
2024
NCSCG
9TH ANNUAL
LIVER SYMPOSIUM
JANUARY 20, 2024
HAYES MANSION | SAN JOSE, CA

# Carvedilol for Portal Hypertension: New Kid on the Block


Varun Saxena, MD MAS

Transplant Hepatology

Chief – Kaiser Permanente South San Francisco

Clinical Lead – Chronic Liver Diseases for TPMG

Director – KPNC Liver Transplant Advisory Board

Director – Hepatology Research Network

Chair – National Transplant Services Liver Clinical Management Committee

Adjunct Clinical Professor - UCSF



PERMANENTE MEDICINE®
The Permanente Medical Group

# Disclosures:

- Collaborative study with Gilead Sciences®
- No pertinent disclosures

# Outline

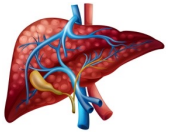
- Case
- Overview of terminology
- Pathophysiology of portal hypertension w/impact of carvedilol
- PREDESCI clinical trial + carvedilol meta-analysis
- AASLD 2023 guidance summary
- Case revisited

# Case of KK

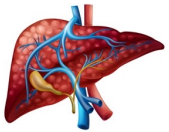
KK is a 62 y/o female (she/her) with BMI 27kg/$m^2$, DM2 (last A1c: 7.8), HTN, HLD and hx of tobacco abuse (quit, >30 pk yr hx)

- Labs by PCP remarkable for “normal” liver enzymes with AST 36 and ALT 22 and plts of 122 x $10^3$
- Lung cancer screening protocol CT chest is negative but mentions “liver not fully evaluated, but nodular liver contour, correlate clinically for cirrhosis”
- You advise PCP to obtain LSM, ultrasound and clinic consultation with you: LSM returns 22.3 kPa (IQR: 9%)
- Liver ultrasound: nodular contour, no hepatoma, no ascites

# Overview of Terminology



**Hepatic Cirrhosis**

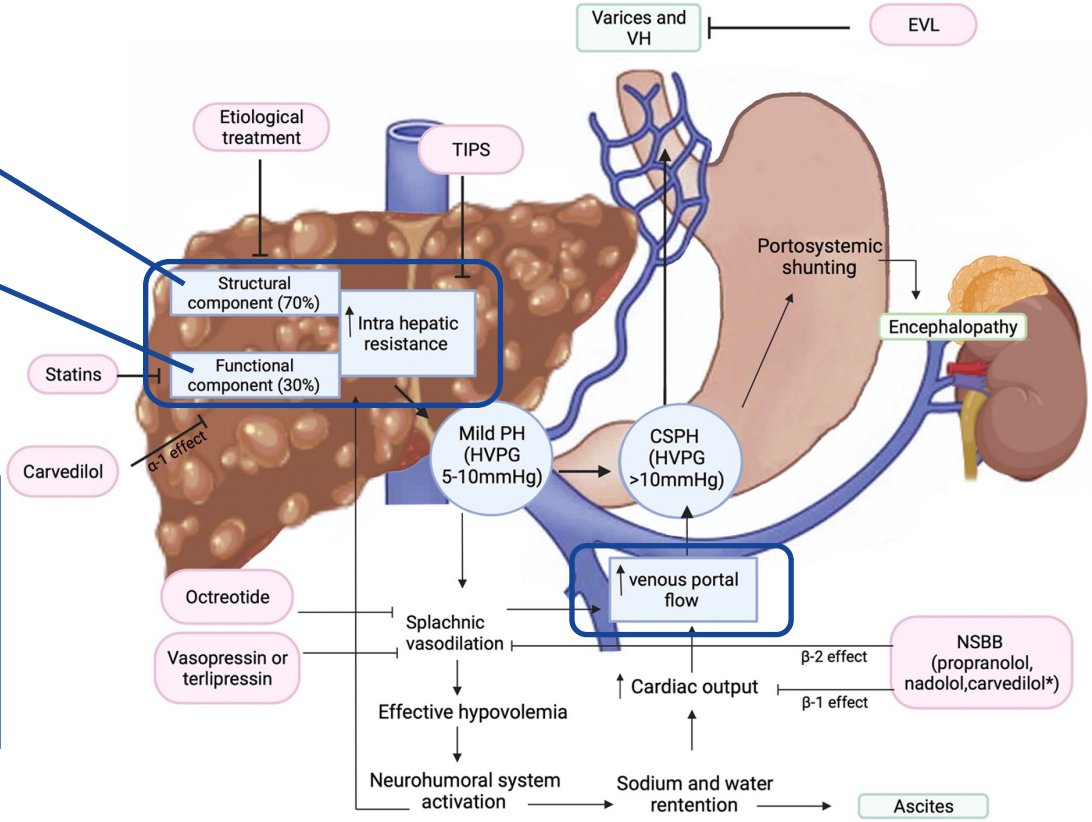


| | Compensated Cirrhosis | Compensated Cirrhosis with Clinically Significant Portal Hypertension | Decompensated Cirrhosis |
|---|---|---|---|
| Term | | | |
| Definition | • No clinically significant portal hypertension (HVPG < 10)<br>• CTP Class A | • Clinically significant portal hypertension (HVPG ≧ 10)<br>• Usually CTP Class A | • Ascites, variceal hemorrhage and/or hepatic encephalopathy<br>• CTP Class B/C |
| Implications | • Median survival is 12+ years<br>• Goals:<br>- Treat underlying etiology | • Median time to decompensation is ~2 yrs<br>• Goals:<br>- Treat underlying etiology<br>- Prevent/delay decompensation | • Median survival is 1.8 years<br>• Goals:<br>- Treat underlying etiology<br>- Treat decompensation<br>- TIPS and/or transplant |

Adapted from Diaz-Soto et al. *Therap Adv Gastroenterol*. 2022.

# Pathophysiology of Portal Hypertension w/ Impact of Carvedilol


- Regenerative nodules and fibrous tissue
- Endothelial dysfunction + decreased NO availability = increased hepatic vascular tone




**Carvedilol Impact**

- α-1 antagonist = decreased hepatic vascular tone (functional component)
- β-1 effect = decrease cardiac output leading to decreased venous portal flow
- β-2 effect = decrease splanchnic vasodilation leading to decreased venous portal flow

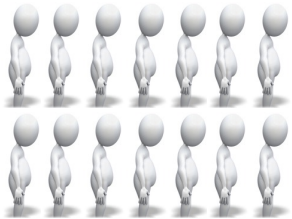
Adapted from Diaz-Soto et al. *Therap Adv Gastroenterol*. 2022.

# PREDESCI Trial

β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial

Càndid Villanueva*, Agustín Albillos, Joan Genescà, Joan C Garcia-Pagan, José L Calleja, Carles Aracil, Rafael Bañares, Rosa M Morillas, María Poca, Beatriz Peñas, Salvador Augustin, Juan G Abraldes, Edilmar Alvarado, Ferran Torres, Jaume Bosch*†

## Population



- 201 patients with compensated cirrhosis and clinically significant portal hypertension w/none or small, non-bleeding esophageal varices (no ascites)

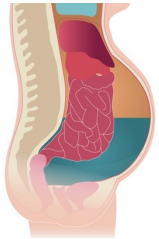
Randomized

## Intervention

- Responders to IV propranolol:
  - Propranolol up to 160mg BID
  - Placebo
- Non-responders to IV propranolol:
  - Carvedilol upto 25mg/day
  - Placebo

Followed

## Outcomes



- Incident decompensated cirrhosis (ascites, variceal bleeding or overt encephalopathy)
- Death

Villanueva et al. *Lancet*. 2019

# PREDESCI Trial

| | Placebo group (n=101) | β-blockers group (n=100) |
|---|---|---|
| **Baseline characteristics** | | |
| Sex | | |
| Male | 64 (63%) | 59 (59%) |
| Female | 37 (37%) | 41 (41%) |
| Age (years) | 59 (11) | 60 (10) |
| Cause of cirrhosis | | |
| Alcohol | 14 (14%) | 19 (19%) |
| Hepatitis C virus | 59 (58%) | 54 (54%) |
| Alcohol and hepatitis C virus | 8 (8%) | 9 (9%) |
| NASH | 8 (8%) | 5 (5%) |
| Others | 12 (12%) | 13 (13%) |
| Diabetes | 21 (21%) | 22 (22%) |
| Dyslipidaemia | 15 (15%) | 12 (12%) |
| Arterial hypertension | 34 (34%) | 45 (45%) |
| Child-Pugh class | | |
| A | 81 (80%) | 80 (80%) |
| B | 20 (20%) | 20 (20%) |
| C | 0 | 0 |
| Child-Pugh score | 5·8 (0·9) | 5·7 (0·9) |
| Model for end-stage liver disease score | 6·8 (0·3) | 6·6 (0·3) |
| Oesophageal varices* | | |
| None | 43 (43%) | 44 (44%) |
| Small | 58 (57%) | 56 (56%) |
| Gastric varices† | 1 (1%) | 2 (2%) |
| Portal-systemic collaterals by ultrasound‡ | 11 (11%) | 18 (18%) |
| Splenomegaly§ | 67 (66%) | 56 (56%) |
| Liver stiffness, kPa¶ | 30·4 (16) | 28·7 (13) |
| Weight, kg | 76 (16) | 76 (15) |
| BMI, kg/m² | 27 (5) | 27 (4) |

(Table 1 continues in next column)

Villanueva et al. *Lancet*. 2019.

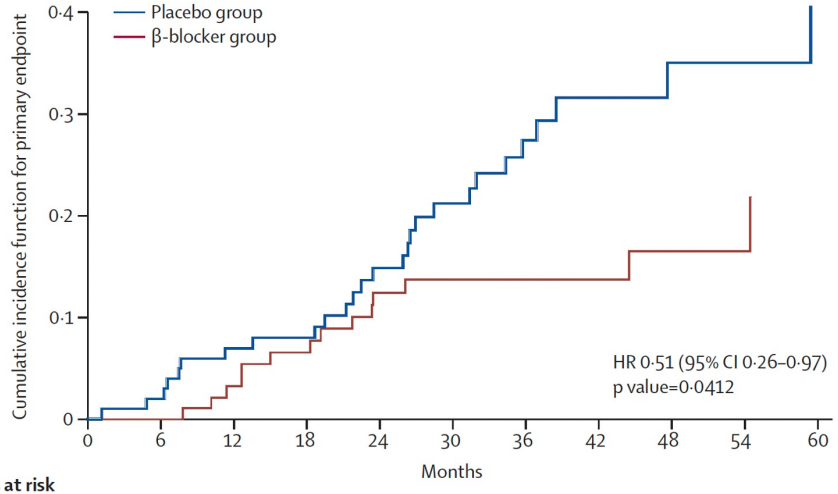
# PREDESCI Trial

| | Placebo group (n=101) | β-blockers group (n=100) |
|---|---|---|
| (Continued from previous column) | | |
| **Procedural characteristics** | | |
| Duration of follow-up (months) | | |
| Mean | 37 (16) | 36 (16) |
| Median (IQR) | 37 (27–47) | 37 (26–47) |
| Lost to follow-up‖ | 4 (4%) | 9 (9%) |
| Abstinence from alcohol** | 88 (87%) | 82 (82%) |
| Development of portal thrombosis | 5 (5%) | 3 (3%) |
| Liver transplantation†† | 1 (1%) | 3 (3%) |
| Randomised to propranolol (or identical tablets of placebo) | | |
| Number of patients | 68 (67%) | 67 (76%) |
| Dose (mg/day) | | |
| Mean | 95 (81) | 95 (76) |
| Median (IQR) | 80 (40–90) | 80 (40–120) |
| Withdrawal‡‡ | 2 | 6 |
| Randomised to carvedilol (or identical tablets of placebo) | | |
| Number of patients | 33 (33%) | 33 (33%) |
| Dose (mg/day) | | |
| Mean | 20 (6) | 19 (7) |
| Median (IQR) | 18·8 (18·8–25) | 18·8 (12·5–25) |
| Withdrawal§§ | 4 | 2 |

Villanueva et al. *Lancet*. 2019.

# PREDESCI Trial

A




| Patients at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| β blockers | 100 | 96 | 87 | 80 | 69 | 60 | 48 | 31 | 20 | 15 | 7 |
| Placebo | 101 | 99 | 94 | 86 | 72 | 59 | 42 | 26 | 19 | 13 | 6 |
| **Primary outcome (deaths)** | | | | | | | | | | | |
| β blockers | | 1 (1) | 3 (1) | 4 (2) | 5 (2) | 1 (1) | 0 | 0 | 1 (1) | 0 | 1 |
| Placebo | | 2 (2) | 5 (1) | 1 | 6 (2) | 5 (1) | 4 (3) | 2 (1) | 1 (1) | 0 | 1 |
| **Censoring events** | | | | | | | | | | | |
| β blockers | | 3 | 6 | 3 | 6 | 8 | 12 | 17 | 10 | 5 | 7 |
| Placebo | | 0 | 0 | 7 | 8 | 8 | 13 | 14 | 6 | 6 | 6 |

| | Placebo group (n=101) | β-blockers group (n=100) | Risk (95% CI)* | p value† |
|---|---|---|---|---|
| **Decompensation or death** | | | | |
| Overall‡ | 27 (27%) | 16 (16%) | 0·51 (0·26–0·97) | 0·0412 |
| **Secondary outcomes** | | | | |
| Ascites | 20 (20%) | 9 (9%) | 0·42 (0·19–0·92) | 0·030 |
| Gastrointestinal bleeding | 3 (3%) | 4 (4%) | 1·52 (0·34–6·82) | 0·61 |
| Overt hepatic encephalopathy | 5 (5%) | 4 (4%) | 0·92 (0·40–2·21) | 0·98 |
| Death from any cause | 11 (11%) | 8 (8%) | 0·54 (0·20–1·48) | 0·23 |
| Varices | 56 (56%) | 58 (58%) | 1·15 (0·65–2·02) | 0·72 |
| High-risk varices§ | 25 (25%) | 16 (16%) | 0·60 (0·30–1·21) | 0·15 |
| Spontaneous bacterial peritonitis | 4 (4%) | 2 (2%) | 0·49 (0·10–2·70) | 0·40 |
| Other bacterial infections¶ | 19 (19%) | 15 (15%) | 0·81 (0·41–1·59) | 0·54 |
| Hepatorenal syndrome | 1 (1%) | 1 (1%) | 0·99 (0·06–15·96) | 0·96 |
| Hepatocellular carcinoma | 17 (17%) | 13 (13%) | 0·76 (0·37–1·54) | 0·43 |

Percentages are crude incidences of events occurring at any time during the follow-up. *Values indicate the hazard ratio of an outcome in the β-blockers group as compared with the placebo group. †Comparison of cumulative incidences by competing-risk analysis (differences assessed by Gray's test). ‡The absolute reduction in the incidence of the primary outcome was of 11% (95% CI 0–22). §Among patients with high-risk varices, oesophageal variceal ligation to prevent bleeding was performed in 18 (72%) of 25 patients in the placebo group versus 11 (69%) of 16 in the non-selective β-blockers group. ¶Including spontaneous bacterial peritonitis, and other documented bacterial infections during follow-up.

***Table 3:*** **Long-term outcomes**

Villanueva et al. *Lancet*. 2019.

# PREDESCI Trial

> Regarding ascites, the benefit of β blockers versus placebo was slightly more apparent in the carvedilol stratum (**HR 0.22, 95% CI 0.02–1.94**) than in the propranolol stratum (**0.50, 95% CI 0.22–1.18**).

Villanueva et al. *Lancet*. 2019.

# PREDESCI Trial

| | Baseline | 12 months follow-up | 24 months follow-up | 36 months follow-up | p values* |
|---|---|---|---|---|---|
| **Patients†** | | | | | |
| β blockers | 100/100 | 78/88 | 44/69 | 22/40 | .. |
| Placebo | 101/101 | 78/87 | 42/69 | 25/46 | .. |
| **Hepatic venous pressure gradient** | | | | | |
| Absolute values, mm Hg | .. | .. | .. | .. | $p_{treat}$<0·001; $p_{treat*time}$=0·075; $p_{time}$=0·98; $p_{stratum}$=0·94 |
| β blockers | 14·5 (14 to 15) | 12·8 (12 to 14) | 13·0 (12 to 14) | 12·9 (12 to 14) | .. |
| Placebo | 14·8 (14 to 16) | 15·0 (14 to 16) | 14·9 (14 to 16) | 14·6 (13 to 16) | .. |
| Change from baseline, % | | | | | |
| β blockers | .. | −12 (−15 to −8) | −10 (−12 to − 5) | −10 (−15 to −4) | .. |
| Placebo | .. | 1·5 (−2 to 5) | 1·2 (−3 to 6) | −0·9 (−6 to 5) | .. |
| **Mean arterial pressure** | | | | | |
| Absolute values, mm Hg | .. | .. | .. | .. | $p_{treat}$=0·007; $p_{treat*time}$=0·227; $p_{time}$=0·28; $p_{stratum}$=0·70 |
| β blockers | 98 (95 to 100) | 92 (89 to 95) | 92 (89 to 96) | 95 (91 to 99) | .. |
| Placebo | 96 (93 to 98) | 91 (88 to 94) | 92 (88 to 95) | 93 (88 to 97) | .. |
| Change from baseline, % | | | | | |
| β blockers | .. | −5 (−7 to 2) | −5 (−8 to −2) | −2 (−6 to 2) | .. |
| Placebo | .. | −3 (−5 to −1) | −2 (−5 to 1) | −2 (−5 to 2) | .. |

Villanueva et al. *Lancet*. 2019.

# Carvedilol Meta-Analysis

Research Article
Cirrhosis and Liver Failure

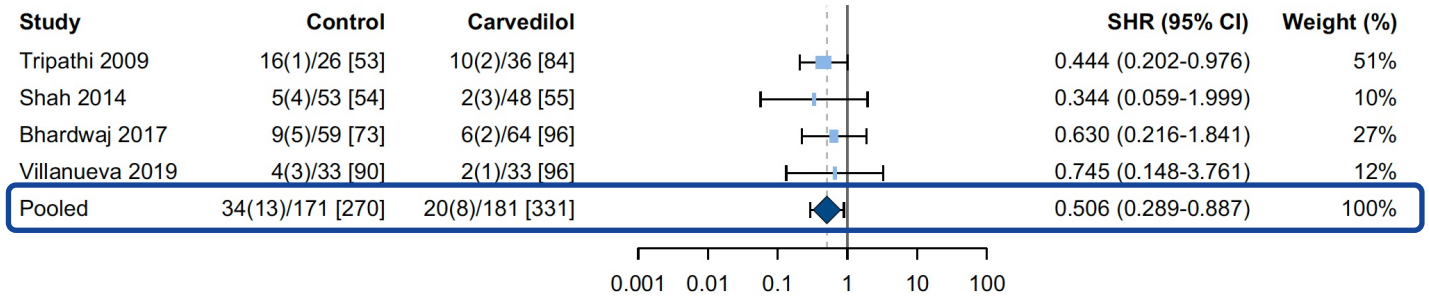
JOURNAL OF HEPATOLOGY

**Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis**

Càndid Villanueva[1,2,*], Ferran Torres[3,4], Shiv Kumar Sarin[5], Hasnain Ali Shah[6], Dhiraj Tripathi[7,8,9], Anna Brujats[1], Susana G. Rodrigues[10,11], Ankit Bhardwaj[12], Zahid Azam[13], Peter C. Hayes[9], Ankur Jindal[5], Shahab Abid[6], Edilmar Alvarado[1,2], Jaume Bosch[2,11], on behalf of the Carvedilol-IPD-MA-group and the Baveno Cooperation: an EASL Consortium

**A**

**Decompensation with liver transplant and death as competing events**




Random effects models. Group effect $p = 0.0173$
Descriptive statistics for control and carvedilol are events(competing-events)/n [person-years]
Heterogeneity: Q = 0.67 (df = 3, $p = 0.8802$), $I^2$: 0.0% [0.0%-31.5%]

Villanueva et al. *JHep*. 2022.

# Carvedilol Meta-Analysis

Research Article
Cirrhosis and Liver Failure

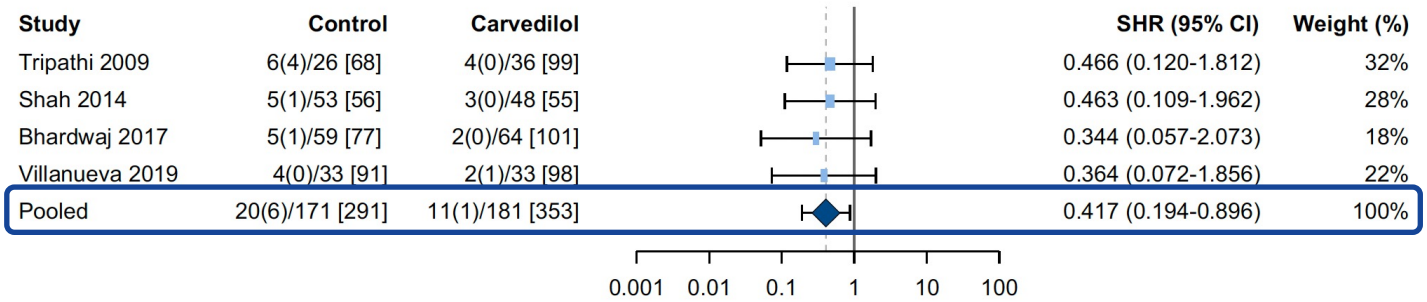
JOURNAL OF HEPATOLOGY

## Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis

Càndid Villanueva[1,2,*], Ferran Torres[3,4], Shiv Kumar Sarin[5], Hasnain Ali Shah[6], Dhiraj Tripathi[7,8,9], Anna Brujats[1], Susana G. Rodrigues[10,11], Ankit Bhardwaj[12], Zahid Azam[13], Peter C. Hayes[9], Ankur Jindal[5], Shahab Abid[6], Edilmar Alvarado[1,2], Jaume Bosch [2,11], on behalf of the Carvedilol-IPD-MA-group and the Baveno Cooperation: an EASL Consortium

**B**

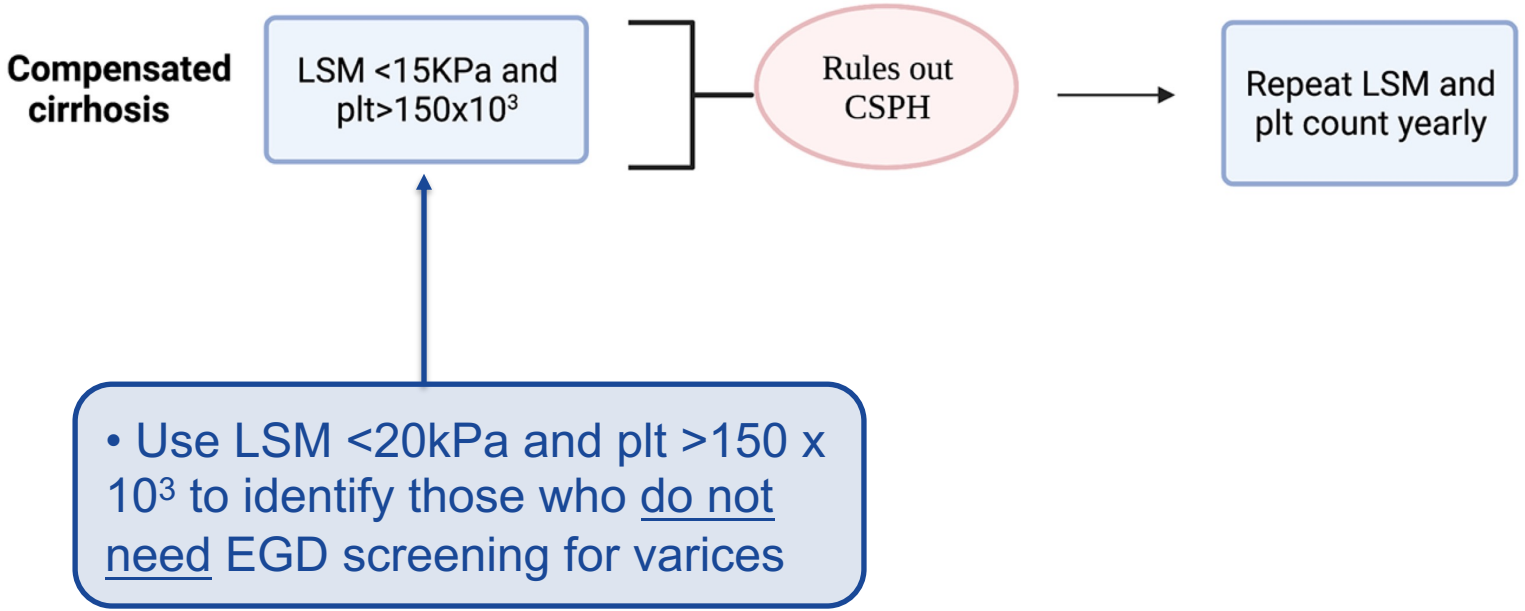
**Death with liver transplant as a competing event**




Random effects models. Group effect $p = 0.0250$
Descriptive statistics for control and carvedilol are events(competing-events)/n [person-years]
Heterogeneity: Q = 0.12 (df =3, $p = 0.9898$), $I^2$: 0.0% [0.0%-0.0%]

Villanueva et al. *JHep*. 2022.

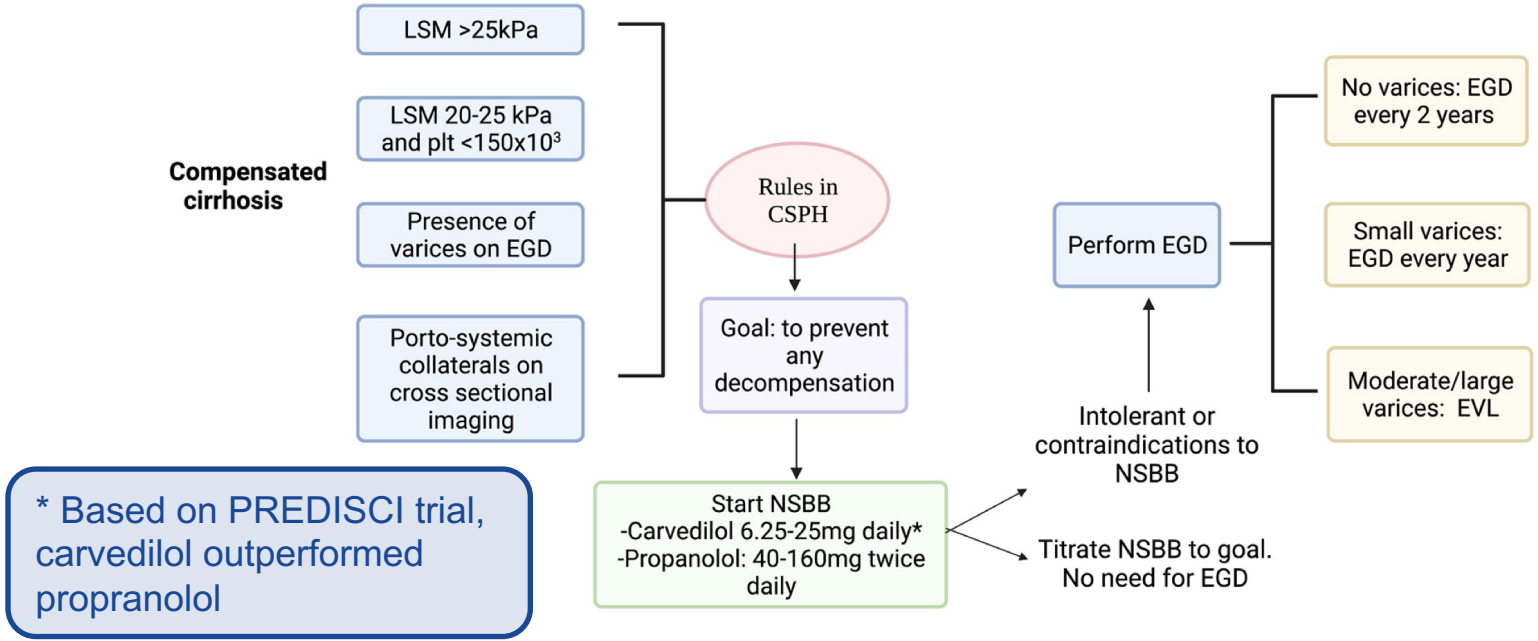
# AASLD 2023 Summary




LSM = Liver stiffness measurement; CSPH = Clinically significant portal hypertension

Adapted from Diaz-Soto et al. *Therap Adv Gastroenterol*. 2022; Kaplan et al. *Hepatology*. 2023. (ePub ahead of Print).

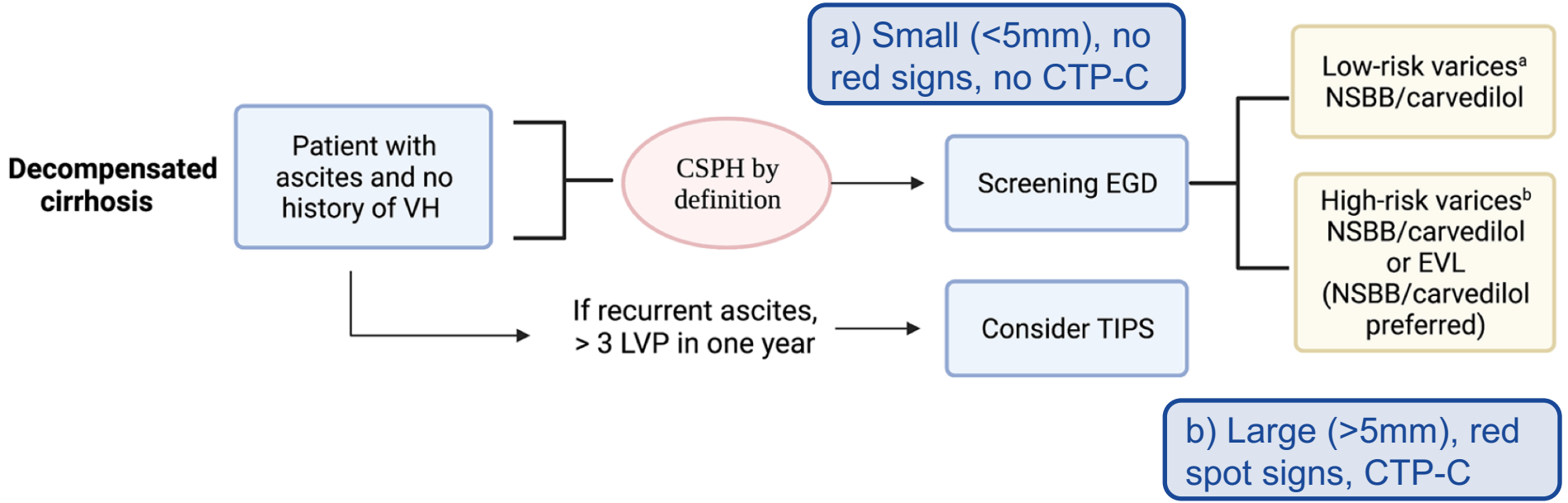
# AASLD 2023 Summary




LSM = Liver stiffness measurement; CSPH = Clinically significant portal hypertension

Adapted from Diaz-Soto et al. *Therap Adv Gastroenterol*. 2022; Kaplan et al. *Hepatology*. 2023. (ePub ahead of Print)

# AASLD 2023 Summary




CSPH = Clinically significant portal hypertension

Adapted from Diaz-Soto et al. *Therap Adv Gastroenterol*. 2022; Kaplan et al. *Hepatology*. 2023. (ePub ahead of Print).

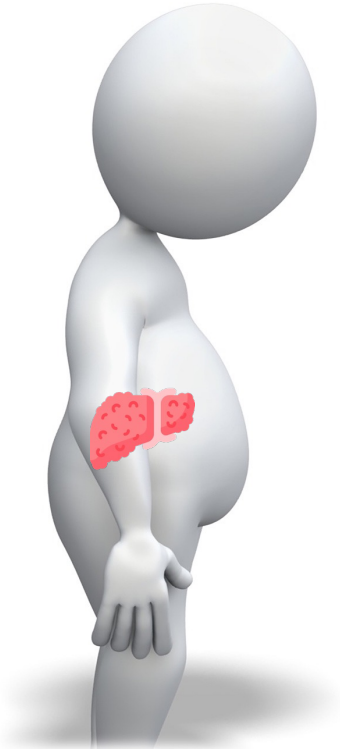
# AASLD 2023 Summary

**Guidance statements:**

1. Carvedilol is recommended as the preferred NSBB for the treatment of PH in patients with cirrhosis.
2. The recommended maintenance dosage of carvedilol is 6.25–12.5 mg/day, after initiating treatment for 2 days with only 6.25 mg at bedtime. Maintenance dosage can be given as a single dose. In patients with concomitant arterial hypertension or cardiac disease, the dose of carvedilol may be further increased to address nonhepatic indications.

Kaplan et al. *Hepatology*. 2023. (ePub ahead of Print).

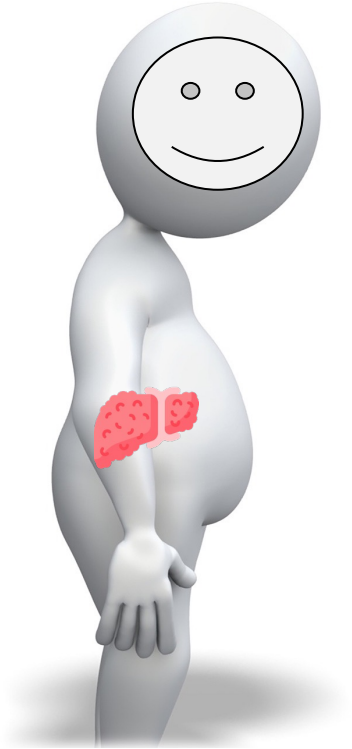
# Case of KK – Revisited



KK is a 62 y/o female (she/her) with BMI 27kg/m2, DM2 (last A1c: 7.8), HTN, HLD and hx of tobacco abuse (quit, >30 pk yr hx)

- Labs by PCP remarkable for “normal” liver enzymes with AST 36 and ALT 22 and plts of 122 x 103
- Lung cancer screening protocol CT chest is negative but mentions “liver not fully evaluated, but nodular liver contour, correlate clinically for cirrhosis”
- You advise PCP to obtain LSM, ultrasound and clinic consultation with you: LSM returns 22.3 kPa (IQR: 9%)
- Liver ultrasound: nodular contour, no hepatoma, no ascites

# Case of KK - Revisited



KK is a 62 y/o female (she/her) with BMI 27kg/m2, DM2 (last A1c: 7.8), HTN, HLD and hx of tobacco abuse (quit, >30 pk yr hx)

**Compensated Cirrhosis with Clinically Significant Portal Hypertension**

↓

**Carvedilol 6.25mg qBedtime x 2 days, then increase to 12.5mg qBedtime (or 6.25mg BID)**

# Questions?

Varun.Saxena@kp.org

or

Varun.Saxena@ucsf.edu


PERMANENTE MEDICINE®
The Permanente Medical Group