Baveno VII Criteria and Portal Hypertension Management

Nancy Reau, MD and David Bernstein, MD

Introduction and Key Points

- Meant to be a thought provoking, healthly debate of important topics
- Statements made may not necessarily be the true view of the speakers
- Despite intense disagreements on stage, Nancy and I remain friends

Topic 1:
Portal Vein Thrombosis

Baveno VII: Portal Vein Thrombosis

8.27 PVT is characterised by the presence of a thrombus in the portal vein trunk or its branches. Portal cavernoma is a network of porto-portal collaterals which develops as a consequence of prior portal vein obstruction. (D.1) Obstruction leading to cavernoma is mostly related to thrombosis in adults, but less likely so in children and young adults.

De Franchis et al. *J Hepatology*. 2022.

Portal Vein Thrombosis

- Common in cirrhotics
  - 5-16%/yr with stable cirrhosis without HCC
  - Risk progresses with advancing disease
- Virchow's Triad
  - Acquired protein C deficiency with high factor VIII and vWF
  - Slow portal vein flow
  - Endothelial injury related to liver disase
- May be complete or partial
- May be acute or chronic
- Usually asymptomatic but may present with pain

Anticoagulation in Portal Vein Thrombosis

Bernstein- PRO

Pro: Anticoagulation in Portal Vein Thrombosis

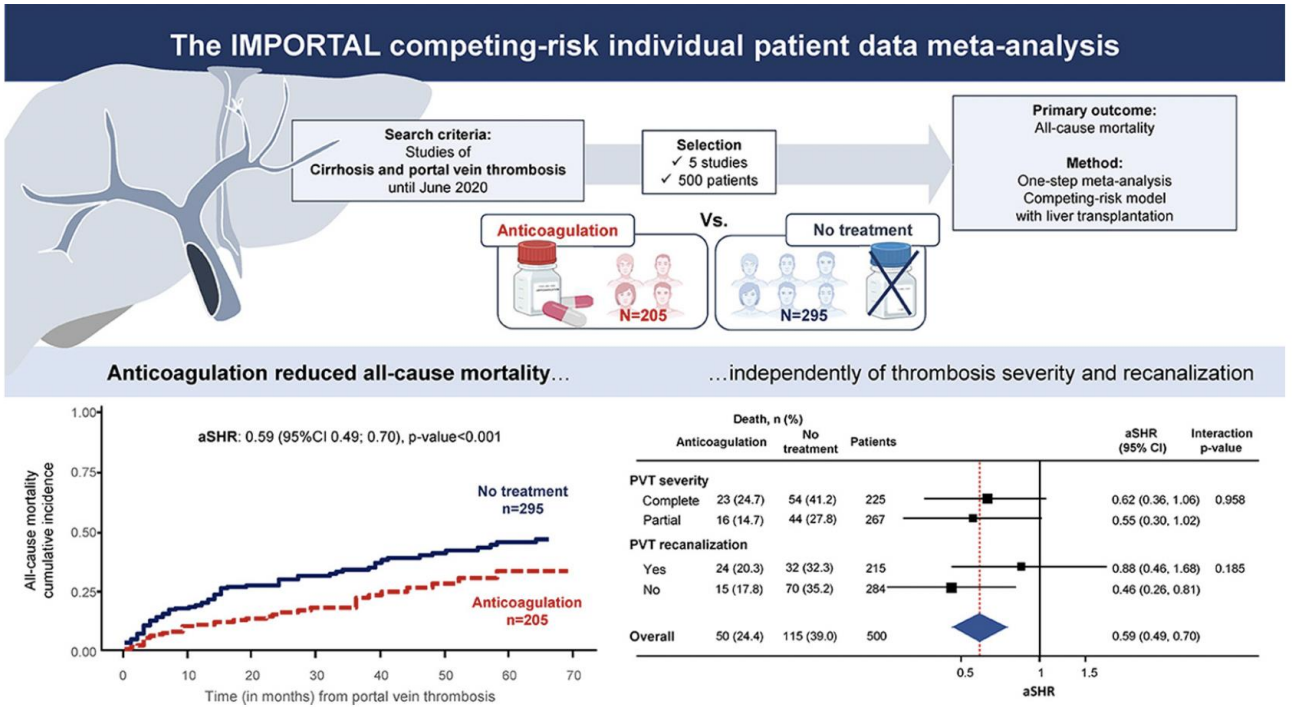
- Rationale for treatment:
  - Rarely resolve spontaneously
  - Prevent clot extension to SMV, SV
  - Allow for recanalization to prevent intestinal infarction
  - Prevent the development of portal hypertension
  - Shown to be safe and effective[1]

Leffredo et al. *Gastro*. 2017.

Pro: Anticoagulation in Portal Vein Thrombosis

- Who to treat?
  - Non-cirrhotics
  - Cirrhotics with
    - Complete or >50% obstruction
    - Symptomatic PVT
    - SMV involvement
    - PVT in OLT candidates
- How to treat
  - Start with LMWH then switch to oral agent
    - Coumadin, DOAC (preferred in cirrhotics)
  - Treatment for at least 6 months or until clot resolution unless non-correctable cause

Pro: Anticoagulation in Portal Vein Thrombosis



Guerro et al. *J Hep*. 2023.

Anticoagulation in Portal Vein Thrombosis

Reau- CON

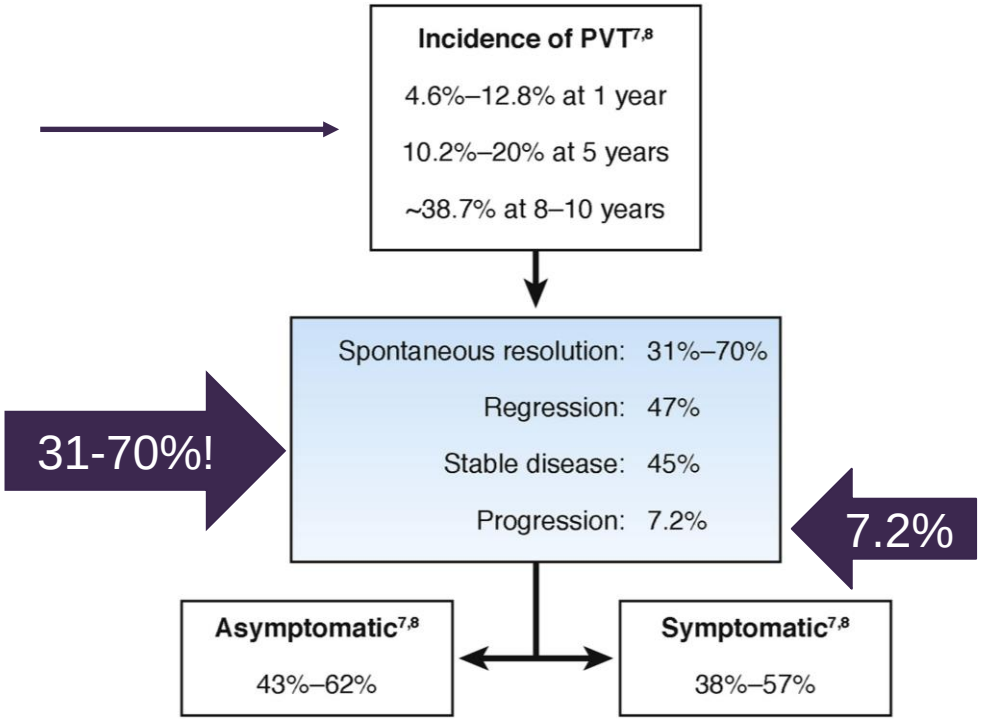
Baveno VII Say…

- PVT without cirrhosis should receive anticoagulation
- PVT should be anticoagulated in patients considered for OLT

- What about PVT in patients with cirrhosis that are NOT transplant candidates

1. Spontaneous Resolution is Common They Don't Always Get Worse or Become Symptomatic

- Frequent complication with cirrhosis
  - Increases with the cirrhosis severity and HCC
- Progression in 9% of treated vs. 33% of untreated
- 40-60% asymptomatic



García-Pagán JHEP Rep. 2020 Aug; 2(4): 100122.

2. Anticoagulation Doesn't Always Work

- Efficacy decreases with chronic PVT or existing cavernoma
- Considerable proportion require alternative treatments
  - TIPS for refractory ascites/EV

Simonetto, Douglas A. MD[1]; Singal, Ashwani K. MD, MS, FACG[2]; Garcia-Tsao, Guadalupe MD, FACG[3]; Caldwell, Stephen H. MD[4]; Ahn, Joseph MD, MS, MBA, FACG[5]; Kamath, Patrick S. MD[1] ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation, The American Journal of Gastroenterology: January 2020 - Volume 115 - Issue 1 - p 18-40 doi: 10.14309/ajg.0000000000000486.

3. PVT Associated With CPT

- PVT more common as liver disease progresses
- EV more likely to be present in CPT B/C
- EV more likely to bleed even if small

- If not OLT candidate, prognosis is poor
  - EV bleeding associated w/ high mortality

	A			B			C		
Red wale markings	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
-	6	10	15	10	16	26	20	30	42
+	8	12	19	15	23	33	28	38	54
++	12	16	24	20	30	42	36	48	64
+++	16	23	34	28	40	52	44	60	76

Estimations are based upon **one-year percentage** probability of bleeding. A, B, C refer to Child class. F1, F2, F3 refer to size of the varix.
Adapted from deFranchis, R, N Engl J Med 1988; 319:983.

4. Bleeding Risk Is Real

- *Our results confirm that anticoagulation does not increase the risk of portal hypertensive bleeding, even in a population where most patients had decompensated cirrhosis.*
- *A word of caution is needed because non-portal hypertension-related bleeding, mainly gastrointestinal, was more frequent in the anticoagulation cohort.*
- *The rate of bleeding in our cohort (9.7%) compares favorably with that of 11.1% recently reported in patients with Child B cirrhosis on VKA for atrial fibrillation.*

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Summary PVT- Who to Anticoagulate?

Yes

- Noncirrhotic
- Acute
- Symptomatic
- Occlusive, Main
- SMVT
- Thrombophilia
- LTx Candidate

No

- High risk of bleeding~ Large varices that have not been Rx
- Nonadherence
- Underlying poor prognosis
- Poor functional status, comorbidities

? Chronic PVT with cavernous transformation- Case by Case

Topic 2:
Statin Use on Cirrhosis

Baveno VII - Statins in Cirrhosis

4.1 The use of statins should be encouraged in patients with cirrhosis and an approved indication for statins since these agents may decrease portal pressure (A.1) and improve overall survival. (B.1)

4.2 In patients with Child-Pugh B and C cirrhosis, statins should be used at a lower dose (simvastatin at max. 20 mg/d) and patients should be followed closely for muscle and liver toxicity.(A.1) In Child-Pugh C cirrhosis the benefit of statins has not been proven yet and their use should be more restrictive. (D.1)

De Franchis et al. *J Hep*. 2022.

Statin Use in Compensated and Decompensated Virrhosis

Reau- PRO

Intro

- Legacy of fear of statin and liver disease
- Studies show that people with CLD and indications for statins are frequently not on lipid therapy

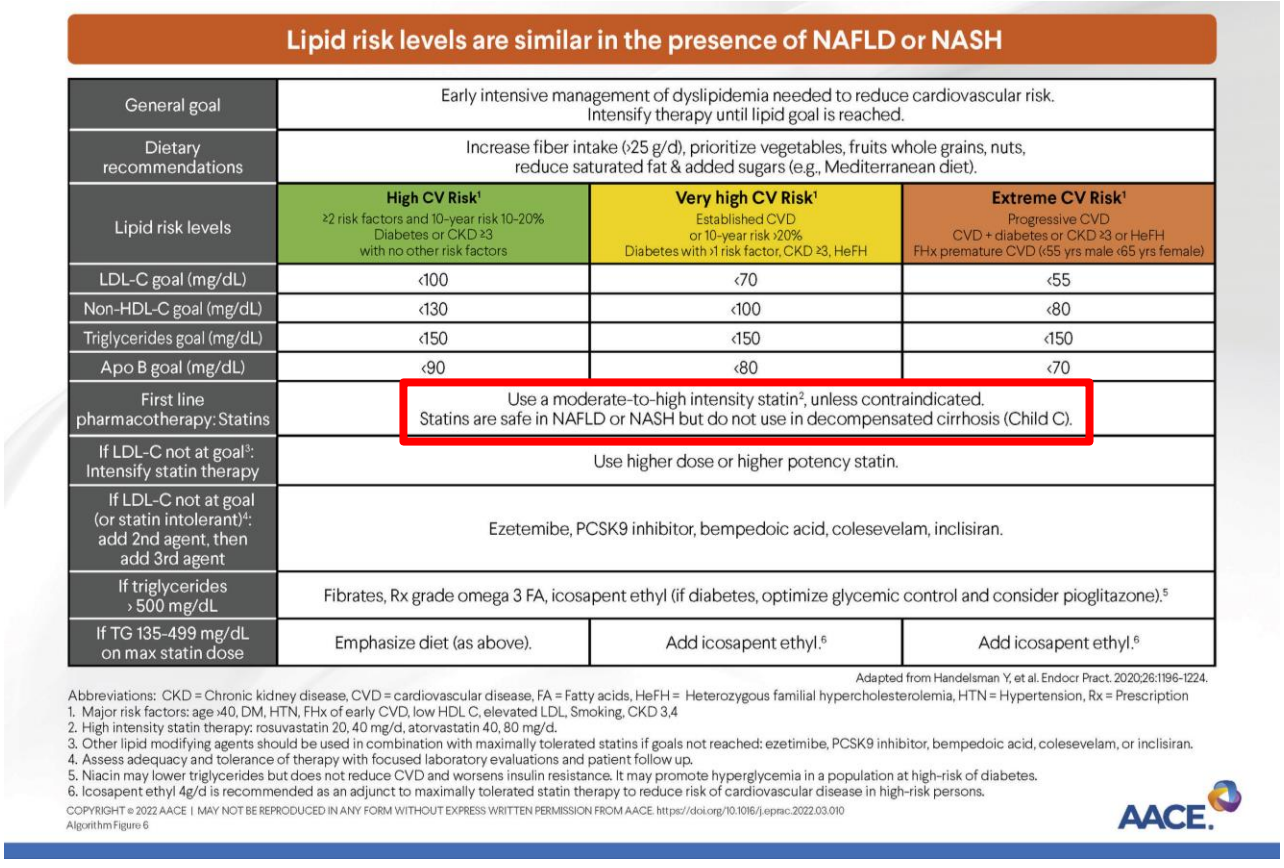
Compensated Cirrhosis

Baveno VII statement:

- The use of statins should be encouraged in patients with cirrhosis **and an approved indication for statins** since these agents may decrease portal pressure (A.1) and improve overall survival. (B.1) (Changed)

- Use if approved indication for statin
- Supported by Baveno VII and AACE 2022
- Favorable impact on PHT, HCC, Mortality

Atherogenic Dyslipidemia Management in NAFLD



Lipid risk levels are similar in the presence of NAFLD or NASH

General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until lipid goal is reached.		
Dietary recommendations	Increase fiber intake (>25 g/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet).		
Lipid risk levels	**High CV Risk**[1] ≥2 risk factors and 10-year risk 10-20% Diabetes or CKD ≥3 with no other risk factors	**Very high CV Risk**[1] Established CVD or 10-year risk >20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV Risk**[1] Progressive CVD CVD + diabetes or CKD ≥3 or HeFH FHx premature CVD (<55 yrs male <65 yrs female)
LDL-C goal (mg/dL)	<100	<70	<55
Non-HDL-C goal (mg/dL)	<130	<100	<80
Triglycerides goal (mg/dL)	<150	<150	<150
Apo B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C).		
If LDL-C not at goal[3]: Intensify statin therapy	Use higher dose or higher potency statin.		
If LDL-C not at goal (or statin intolerant)[4]: add 2nd agent, then add 3rd agent	Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran.		
If triglycerides > 500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone).[5]		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above).	Add icosapent ethyl.[6]	Add icosapent ethyl.[6]

Adapted from Handelsman Y, et al. Endocr Pract. 2020;26:1196-1224.

Abbreviations: CKD = Chronic kidney disease, CVD = cardiovascular disease, FA = Fatty acids, HeFH = Heterozygous familial hypercholesterolemia, HTN = Hypertension, Rx = Prescription

1. Major risk factors: age >40, DM, HTN, FHx of early CVD, low HDL C, elevated LDL, Smoking, CKD 3,4
2. High intensity statin therapy: rosuvastatin 20, 40 mg/d, atorvastatin 40, 80 mg/d.
3. Other lipid modifying agents should be used in combination with maximally tolerated statins if goals not reached: ezetimibe, PCSK9 inhibitor, bempedoic acid, colesevelam, or inclisiran.
4. Assess adequacy and tolerance of therapy with focused laboratory evaluations and patient follow up.
5. Niacin may lower triglycerides but does not reduce CVD and worsens insulin resistance. It may promote hyperglycemia in a population at high-risk of diabetes.
6. Icosapent ethyl 4g/d is recommended as an adjunct to maximally tolerated statin therapy to reduce risk of cardiovascular disease in high-risk persons.

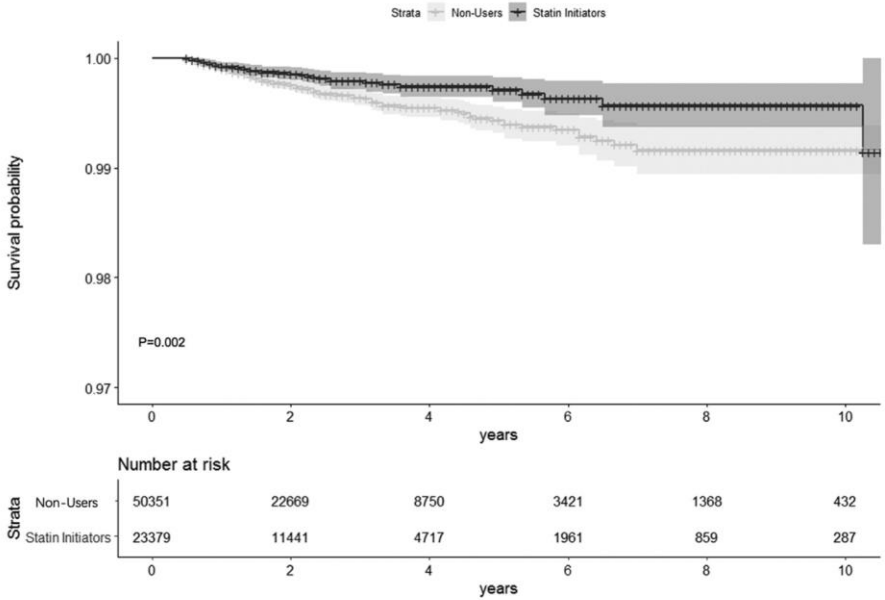
Algorithm Figure 6

AACE

Statins reduce HCC

Statin Use and Reduced Hepatocellular Carcinoma Risk in Patients With Nonalcoholic Fatty Liver Disease

Biyao Zou,[*,‡] Michelle C. Odden,[‡] and Mindie H. Nguyen[*,‡]



Clinical Gastroenterology and Hepatology 2023;21:435–444.

Treatment With HMG-CoA Reductase Inhibitors (Statins) is Associated With Preservation Of Hepatic Function in Advanced Chronic Liver Disease (CLD): Results from the Shunt-v Study

Objective

- Evaluate impact of NASH, T2DM and drug therapy on hepatic function and portal-systemic shunting in subjects enrolled in the SHUNT-V study

Methods

- F3/4 with PLT <175

Authors Conclusion:

- In the SHUNT-V study of clinically stable but advanced CLD, concomitant use of statins was independently associated with preserved hepatic function and reduced portal-systemic shunting.

Abstract 144.

Statins Are Associated With Reduced Development of Acute on Chronic Liver Failure in a Large National Cohort of Patients With Cirrhosis

Objective

- Can statins reduce the likelihood of ACLF in patients with cirrhosis

Methods

- Retrospective cohort study large VA database

- Authors conclusions:
  - **Conclusion:** In this large, inverse probability-weighted analysis, statin therapy was significantly associated with reduced risk of subsequent ACLF-2/3 hospitalization events.

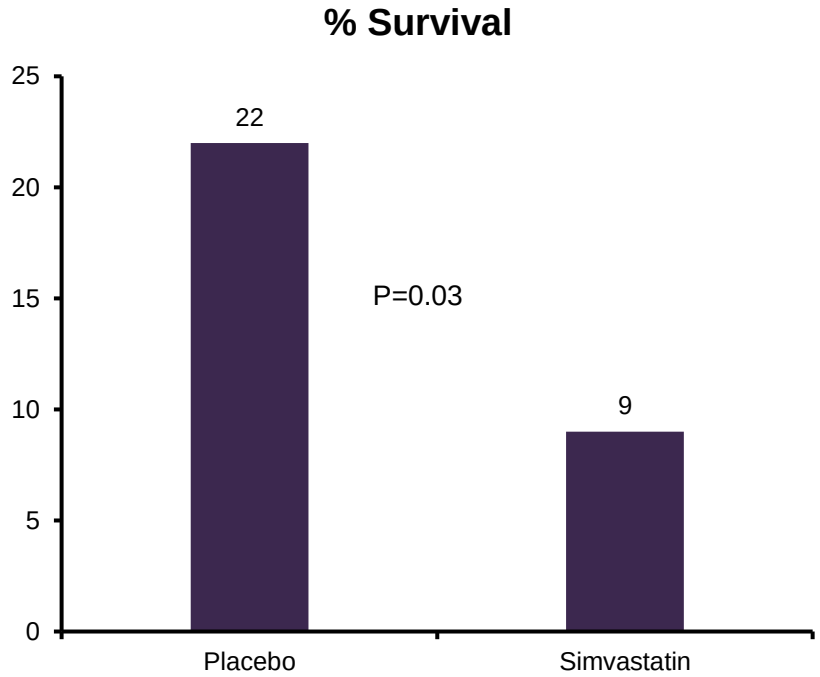
Abstract 205.

Decompensated Cirrhosis: Baveno VII

- In patients with Child-Pugh B and C cirrhosis, statins should be used at a lower dose (simvastatin at max. 20 mg/d) and patients should be followed closely for muscle and liver toxicity.(A.1)
- In Child-Pugh C cirrhosis the benefit of statins has not been proven yet and their use should be more restrictive. (D.1) (Changed)

Simvastatin Increased Survival in Cirrhotics

- Bleeding prevention with Simvastatin study (Spain)
- 1:1 Simvastatin or Placebo started 5-10 days after index variceal bleed
  - 2 years F/U
- 158 patients enrolled
  - 50% Alcoholic liver dz
- No impact on rebleeding
- No difference in AEs or SAEs



Abraldes et al. *Gastroenterology*. 2016.

Statin Use in Compensated and Decompensated Cirrhosis

Bernstein- CON

Con: Statin Use in Compensated Cirrhosis

- Use with caution
- Cannot use if patient actively drinking ETOH
- Avoid with significant cholestasis
  - Statins excreted in the bile
  - Associated with increased risk of toxicity[1]
- Avoid atorvastatin due to risk of rhabdomylosis[2]
  - I concede other statins not extensively metabolized may be used

1. Wright et al. *Frontline Gastro*. 2015; 2. Weersink et al. *Drug Safety*. 2018.

Con: Statin Use in Decompensated Cirrhosis

- Should not be used in decompensated cirrhosis
  - Increased risk of hepatotoxicity
- Some patients in DC will die from liver failure before experiencing any benefits from lipid lowering

Topic 3:
carvedilol +/- egd

Baveno VII – Prevention of Variceal Hemorrhage

5.14 Treatment with NSBBs (propranolol, nadolol or carvedilol*) should be considered for the prevention of decompensation in patients with CSPH. (B.1) (New) *In contrast with the traditional NSBBs (i.e. propranolol and nadolol), carvedilol has intrinsic anti-alpha adrenergic vasodilatory effects that contribute to its greater portal pressure reducing effect.

De Franchis et al. *J Hepatology*. 2022.

Baveno VII - Carvedilol

5.15 Carvedilol is the preferred NSBB in compensated cirrhosis, since it is more effective at reducing HVPG (A.1), has a tendency towards greater benefit in preventing decompensation and towards better tolerance than traditional NSBBs and has been demonstrated to improve survival (B.1)compared to no active therapy in compensated patients with CSPH.

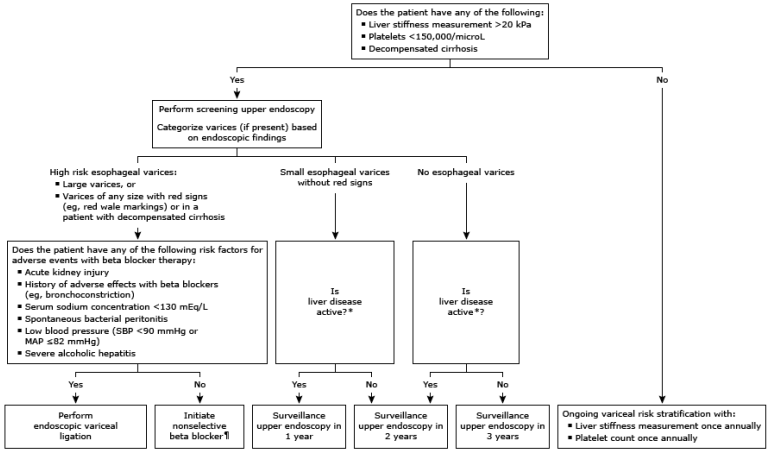
De Franchis et al. *J Hepatology*. 2022.

Prevention of Variceal Hemorrhage

- Primary prevention – subject of this debate
- Secondary- all agree combination of NSBB and EVL
- Carvedilol initial dose 3.125 BID and titrate to a maximum dose of 6.25 mg BID while maintain a MAP >82 and HR 55-60

Screening for Esophageal Varices

Approach to screening for esophageal varices and preventing variceal bleeding in adults with cirrhosis



This algorithm summarizes the general approach to screening for esophageal varices and preventing variceal bleeding in adults with cirrhosis. This algorithm is intended for use in conjunction with other UpToDate content. Refer to UpToDate's topic on prevention of variceal bleeding for additional details, including the evidence supporting the efficacy of these preventive strategies.

SBP: systolic blood pressure; MAP: mean arterial pressure.

* Patients with cirrhosis and active liver disease include those with ongoing liver inflammation (eg, untreated viral hepatitis, active alcohol use disorder, metabolic syndrome).

¶ The goal resting heart rate for patients on nonselective beta blocker therapy is 55 to 60 beats per minute, provided that MAP remains >82 mmHg. We continue the beta blocker indefinitely while monitoring for adverse effects (eg, hypotension).

UpToDate®

Uptodate.com. Accessed 2/20/2023.

Baveno Beta Blocker (Carvidolol) - EGD

Bernstein- PRO

Pro: Carvedilol Without EGD

- Carvedilol has intrinsic anti-alpha adrenergic activity in addition to being a NSBB
  - Anti-alpha 1 adrenergic activity lowers hepatic vascular tone and hepatic resistance
  - Greater decrease in HVPG than propranolol and nadolol[1]
- Primary prophylaxis
  - Carvedilol alone without EGD if CSPH present (HVPG > 10)

1. Reiberger et al. *Gut*. 2013; 2. Jachs et al. *Clin Gastro/Hep.* 2022.

Pro: Carvedilol Without EGD

- Compared to EVL, carvedilol associated with significant survival benefit[1]
  - Prevention of first variceal bleed
  - **Evaluated 20-year effects of carvedilol**
  - **Survival benefit may not be liver related but associated with systemic effects**
    - **Cardiac, reduction of bacterial translocation**

McDowell et al. *Aliment Pharm*. 2021.

Pro: Carvedilol Without EGD

- Special populations
  - Decompensated cirrhosis
    - Carvedilol can be used provided the systolic BP remains >90 mmHg
  - Gastric varices[1]
    - Although limited data, carvedilol may be effective
    - No role for EGD in primary prophylaxis

Garcia Tsao et al. *Hepatology*. 2017.

Baveno Beta Blocker (Carvidolol) + EGD

Reau- CON

Baveno VII – Renewing Consensus in PHT

- Patients with compensated cirrhosis who are not candidates for initiating NSBBs should undergo an endoscopy for variceal screening **if LSM by TE is >−20 kPa or platelet count is <−150x109L** (A.1) (New)
- LSM by TE <−15 kPa plus platelet count >−150x109/L rules out CSPH
- LSM value by TE of >−25 kPa is sufficient to rule in CSPH → NSBB
- LSM values <25 kPa, the ANTICIPATE model can be used to predict the risk of CSPH
  - LSM values between **20- 25 kPa and platelet count <150x109/**L or LSM values between **15-20 kPa and platelet count <110x109/L** have a CSPH risk of at least 60%. (B.2) (New) → NSBB
- Treatment with NSBBs (propranolol, nadolol or carvedilol*) should be considered for the prevention of decompensation in patients with CSPH. (B.1) (New)
  - Carvedilol is the preferred NSBB in compensated cirrhosis
- Patients with compensated cirrhosis who are on NSBBs for the prevention of decompensation do not need a screening endoscopy for the detection of varices since endoscopy will not change management (B.2) (New)

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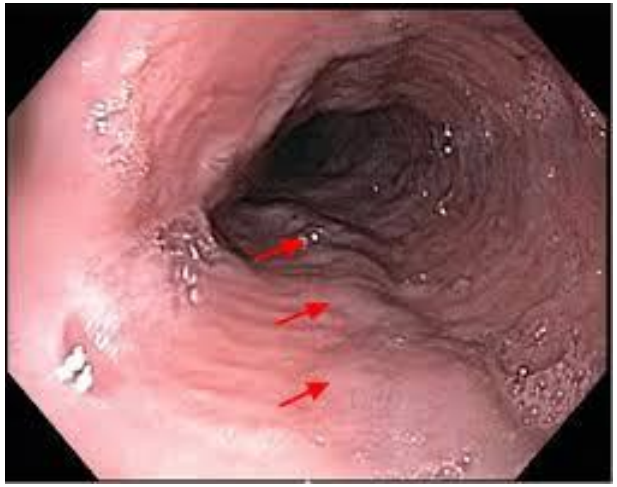
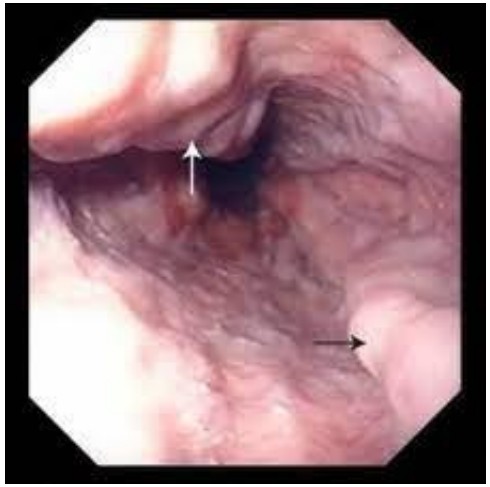
NOT Obese NASH

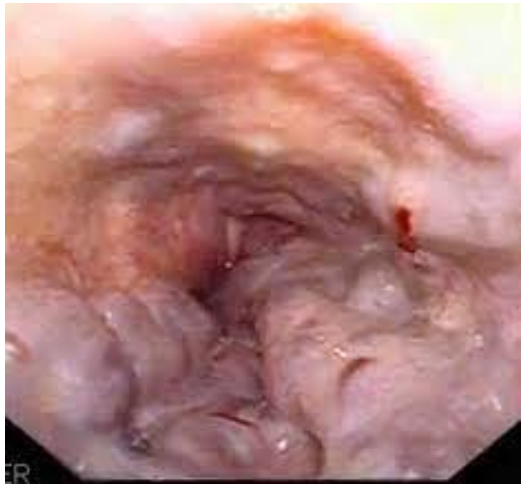
virus- and/or alcohol-related cACLD and non-obese (BMI <30 kg/m2) NASH-related cACLD

Do You Agree?

5.17 Patients with compensated cirrhosis who are on NSBBs for the prevention of decompensation do not need a screening endoscopy for the detection of varices since endoscopy will not change management. (B.2) (New)







- Would you treat these equally?

Not Everyone With CSPH Has Varices

- Persons with compensated cirrhosis will typically develop varices at a rate of 7 to 8% per year
- BB do not prevent the formation of EV
- Varices are present in 30 to 40% of persons with compensated cirrhosis and in 60 to 85% of those with decompensated cirrhosis
  - Unnecessary treatment in up to 70% of compensated cirrhosis

ORIGINAL ARTICLE

Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis

Roberto J. Groszmann, M.D., Guadalupe Garcia-Tsao, M.D., Jaime Bosch, M.D., Norman D. Grace, M.D., Andrew K. Burroughs, M.B., Ch.B., Ramon Planas, M.D., Angels Escorsell, M.D., Juan Carlos Garcia-Pagan, M.D., David Patch, M.B., B.S., Daniel S. Matloff, M.D., Hong Gao, M.D., Ph.D., and Robert Makuch, Ph.D. for the Portal Hypertension Collaborative Group

CONCLUSIONS

Nonselective beta-blockers are ineffective in preventing varices in unselected patients with cirrhosis and portal hypertension and are associated with an increased number of adverse events.

November 24, 2005
N Engl J Med. 2005; 353:2254-2261.

We Don’t Maximize Our NSBB

- Established after titration according to heart rate, arterial pressure and clinical tolerance
- The proportion of responders increases to about 75% when using carvedilol (even in propranolol non-responders)

Gut. 2013;62(11):1634–1641.

Potential Side Effects And Controversy

- Asthma
- Hypotension
- Ascites, especially refractory ascites with risk for HRS

Summary

- Anticoagulation for PVT
- Statin use in Cirrhosis
- Carvedilol +/- EGD