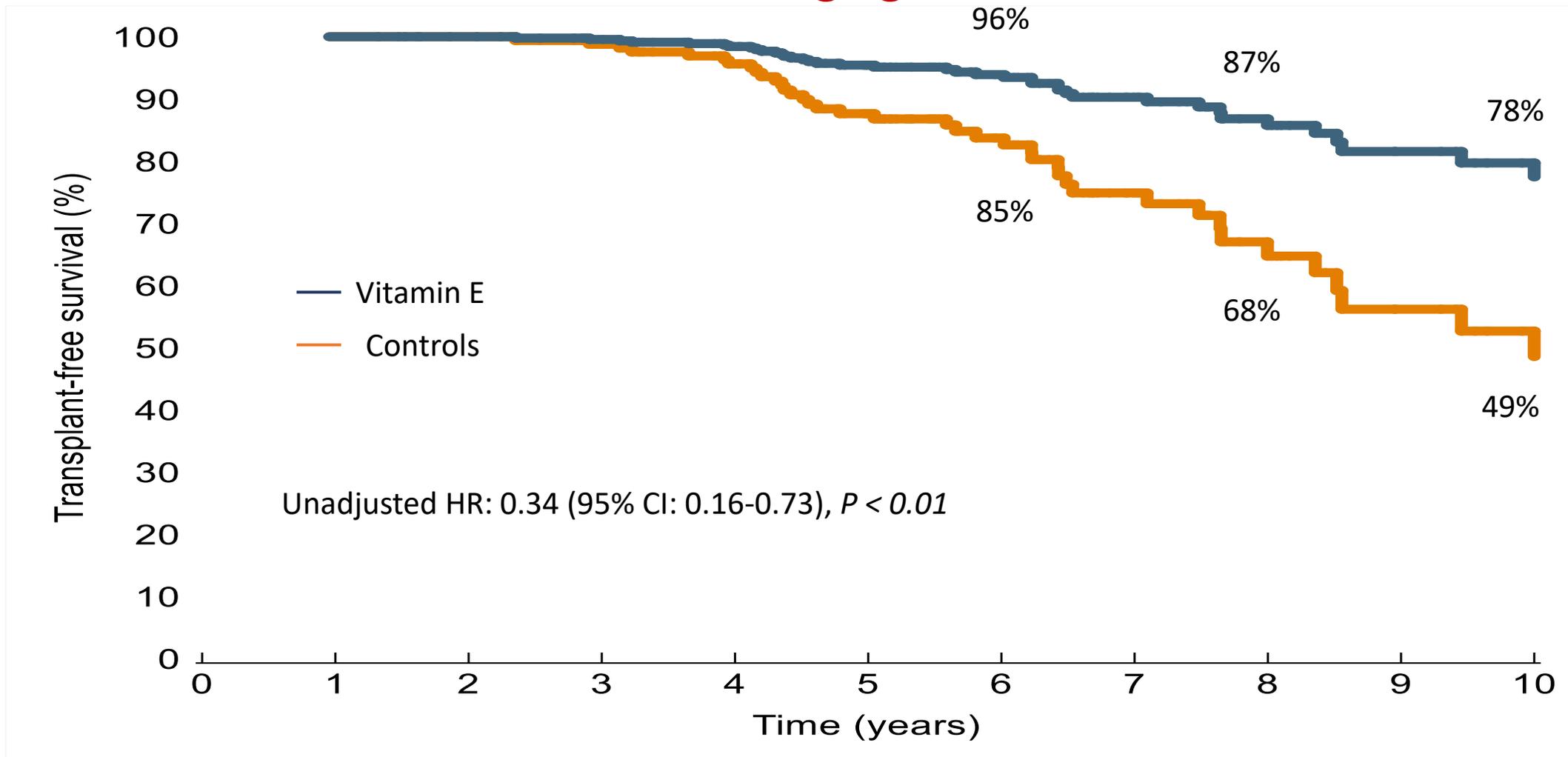
Vitamin E improves liver histology and may improve patient outcomes in patients with NASH

AASLD Practice Guidance*

- Vitamin E administered at a daily dose of 800 IU/d improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.
- Until further data become available, vitamin E is not recommended for NASH in diabetics, NAFLD without biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

**Chalasani N, et al. Hepatology 2018; 67: 328-357*

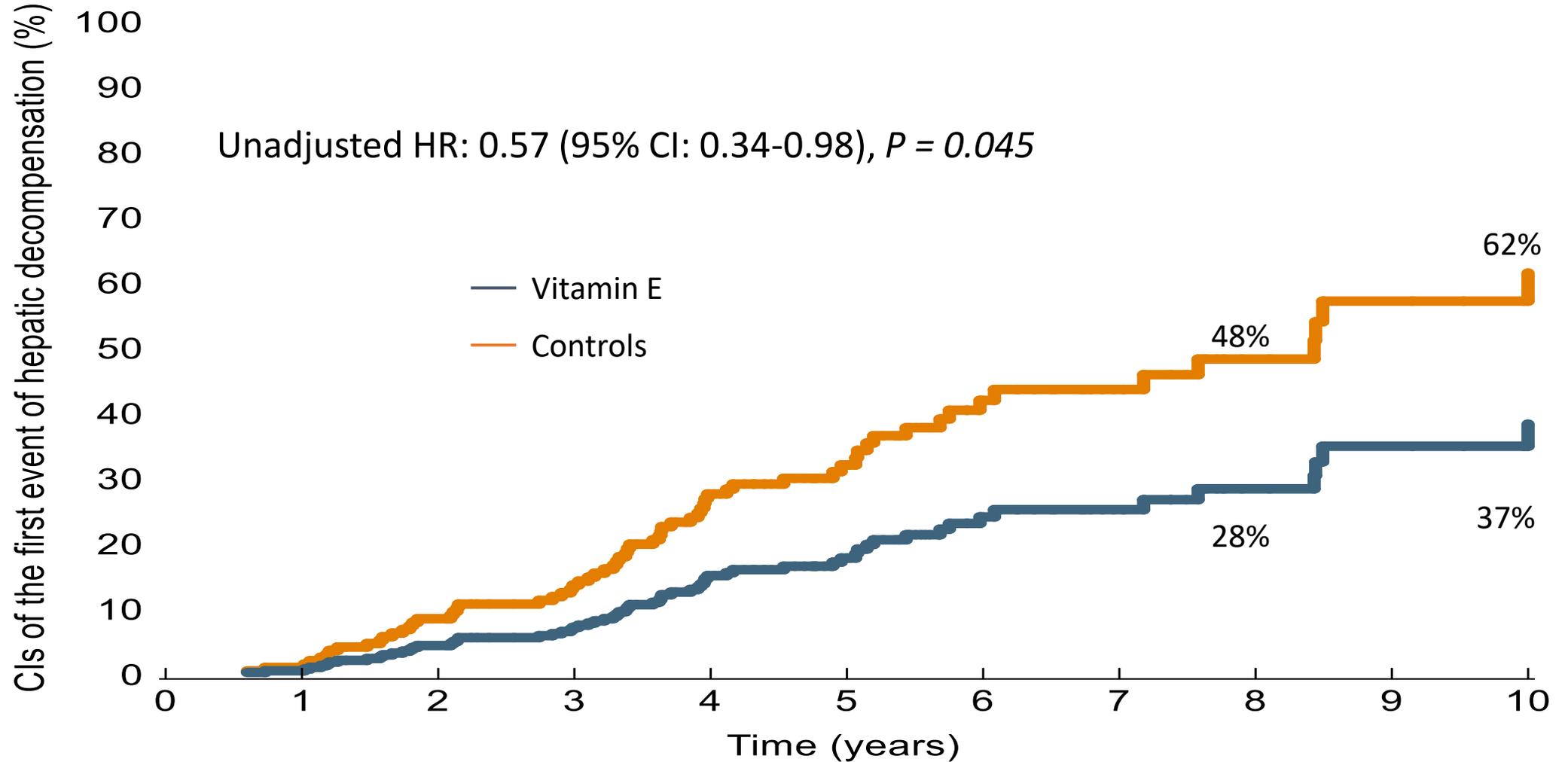
Long-term vitamin E effect on transplant-free survival in patients with NASH cirrhosis and bridging fibrosis



Vitamin E
Controls

90	89	84	77	67	55	38	21	13	10	8
90	90	89	85	76	55	41	29	19	12	8

Long-term vitamin E effect on hepatic decompensation in patients with NASH cirrhosis and bridging fibrosis

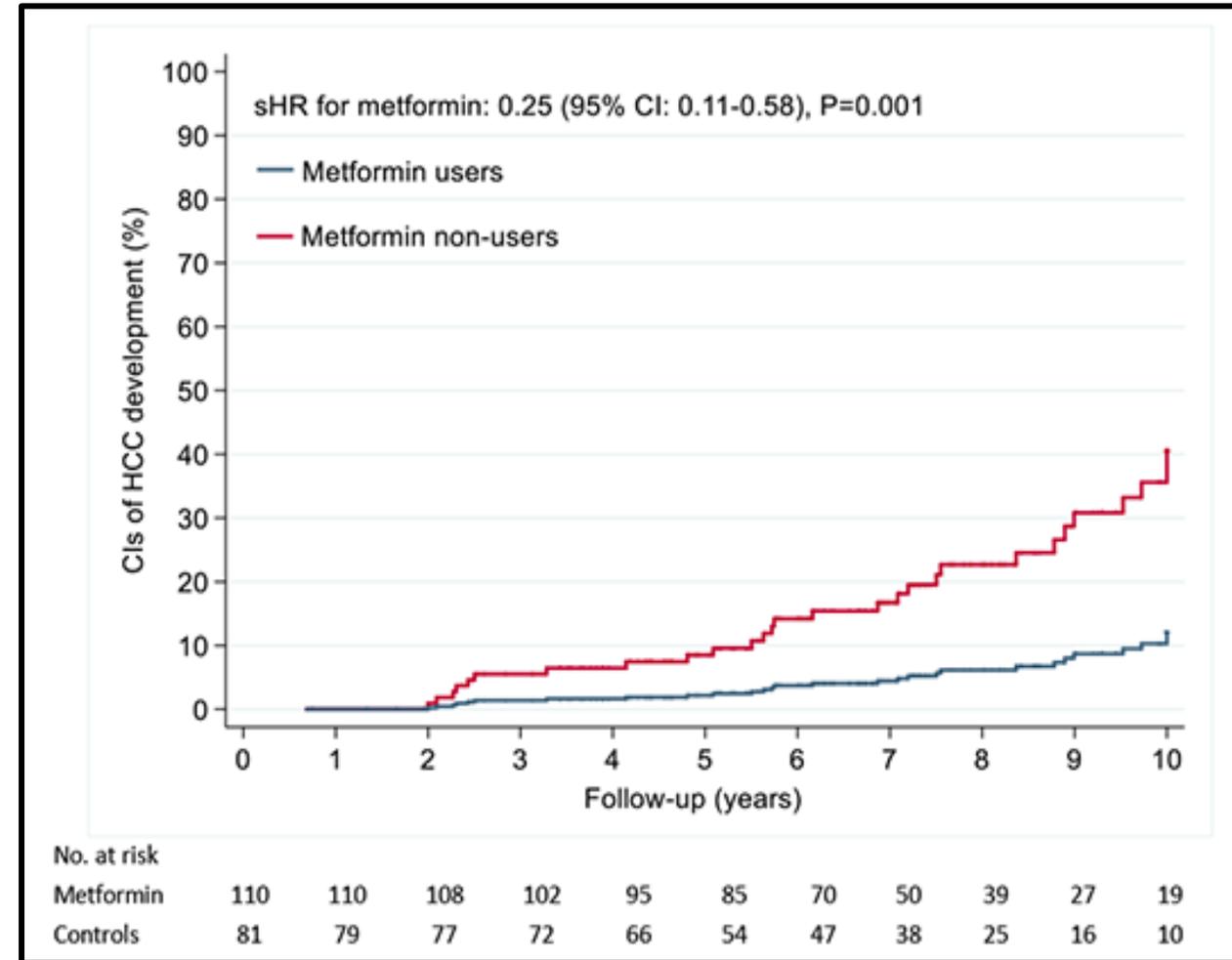


Vitamin E
Controls

90	88	75	68	55	43	26	19	12	9	6
90	90	83	74	54	34	20	15	8	5	5

Metformin may improve outcomes and lower the risk of HCC in NASH bridging fibrosis & cirrhosis

- 191 diabetic NAFLD patients with bridging fibrosis or cirrhosis
- 110 metformin users – median duration 6 years
- Metformin use was associated with lower risk of overall mortality or transplantation (HR: 0.42, 95% CI: 0.24-0.74) and liver cancer (sHR: 0.25, 95% CI: 0.11-0.58).
- No lactic acidosis or hepatotoxicity



Use of statins in NAFLD patients with dyslipidemia

- Dyslipidemia and both prevalent and incident cardiovascular disease are common in patients with NAFLD.
- There is high prevalence of NAFLD in patients with dyslipidemia.
- Numerous studies demonstrated statins are safe and efficacious in patients with NAFLD and NASH
- Statins can be used to treat dyslipidemia in patients with NAFLD and NASH. They can be used in patients with NASH cirrhosis, but should be avoided in patients with decompensated cirrhosis.

Take home messages

- Only subsets of NAFLD patients with NASH and fibrosis stage ≥ 2 are candidates for liver-directed pharmacotherapy.
- Patients with NAFLD and NASH are heavily enriched with metabolic comorbidities such as type2 diabetes, obesity, and hyperlipidemia. Their aggressive management is critical.
- Off-label use of vitamin E or pioglitazone may be appropriate for improving liver histology in select patients with NASH and fibrosis.