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Contact Hours:

ANMC designates this activity for a maximum of 12 contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

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ALASKA NATIVE MEDICAL CENTER

Portal Hypertension & Beta blockers

YOUSSEF BARBOUR M.D

Objectives

- Diagnosis of portal HTN
- Complications of portal HTN
- Treatment of portal HTN
- Role of beta blockers in portal HTN

Pre-test 1

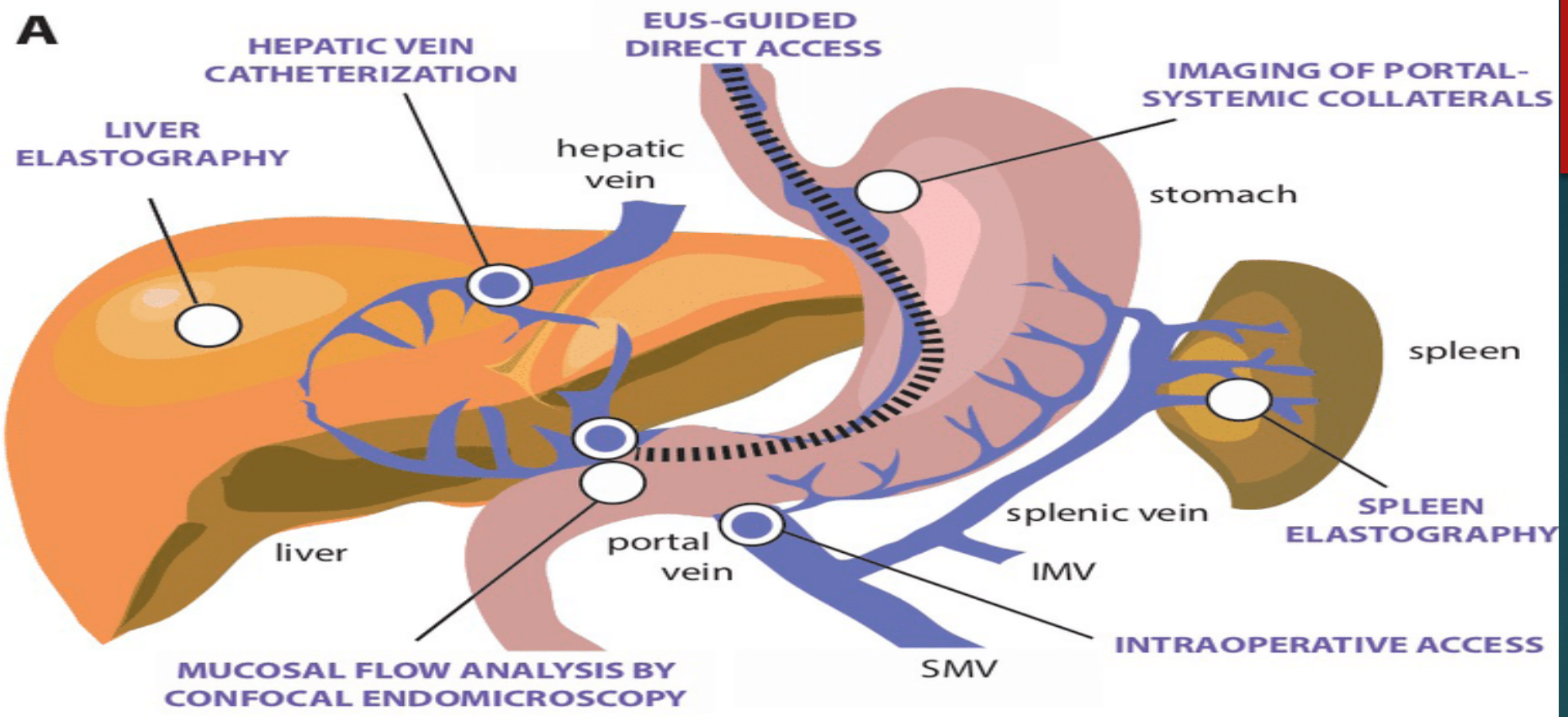
- What is the lowest pressure considered to be clinically significant portal pressure, using HVPG measurement?

- A- 6 mmHg
- B- 8 mmHg
- C-10 mmHg
- D-12 mmHg

Pre-test 2

- There is evidence that the use of Coreg in compensated cirrhosis may delay the onset of:

- A- Variceal bleed
- B- Ascites
- C- Hepatic encephalopathy
- D- all of the above


A
EUS-GUIDED
DIRECT ACCESS
HEPATIC VEIN
CATHETERIZATION
IMAGING OF PORTAL-
SYSTEMIC COLLATERALS
LIVER
ELASTOGRAPHY
hepatic
vein
stomach
spleen
SPLEEN
ELASTOGRAPHY
splenic vein
IMV
liver
portal
vein
INTRAOPERATIVE ACCESS
SMV
MUCOSAL FLOW ANALYSIS BY
CONFOCAL ENDOMICROSCOPY

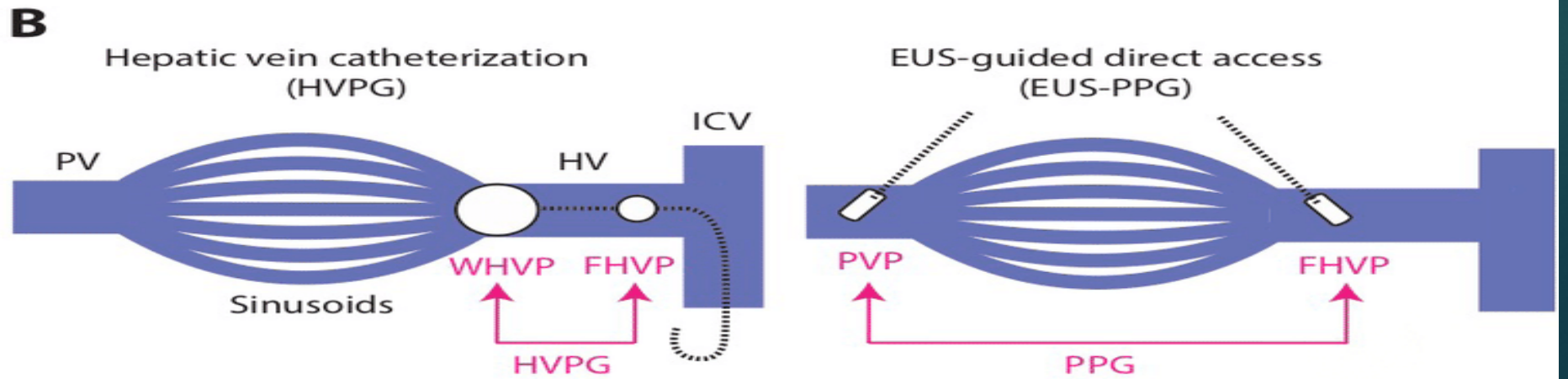

B
Hepatic vein catheterization
(HVPG)
EUS-guided direct access
(EUS-PPG)
ICV
PV
HV
WHVP
FHVP
Sinusoids
HVPG
PVP
FHVP
PPG

Table 2 Hepatic Vein Pressure Measurements in the Different Types of Portal Hypertension

		Hepatic Vein Pressure Measurement		
Type of PHa		**Wedged (WHVP)**	**Free (FHVP)**	**Gradient† (HVPG)**
Prehepatic (portal vein thrombosis)		Normal	Normal	Normal
Presinusoidal (cirrhosis attributed to cholestatic liver disease, schistosomiasis, and idiopathic portal hypertension)b		Normal	Normal	Normal
Sinusoidal (cirrhosis attributed to alcohol/HCV/NASH)		↑	Normal	↑
Postsinusoidal	Sinusoidal obstruction syndrome	↑	Normal	↑
	Budd-Chiari syndrome		Unable to catheterize hepatic vein	
Posthepatic	Right heart failure	↑	↑	Normal

a PH is classified by the site of increased resistance to blood flow.

Gradient or HVPG is calculated by subtracting the FHVP from the WHVP.

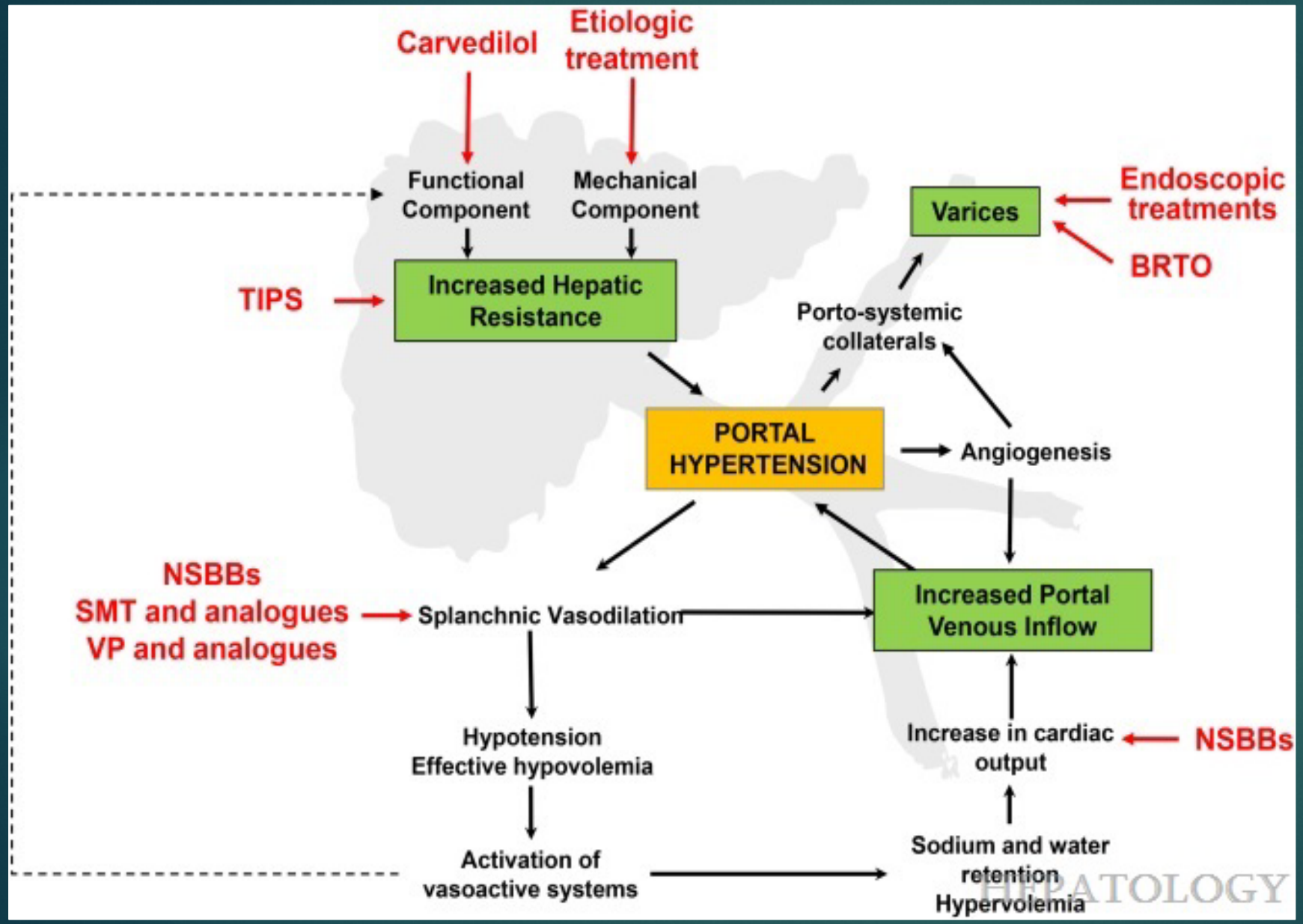
b In advanced stages of presinusoidal causes of PH, the WHVP and HVPG will increase.

Abbreviations: WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PH, portal hypertension.

What is portal HTN

- The portal pressure using HVPG normally between **3-5 mmHg**.
- *HVPG above 5 mmHg is considered portal HTN*.
- At this stage, the liver disease is called **compensated Advanced Chronic Liver Disease (cACLD)**, the term is used to emphasize that the portal pressure may increase before the anatomical structure of cirrhosis is formed.
- HVPG between 5 mmHg and 10 mmHg is evolving **asymptomatically**, often called compensated cirrhosis.
- **HVPG above 10 mmHg is called clinically significant portal HTN**

Figure 2



Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases

Garcia-Tsao, Guadalupe; Abraldes, Juan G.; Berzigotti, Annalisa; Bosch, Jaime

Hepatology65(1):310-335, January 2017.

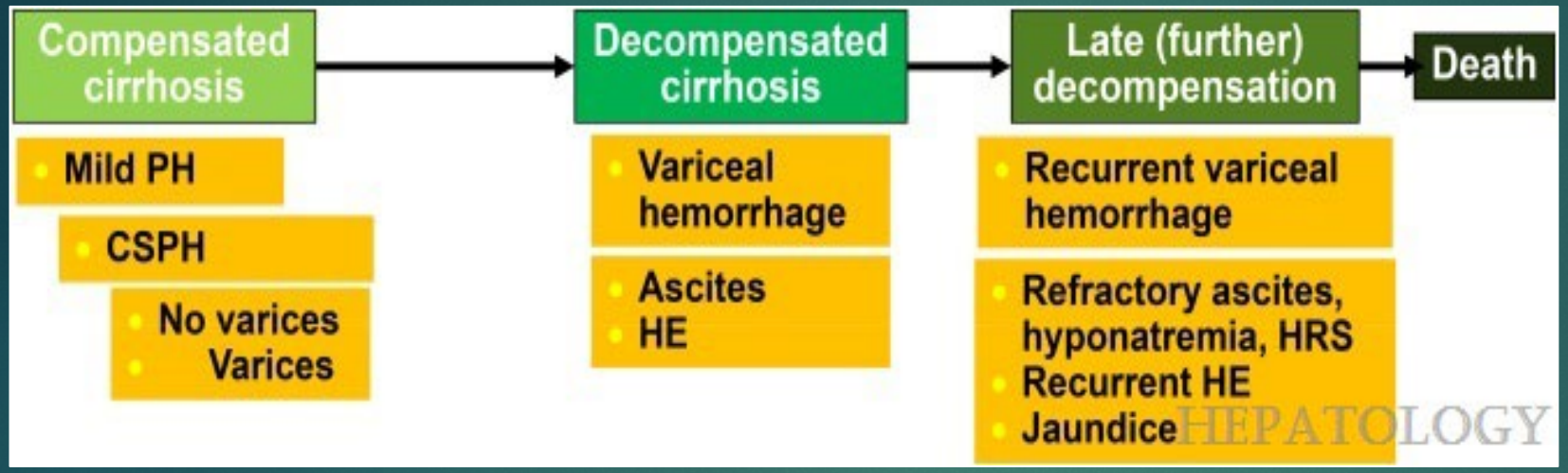
doi: 10.1002/hep.28906

Pathogenesis of PH and sites of action of currently recommended therapies to reduce PP or obliterate varices. In cirrhosis, PP increases initially as a consequence of an increased intrahepatic resistance to portal flow attributed to structural mechanisms (e.g., fibrous tissue, regenerative nodules) and an increased intrahepatic vascular tone (functional component). One of the initial consequences of PH is the formation of portosystemic collaterals. Concomitant or even preceding development of collaterals, splanchnic vasodilatation occurs, leading to increased flow into the gut and into the portal venous system. Vasodilation leads to activation of neurohumoral and vasoconstrictive systems, sodium and water retention, increased blood volume, and increased cardiac output; that is, a hyperdynamic circulatory state that further increases portal venous inflow and PP. Additionally, activated vasoconstrictive systems to further contribute to intrahepatic vasoconstriction. Treatment of etiology, by ameliorating fibrosis/inflammation, target the mechanical component of the increased intrahepatic resistance. Vasodilators (like the a-adrenergic blocking effect of carvedilol) target its functional component (this is the site of action of statins). NSBBs (β2-adrenergic blocking effect), SMT, and VP act by causing splanchnic vasoconstriction, thereby reducing portal venous inflow. NSBBs also act by decreasing cardiac output (β1-adrenergic blocking effect). The TIPS connects the hypertensive portal vein with a normotensive hepatic vein, thereby bypassing the site of increased resistance. Varices can be obliterated either endoscopically (EVL or cyanoacrylate injection) or by an endovascular approach (BRTO).

Complications of clinically significant portal HTN (CSPH)

- Varices, and hemorrhage.
- Ascites
- Hepatic Encephalopathy
- Post surgical decompensation
- HCC

Figure 1



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Stages and substages of cirrhosis. The two main stages are the compensated and decompensated stages. The latter is characterized by the presence of clinically overt complications: ascites, VH, or HE. The compensated stage is the longest stage, and it is asymptomatic. There are at least two main substages of compensated cirrhosis with different prognostic and predominant pathophysiological mechanisms: patients with mild PH and those with CSPH. Patients in the latter stage are at risk of developing decompensation, particularly those who have GEV. The decompensated stage is much shorter and can rapidly progress to a stage of further decompensation in which renal failure (HRS) and liver failure (encephalopathy and jaundice) develop, leading to a high mortality.

Can we prevent decompensation of cirrhosis.

- Can we prevent variceal hemorrhage, Ascites development, and Hepatic Encephalopathy?
- We have 1 answer in the practice guidelines, the use of non selective beta blockers, to prevent variceal bleed.

AASLD practice guidance, 2016

- In patients with cirrhosis and CSPH but without varices, the objective of treatment should no longer be to prevent varices, but to prevent clinical decompensation.
- There is no evidence at present to recommend the use of NSBBs in preventing *formation of varices*.
- Either traditional NSBBs (propranolol, nadolol), carvedilol, or EVL is recommended for the prevention of first VH (primary prophylaxis) **in patients with medium or large varices** .
- NSBB is the recommended therapy for patients with high-risk **small EV .**

PREDESCI clinical trial

- investigator-initiated, double-blind, randomized controlled trial done in eight hospitals in Spain.
- Between Jan 18, 2010, and July 31, 2013, 631 patients were evaluated and **201** were randomly assigned. 101 patients received placebo and 100 received active treatment (67 propranolol and 33 carvedilol).
- All participants had HVPG measurements with assessment of acute HVPG-response to intravenous propranolol. Responders (HVPG-decrease ≥10%) were randomly assigned to propranolol (up to 160 mg twice a day) versus placebo and non-responders to carvedilol (≤25 mg/day) versus placebo.
- Published in The Lancet, March 2019

Primary end points

- The primary endpoint was incidence of cirrhosis decompensation (defined as development of **ascites**, **bleeding**, or **overt encephalopathy**) or **death**. Since death in compensated cirrhosis is usually unrelated to the liver, an intention-to-treat analysis considering deaths unrelated to the liver as competing events was done.
- The primary endpoint occurred in ***16 (16%) of 100 patients in the β blockers group versus 27 (27%) of 101 in the placebo group*** (hazard ratio [HR] 0·51, 95% CI 0·26–0·97, p=0·041). The difference was due to a reduced incidence of ascites (HR 0·42, 95% CI 0·19–0·92, p=0·03).

Interpretation/Weakness

Interpretation

- Long-term treatment with β blockers could increase decompensation-free survival in patients with compensated cirrhosis and CSPH, mainly by reducing the incidence of ascites.

Weakness

- It is invasive, requiring HVPG measurement to assess CSPH in asymptomatic patients.

So, do beta blockers work in real life to prevent decompensation?

Nonselective beta blockers, hepatic decompensation, and mortality in cirrhosis: A national cohort study

- A retrospective cohort study of the Veterans Health Administration (VHA).
- Data used from the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) cohort.
- The Vocal cohort includes nearly 130000 veterans diagnosed with cirrhosis from January 1, 2008, to December 31, 2018
- Method used: active comparator, new user (ACNU). Creating a cohort of new users of carvedilol (n=123) versus new users of selective beta blockers (SBBs) (n=561) and followed patients for up to 3 years

Results:

- In the VOCAL cohort, any decompensation occurred in 8.8% with carvedilol and 17% of the SBB-treated patients, respectively.
- **The composite outcome of any decompensation or liver related mortality was 11% with carvedilol and 22% with SBBs.**
- *The more common decompensations were ascites and HE; variceal hemorrhage was rare at about 1%.*
- All-cause mortality was similar in each group (22% with carvedilol and 24% with SBBs), whereas **liver related mortality was 2% with carvedilol and 5.1% with SBBs**
- **The study did not find benefits of carvedilol among patients with cirrhosis, age >65**

Quantifying the benefit of nonselective beta-blockers in the prevention of hepatic decompensation: A Bayesian reanalysis of the PREDESCI trial

- Bayesian analyses enhance the interpretation of trials. The purpose of this study was to provide clinically meaningful estimates of both the probability and magnitude of benefit of beta-blocker treatment across a range of patient types.
- Typically, randomized trials are analyzed in a frequentist framework and are interpreted as “positive” or “negative”, the use of Bayesian inference informs clinical decision-making, regardless of the frequentist outcome, since the probability of a clinical effect of the intervention can be estimated.

Results:

-The probability for any benefit of NSBB in patients with compensated cirrhosis was > 0.9

-The probability of important clinical benefit (HR<0.85), ranged from 0.79 to 0.95

-The probability of an outstanding benefit (HR<0.5), ranged from 0.078 to 0.49

conclusion

- ***Beta blocker treatment is associated with a high probability of clinical benefit. This likely translates to a substantial gain in decompensation-free life years at the population level***

The question remains: how to measure portal pressure in non-invasive way?

The Anticipate Study

Published 2016, Abraldes JG, et al

Anticipate model

- ***The aim is to develop noninvasive tests-based risk prediction models to provide a point-of-care risk assessment of cACLD patients***

- ***Analyzed 518 patients with cACLD from 5 centers in Europe/Canada with paired noninvasive tests (liver stiffness measurement by Transient elastography, platelets count, and spleen diameter with calculation of liver stiffness to spleen/platelet score and platelets-spleen ratio and endoscopy/HVPG measurement.***

Update on the role of elastography in liver disease

Published in Therapeutic Advances Gastroenterology, 2022

- In patients with virus- and/or alcohol-related and non-obese NASH-related cACLD with LSM values < 25 kPa, the ANTICIPATE model can be used to predict the risk of CSPH.
- Based on this model, patients with LSM values between 20 and 25 kPa and platelet count <150,000/mm3 or LSM values between 15 and 20 kPa and platelet count <110,000/mm3 have a CSPH risk of at least 60%.
- In patients with NASH-related cACLD, the ANTICIPATE NASH model (including LSM, platelet count, and BMI) may be used to predict the risk of CSPH but further validation is needed

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Thank you.

ANY QUESTIONS?

Today, noon – 1pm:
AK ID ECHO: HCV-HIV-PrEP-STIs

Mycoplasma genitalium STI

Presenter:

Theresa Savidge, State of Alaska
Katie Presser, PharmD, ANTHC
Mercedes Cheslock, PhD, Mountain Region for Hologic

https://anthc.org/project-echo/hcv-hiv-prep-stis-echo/

Continuing Education credits are available.

August 17, 2023, next Thursday, noon – 1pm

AK Liver Disease ECHO

Didactic:

Importance of diabetes management in NAFLD/NASH

Presenter:

Kena Desai, MD

https://anthc.org/project-echo/alaska-liver-disease-echo/

Continuing Education credits are available.

Next LiverConnect

September 12, 2023

Topic:

Pediatric NAFLD

Presenter: **Brian McMahon, MD**

To view past presentations, visit: anthc.org/hep, click on the LiverConnect-AK ECHO link, Scroll down and select a recording to view.