Optimal and Effective Use of Medications in Cirrhosis and Liver Disease

Bilal Hameed, MD

Clinic Chief, Hepatology

University of California, San Francisco

Outline

- Drug response in cirrhosis
- Does patients with cirrhosis are at increase risk of DILI?
- Polypharmacy and drug interactions in cirrhosis
- Important medication class and use in cirrhosis

1. Statin
2. Beta-blockers
3. PPI

Drug use and response in cirrhosis

- Response can be altered or unchanged?
  - Therapeutic effects: Increased or decreased
  - Adverse effects: Increased or decreased
- Response correlate with the severity of liver disease
- No clear marker to determine liver dysfunction
- Understanding of how cirrhosis can effect drug response is important

Potential changes in drug handling in cirrhosis

Pathophysiological Factors	Clinical Consequence
Impaired Hepatocytes	Altered metabolism/clearance
Hypoalbuminemia	Less protein (increase drug concentration)
Portal Shunting and Reduced hepatic flow	Higher bioavailability/serum levels
Ascites	Increase volume of distribution
Portal gastropathy	Altered drug absorption
Increased bilirubin	Decrease bile excretion and increase drug concentration
Renal dysfunction	Decrease excretion and increase drug concentration
Loss of CYP metabolic activity	Reduced 1st pass metabolism/clearance

Modified from Lewis & Stine. Aliment PharmarcolTher2013; 37: 1132-1156

Effects of cirrhosis on therapeutic drug response

Increased pharmacodynamic effects	
Precipitate Encephalopathy	Opioids, anxiolytics, sedatives
Precipitate Renal Failure	NSAIDs
Worsen/Precipitate GI bleed	NSAIDs

Decreased therapeutic response seen with:
Beta blockers
Diuretics
Codeine

Does patients with CLD and cirrhosis are at increased risk of drug induced liver injury (DILI)?

Drugs reported (or predicted) to have an increased risk of hepatotoxicity in patients with liver disease with evidence

Anti-tuberculosis drugs (INH, pyrazinamide, rifampicin)
HAART
Methimazole
Methotrexate
Valproate
Propoxyphene
Vitamin A
Nefazodone

Modified from Lewis & Stine. Aliment PharmarcolTher2013; 37: 1132-1156

Underlying HBV & DILI due to anti-TB drugs

	Anti-TB therapy (N=319)		HBV controls not on ATT (N=86)
	HBV carriers (n=43)	Non-HBV carriers (n=276)	
BMI (kg/m2)	20.6 ± 4.9	22 ± 5.9	21.4 ± 6.0
HBeAg/anti-HBe	9/34	-	17/69
Elevated baseline ALT (%)	23	18	17
Suspected DILI (%)	**34.9¶**	**9.4**	**8.1**
Bilirubin > 3 ULN	3	7	0

¶p<0.001 compared to other two groups

- Definition of DILI: ALT > 1.5 X ULN at least 2 consecutive occasions within 4 weeks
- Most of the episodes of ALT elevation were associated with an increase in HBV DNA

Wong WM et al. Hepatology 2000; 31: 201-206

DILI in pre-existing liver disease is associated with worse outcomes

- In the DILIN prospective study, 10% had pre-existing liver disease
- Higher frequency of azithromycin DILI (5.6% vs.1.5%, p=0.02)

	Known pre-existing liver disease (n=89)	No pre-existing liver disease (n=810)	P-value
6 month Outcomes (%)			
- All-cause mortality	16	5.2	<0.001
- Liver-related mortality	9.1	2.4	0.04
- Transplant	3.4	4.1	1.0

Chalasani N, et al for the US DILIN. Gastroenterology 2015.

Obeticholic Acid: Post-marketing experience

- Since marketing approval in May 2016 for PBC, the FDA Adverse Event Reporting System received reports of 19 deaths and 11 cases of serious liver injury in patients taking OCA.
- It has highly striking that much higher than recommended doses were prescribed to patients with moderate to severe hepatic impairment (5 mg once daily instead of 10 mg twice weekly)
- Primary pattern of liver injury is cholestatic jaundice

https://www.fda.gov/Drugs/DrugSafety/ucm576656.htm
https://livertox.nih.gov/ObeticholicAcid.htm

GI/Hepatologist are the Key in Making Decisions about Medications in Cirrhosis

Most common medications used in cirrhosis

1. Beta-blockers (40% patients)
2. PPI (40% patients)
3. Diuretics
4. Statins
5. Diabetic medications (30% patients)
6. Antibiotics
7. Cardiac and hypertensive
8. Pain medications

Most common medications used in cirrhosis

1. Beta-blockers (40% patients)
2. PPI (40% patients)
3. Diuretics
4. Statins
5. Diabetic medications (30% patients)
6. Antibiotics
7. Cardiac and hypertensive
8. Pain medications

Polypharmacy and drug interactions in cirrhosis

Most common medications associated with drug related events
1. Furosemide and spironolactone
2. Sedatives including benzodiazepines
3. NSAID's and opiates
4. Antimicrobials including penicillins
5. Beta-blockers
6. Potassium supplements

Franz CC et al. Eur J Clin Pharmacol 2012.
Cheema E et al. Eur J Clin Pharmacol 2019.

Statins use in liver disease

- DILI related to statins is extremely rare (<2 cases/1,000,000 patients-years) and mainly idiosyncratic
- Statins are also safe in patients with liver disease
- Indications for statin mainly is hyperlipidemia and CAD
- ? Whether expanding indication for patients with cirrhosis and portal hypertension (anti-inflammatory and anti-fibrotic properties)

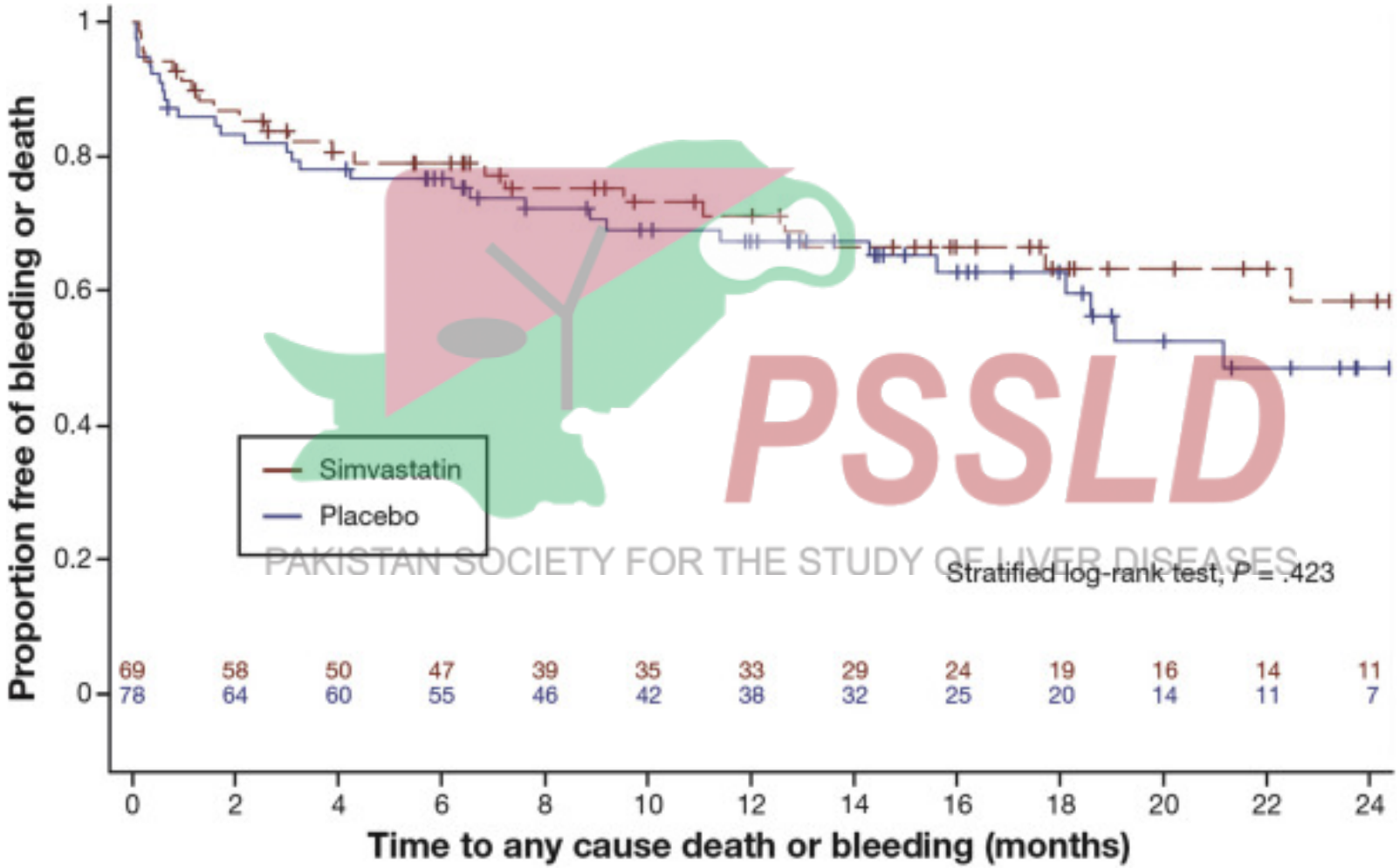
Law M et al. Am J Cardiol 2006;97:52C–60C.
Björnsson E et al. J Hepatol 2012;56:374–380.

Statins improve survival after EV bleed

- RCT of patients with recent EV bleed: band ligation (EBL)+ Beta blockers (BB) + placebo vs EBL + BB + statin
- 2010-2013, n=158 patients, groups stratified by CTP score
- Simvastatin 20mg daily started 5-10 post bleed, escalated to 40mg daily by day 15
- Patients followed to 24 months

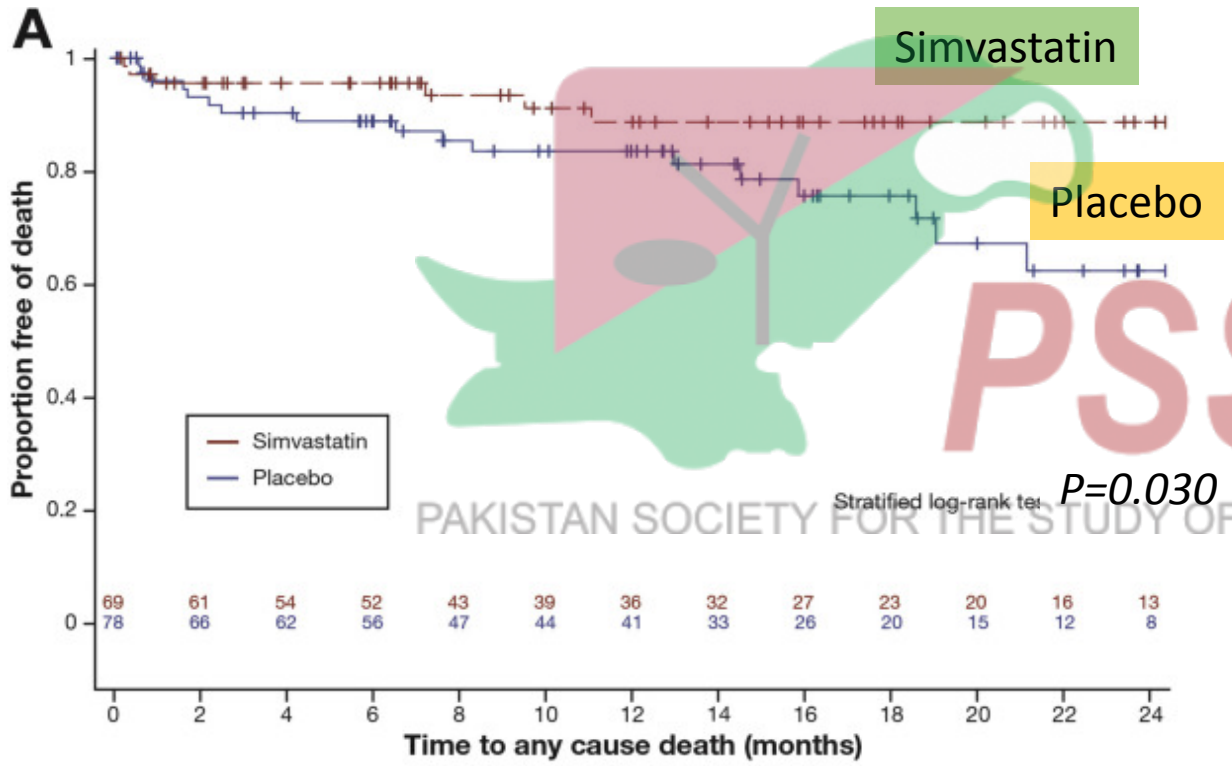
Abraldes et al. Gastro, 2016.

Statins has no effect on rebleeding



Abraldes et al. Gastro. May 2016.

Statins improve survival after variceal bleed



Seventeen patients in the placebo group died (22%) vs. 6 patients in the simvastatin group (9%)

Abraldes et al. Gastro, 2016.

Statins decrease risk of decompensation and death

- Retrospective, VA study of 40K men
- From 1996-2009, all men with compensated HCV cirrhosis
- Statins were associated with decreased risk:
  - Decompensation: HR 0.55; 95% CI, 0.39-0.78
  - Mortality: HR 0.55; 95% CI 0.45-0.68

(Adjusted for age, serum albumin, MELD and CTP)

Mohanty et al, Gastroenterology, Feb 2016.

Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY):

Pose E et al. The Lancet Gastroenterology and Hepatology 2019

- Randomized, double-blind, placebo-controlled, phase 2 trial
- Child-Pugh class B or C disease
- Patients (1:1:1) to receive either simvastatin 40 mg/day plus rifaximin 1200 mg/day (n=18), simvastatin 20 mg/day plus rifaximin 1200 mg/day (n=16) or placebo of both medications (n=16) for 12 weeks
- Primary endpoint was development of liver or muscle toxicity

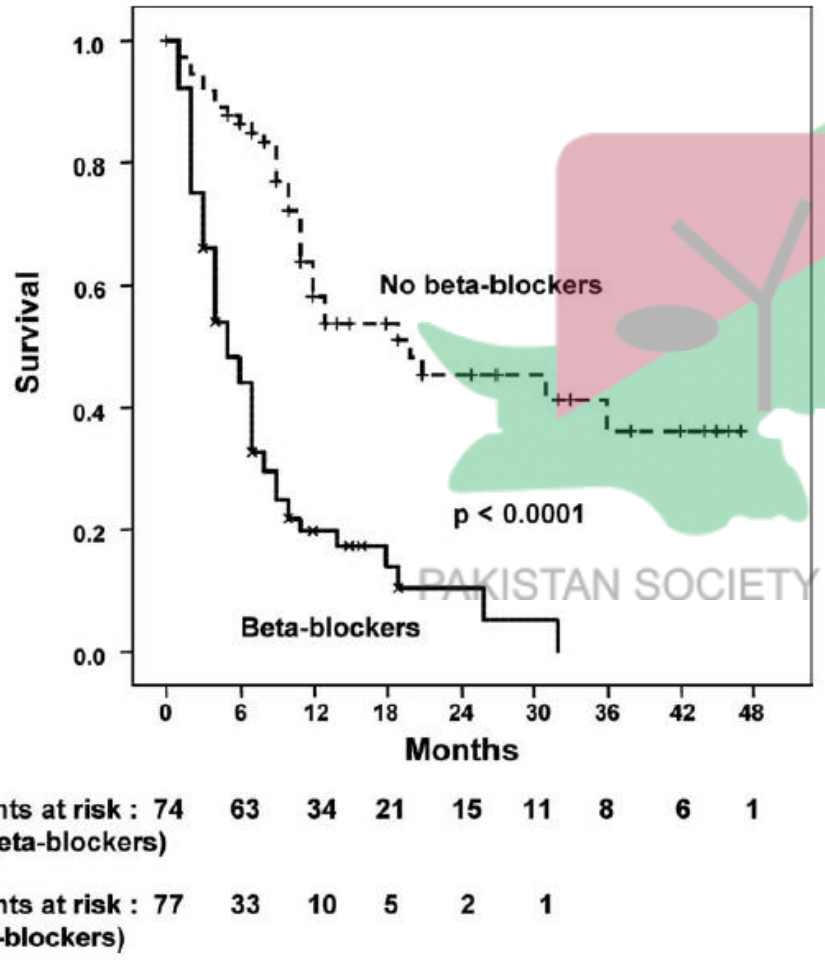
Simvastatin 40 mg + rifaximin in decompensated cirrhosis was associated with a significant increase in AST/ALT and CK level requiring treatment withdrawal, compared with simvastatin 20 mg + rifaximin or placebo.

Summary: Statin in CLD

- Retrospective and randomized control trials results have shown benefits of statin in cirrhosis
- Additional RCTs studies are needed with hard endpoints, before statins can be recommended for use in patients with chronic liver disease
- Caution in CTP C and high dose statin (increase CK)
- Drug interactions are common

Use of Beta Blockers in Cirrhosis?

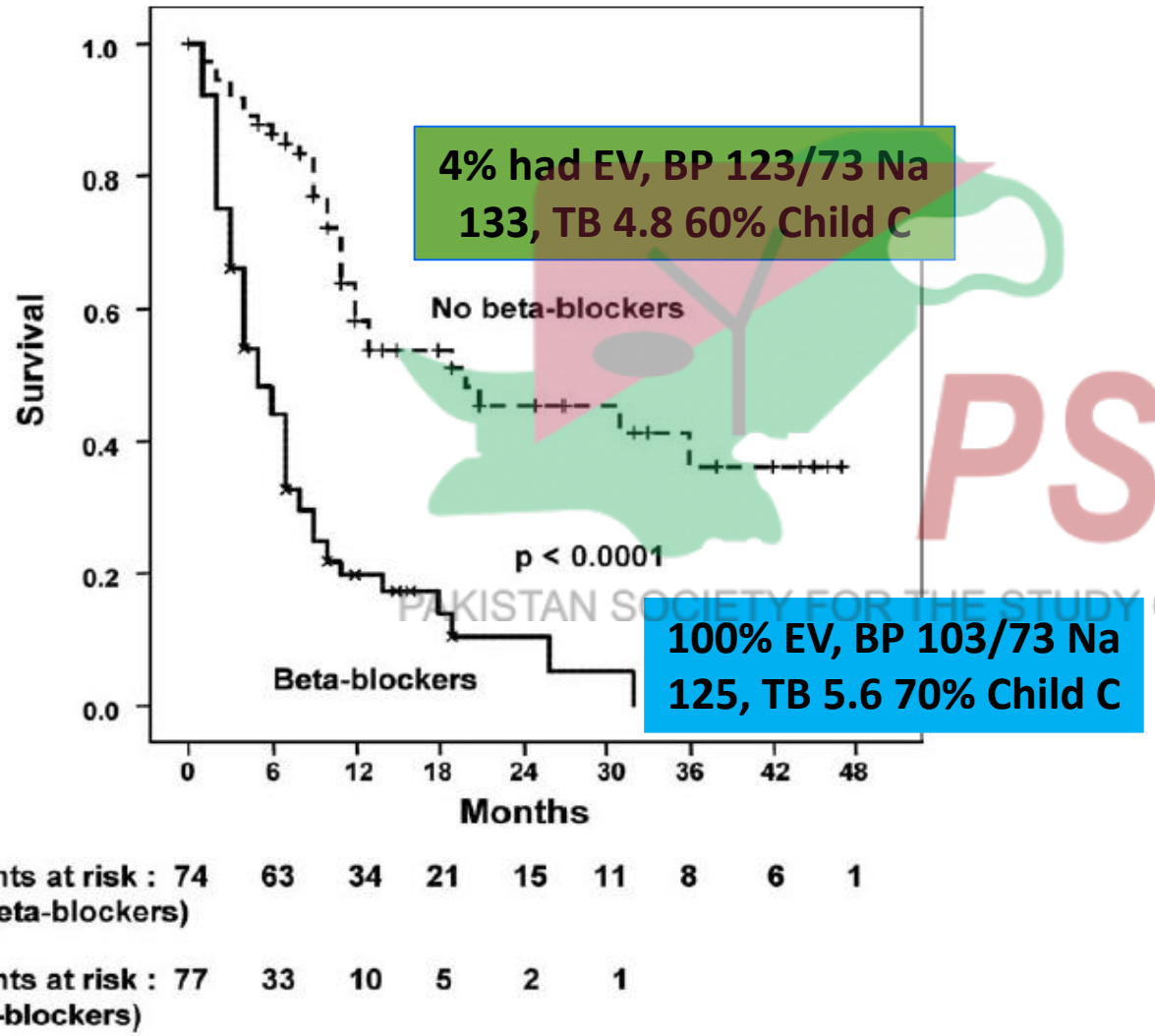
Deleterious effects of Beta-Blockers on survival in patients with refractory ascites



- Single-center, observational, prospective study
- **151** patients with cirrhosis and refractory ascites (67% CP-C)
- The 1-year probability of survival was significantly lower in patients who received propranolol **(19%)** vs those who did not **(64%)**, p <0.0001

Sersté T, et al. Hepatology 2010;52:1017-22

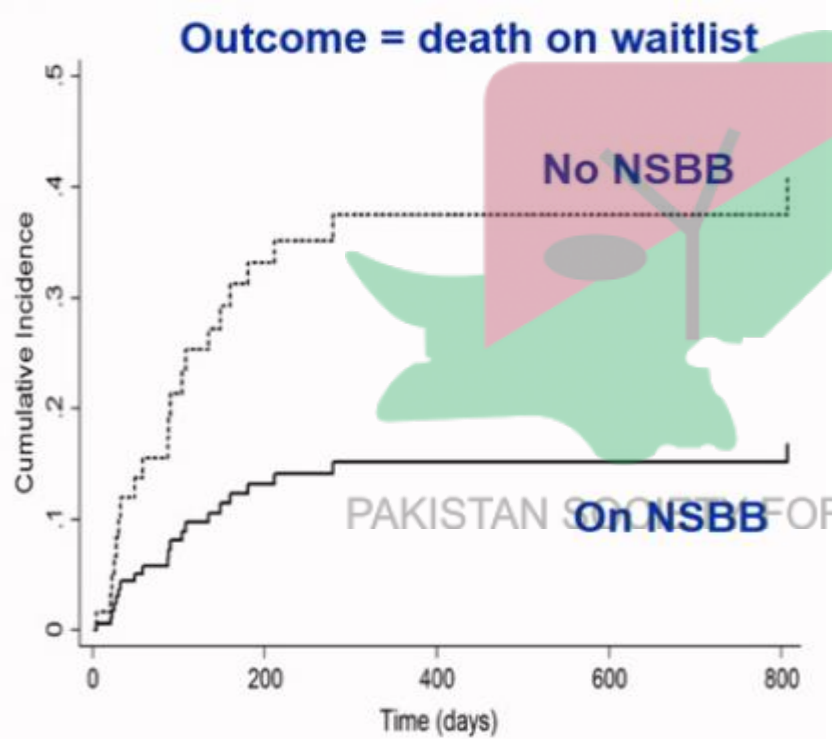
Deleterious effects of Beta-Blockers on survival in patients with refractory ascites



- Not an RCT: significant differences in patients' characteristics between groups
- Mean propranolol dose 113 ± 46 mg/d
- Causes of death in 97 patients: 50 from sepsis, 13 from HCC, 25 from unknown causes

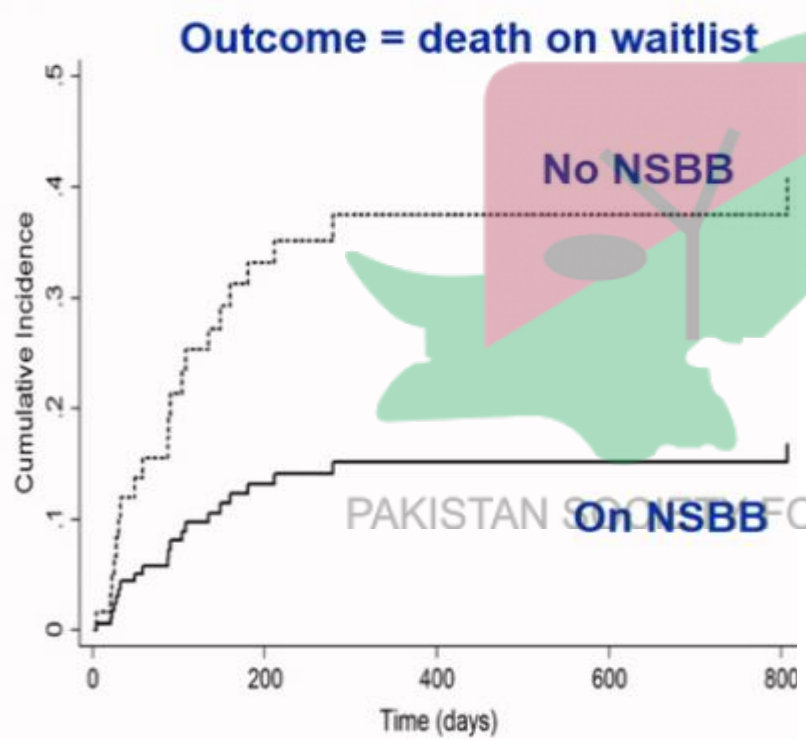
Sersté T, et al. Hepatology 2010;52:1017-22

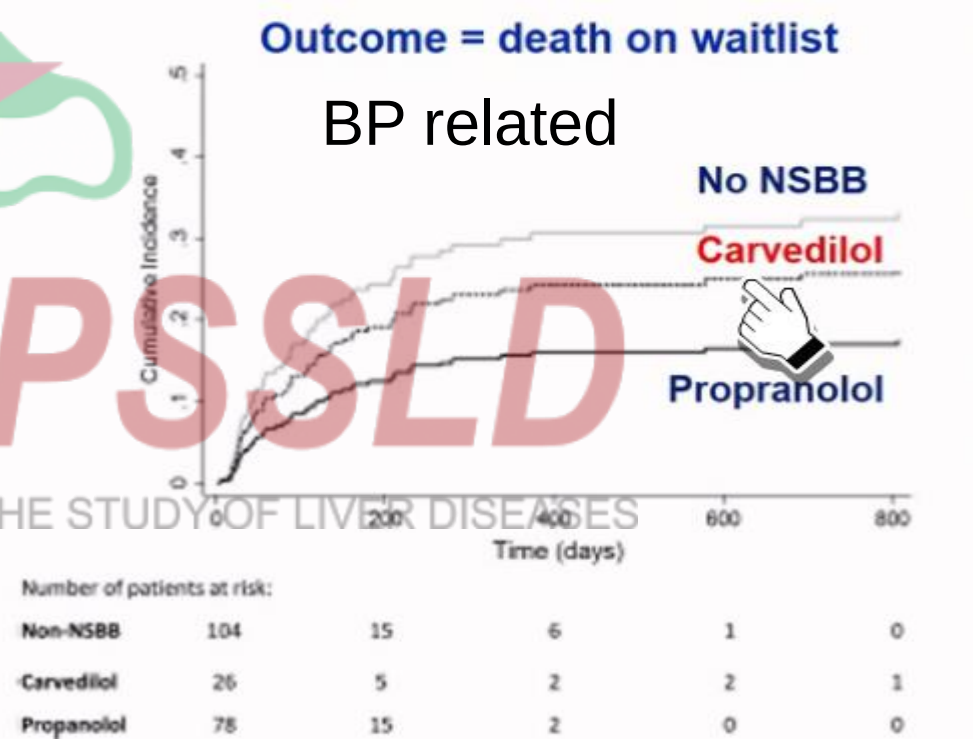
Incidence of death lower in Pts with refractory ascites on NSBB



Leithead et al. Gut 2015; 64:1111-9

Incidence of death lower in Pts with refractory ascites on NSBB

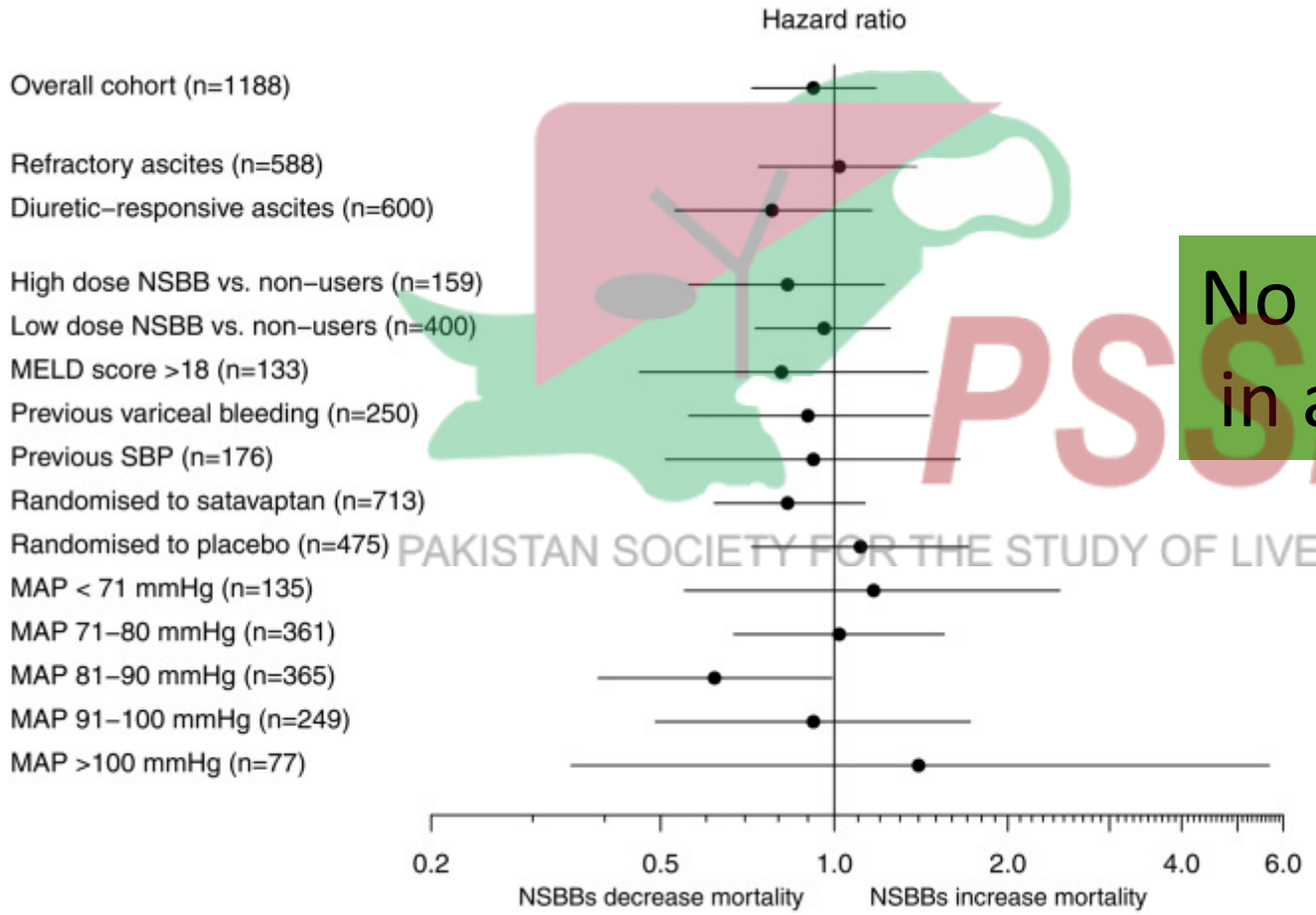




Leithead et al. Gut 2015; 64:1111-9

Beta-Blockers and Ascites

1188 patients with Ascites from 3 RCT's



No increase in mortality in any subgroup

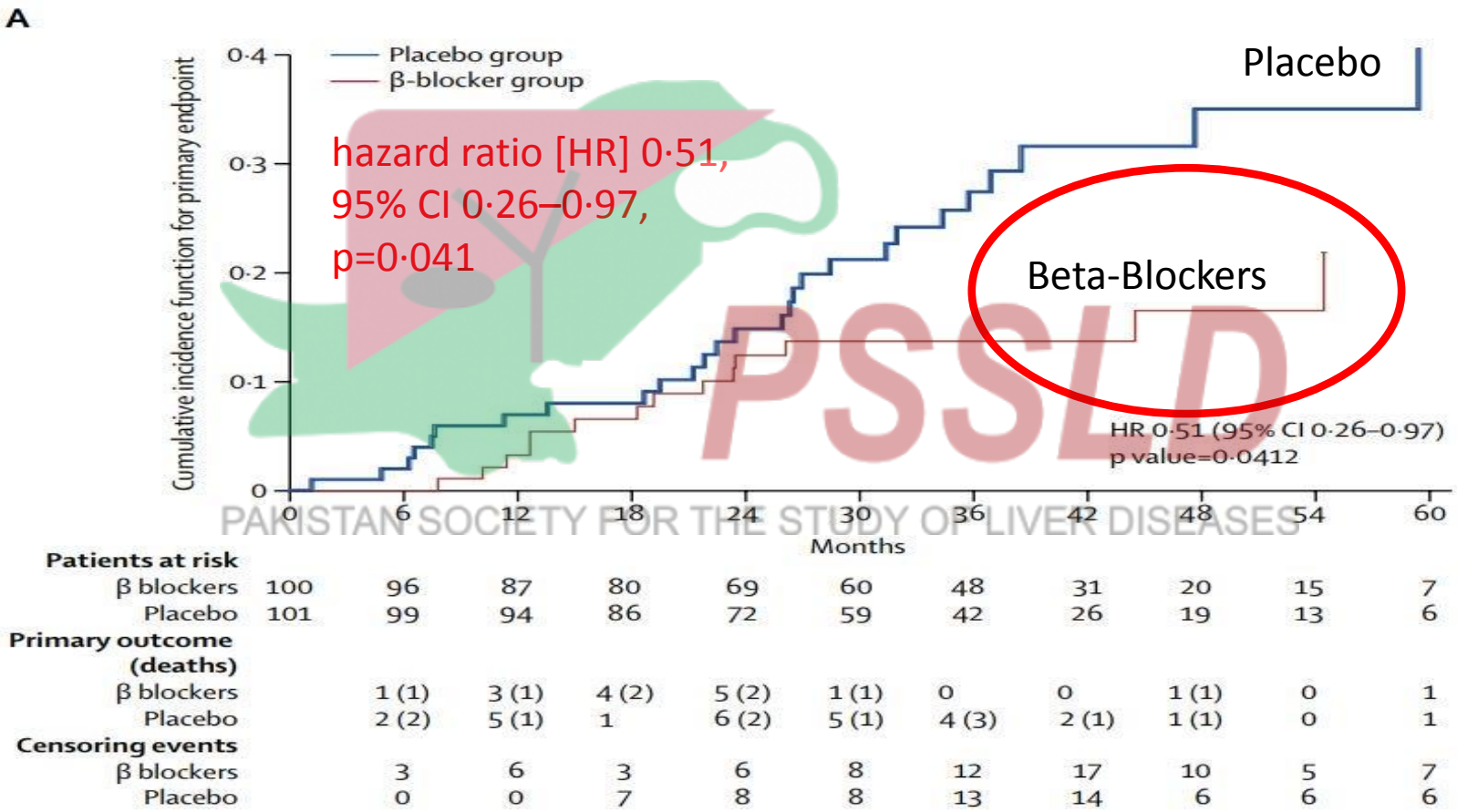
Bossen et al. Hepatology 2015.

NSBB prevent decompensation in CSPH (PREDESCI Study)

- 201 patients with compensated cirrhosis (HVPG >10 mmHg)
- No or small varices
- Randomized to NSBB (propranolol or carvedilol) vs. placebo
- Primary endpoint: Decompensation
- Median F/u 3 years

Villanueva C et al. Lancet 2019.

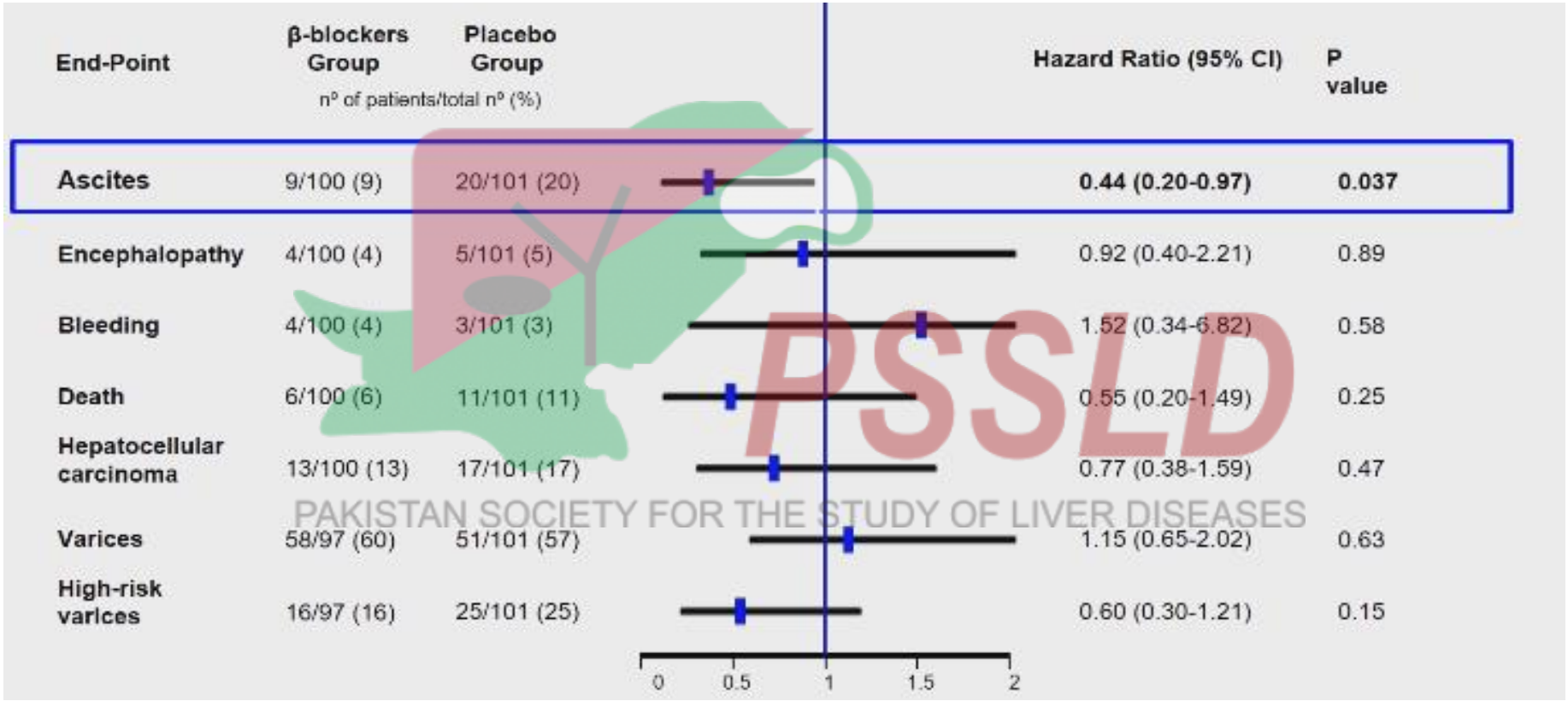
PREDESCI Study: Primary Endpoint (Decompensation)



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

Villanueva C et al. Lancet 2019.

PREDESCI Study: Secondary Endpoint



Reduced incidence of ascites (HR 0·42, 95% CI 0·19–0·92, p=0·03)

Villanueva C et al. Lancet 2019.

Baveno recommendations for BB in refractory ascites

- In cirrhosis and refractory ascites NSBB should be used cautiously with close monitoring of BP, sodium and creatinine
- Until randomized trials are available NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events :

  - Systolic blood pressure <90 mmHg

  - Hyponatremia

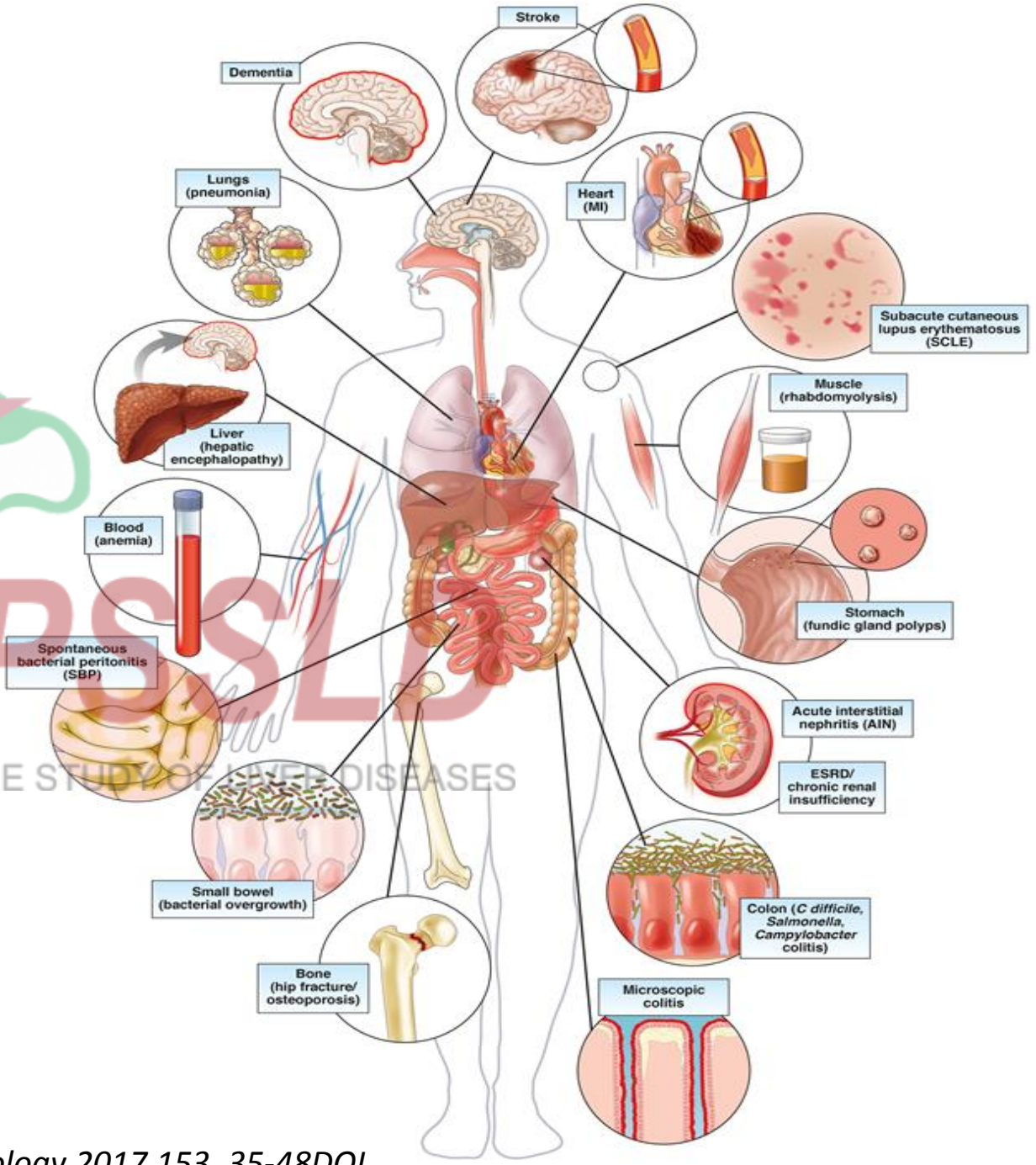
  - Acute Kidney injury

- **Carvedilol should not be used in cirrhosis with ascites**
- **Avoid high doses (ie nadolol >80mg, propanolol >160mg/day**

Franchis , R et al. Journal of Hepatology 2015 vol. 63 j 743–752

Proton pump inhibitors

- In 2015 PPI's ranked in the top 10 national health-related drug expenditures in the US
- Evidence regarding associations with adverse outcomes is predominantly based on observational studies



Vaezi M et al. Gastroenterology 2017 153, 35-48DOI

PPI use in Cirrhosis

- Most prescribed class of medications in cirrhosis (40% patients)
- 2/3rd have no indication for the use of PPI
- PPIs are all metabolized by the liver.
- PPI are associated with SBP, C.diff and worsening HE
- Most of these were observational and cross-sectional by design and provide conflicting result
- PPI related acid suppression can cause intestinal bacterial overgrowth and translocation as possible causes

Franz CC et al. Eur J Clin Pharmacol 2012.
Goel et al. Clin Gastroenterol Hepatol 2012.
Dultz G et al. Aliment Pharmacol Ther 2015.

PPI guidance based on liver disease severity

	CTP A/B	CTP C
Esomeprazole	No additional risk known	No additional risk known
Lansoprazole	Unsafe	Unsafe
Omeprazole	No additional risk known	Unsafe
Pantoprazole	Unsafe	Unsafe
Rabeprazole	No additional risk known	Unsafe

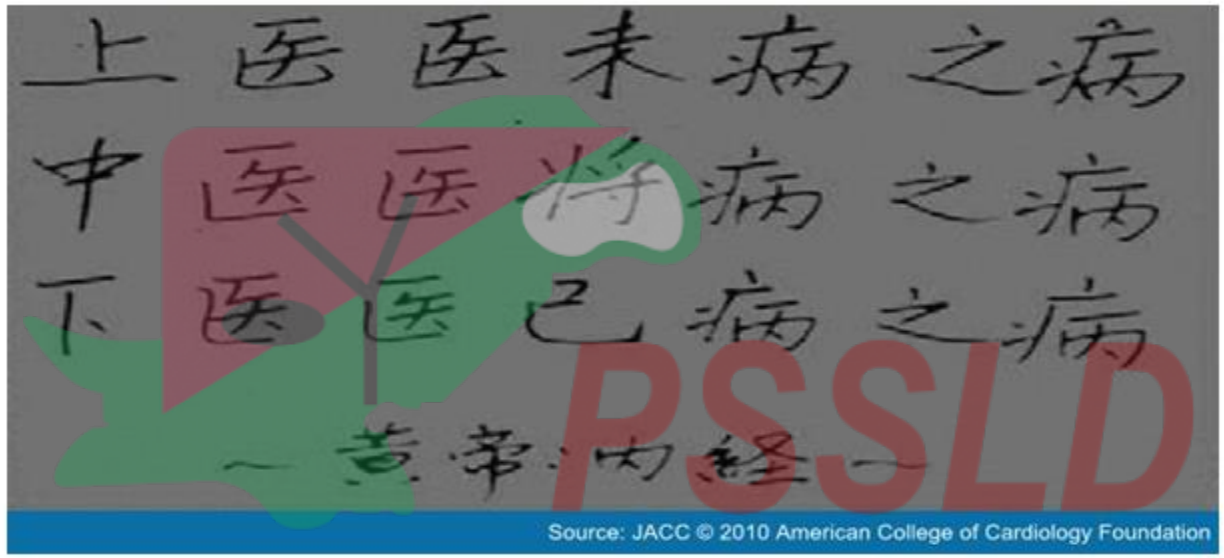
Weersink, R et al. Br J Clin Pharmacol 2018.

“Weaning a patient off a PPI can be one of the most challenging endeavors in medicine.”

Summary

- Safe use of medications in cirrhosis is an ongoing challenge
- Lower doses are recommended for the use of most drugs in cirrhosis
- Polypharmacy and adverse drug effects are common in cirrhosis
- Statins are safe in liver disease and need further studies to understand benefits for liver disease
- Avoid carvedilol in cirrhosis with ascites
- PPI should be stopped in cirrhosis if no clear indication

Thank You



Huang Dee: Nai-Ching (2600 BC, First Medical Text)

Translation:

Superior doctors prevent the disease

Mediocre doctors treat the disease before evident

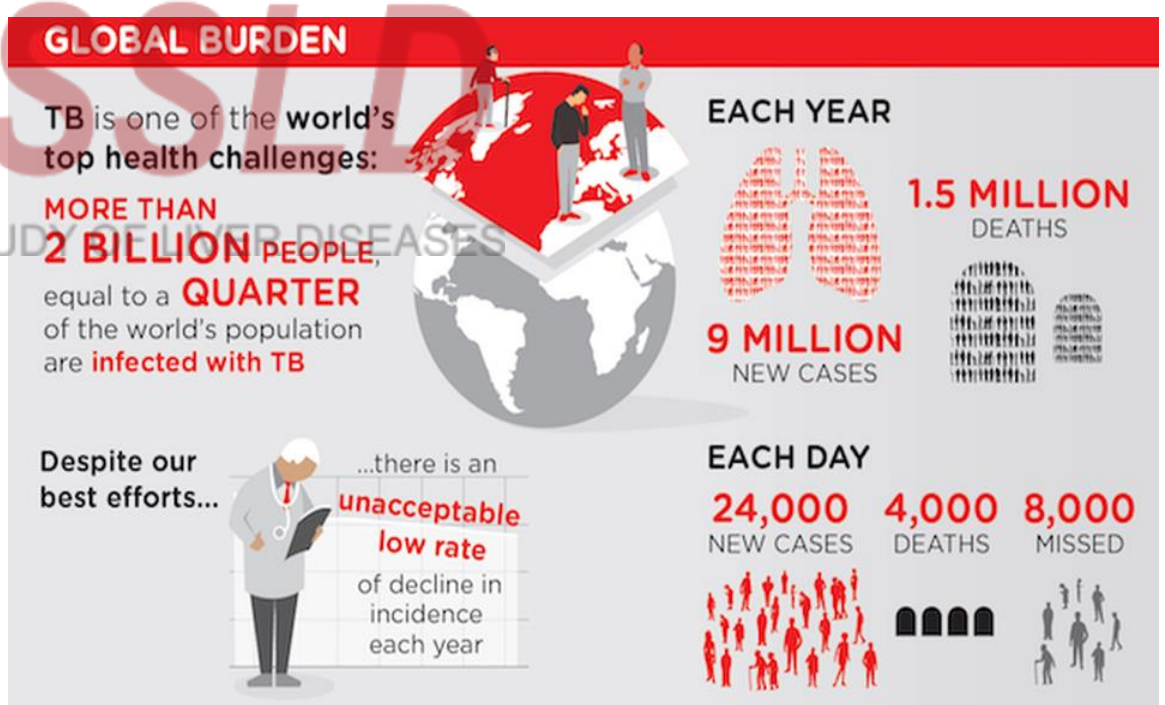
Inferior doctors treat the full-blown disease

Tuberculosis Treatment in Cirrhosis

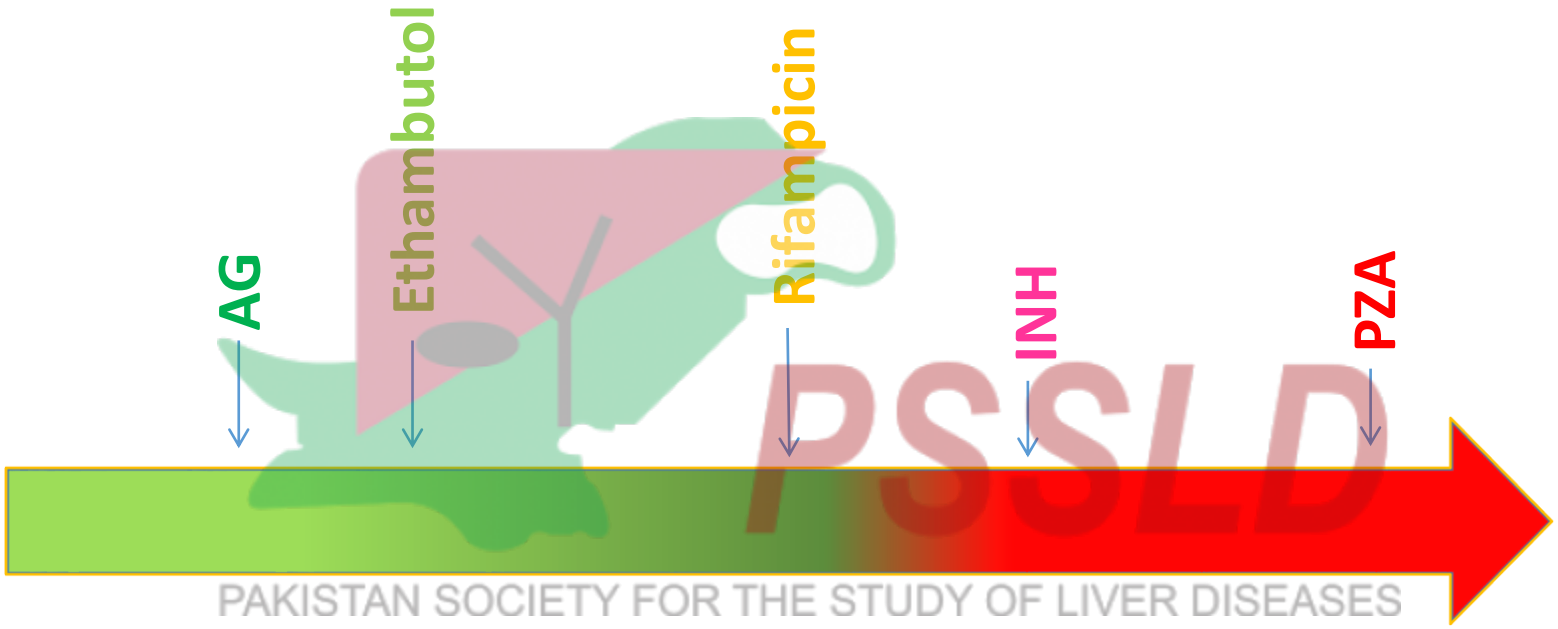
Challenges in Treatment of Cirrhosis & TB

- No Consensus & guidelines
- Drug-induced liver injury (DILI) likely higher
- Outcome of DILI in CLD patients is poor
- Monitoring DILI is challenging
- Need close monitoring
- 25% Pulmonary TB cases had

CLD (HCV & HBV) in Pakistan



Hepatotoxicity of 1st Line ATT



Hepatotoxicity of Anti-TB Drugs

Potentially Hepatotoxic Drugs	Less Hepatotoxic Drugs
First Line ATDs	**First Line ATDs**
INH (H) = 3 times	Aminoglycosides (AG)
Rifampicin (R) = 1	- SM, Ak, Km
PZA (Z)= 10 times	Capreomycin (Cm)
	Ethambutol (E)
Second Line ATDs	**Second Line ATDs**
Ethionamide (Eto)	Fluoroquinolones (FQs)
Prothionamide (Pto)	(Ofloxacin, Levofloxacin,
PAS	Ciprofloxacin, Moxifloxacin)
Rifabutin	Cycloserine (Cs)

ATT Recommendations in liver disease

Status of Liver	ATT Treatment Recommendation
CTP A	• Two hepatotoxic drugs can be used namely INH & rifampicin with/without pyrazinamide (low dose) • Duration 6-9 months
CTP B	• Ideally one hepatotoxic drug is used in combination • Pyrazinamide generally avoided • Duration generally 9-12 months
CTP C	• No hepatotoxic drugs to be used. • Can use second-line drugs like streptomycin, ethambutol, quinolones etc • Extended duration 12 months or more • Caution with aminoglycosides (renal function)

Kumar N et al. World J Gastroenterol. 2014.

PSSLD

PAKISTAN SOCIETY FOR THE STUDY OF LIVER DISEASES

Patients with refractory ascites or after SBP

- NSBBs are *not* absolutely contraindicated in patients with refractory ascites and SBP
  - However, high doses (over 160mg/day of propranolol or over 80 mg/day of nadolol) may be associated with worse outcomes and should be avoided.
- In patients with refractory ascites and severe circulatory dysfunction, decrease the dose of NSBBs or temporarily hold the drug. Consider reintroducing NSBBs if circulatory dysfunction improves.

Garcia-Tsao, G. et al. Hepatology 2017.

Statins use in liver disease

- Retrospective and randomized control trials results have shown benefits of statin in cirrhosis

➢Decrease risk of decompensation

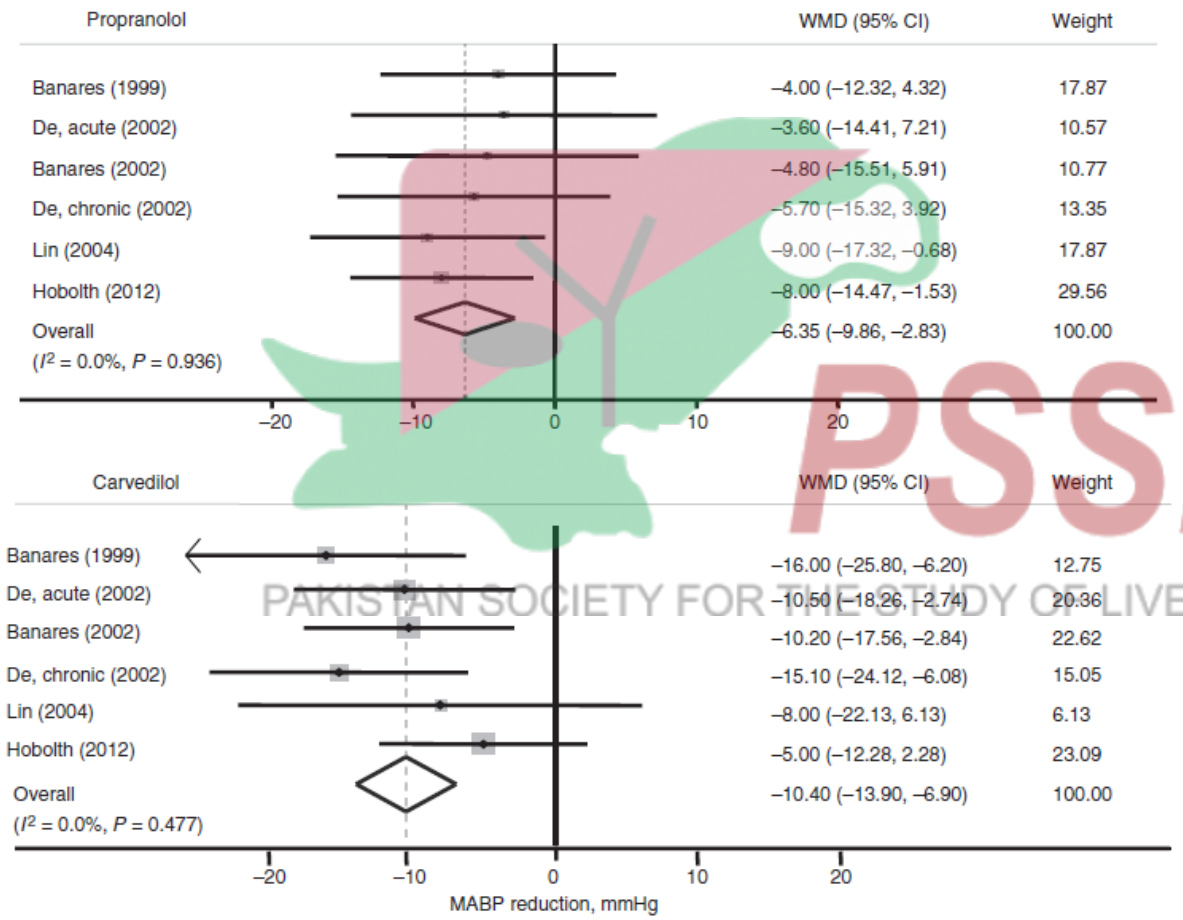
➢Increase survival

- Whether dose and severity of liver disease is important?

Pose E et al. Journal of Hepatology 2019.

Meta-analysis: MABP reduction propranolol vs carvedilol

5 studies (n=175) were included

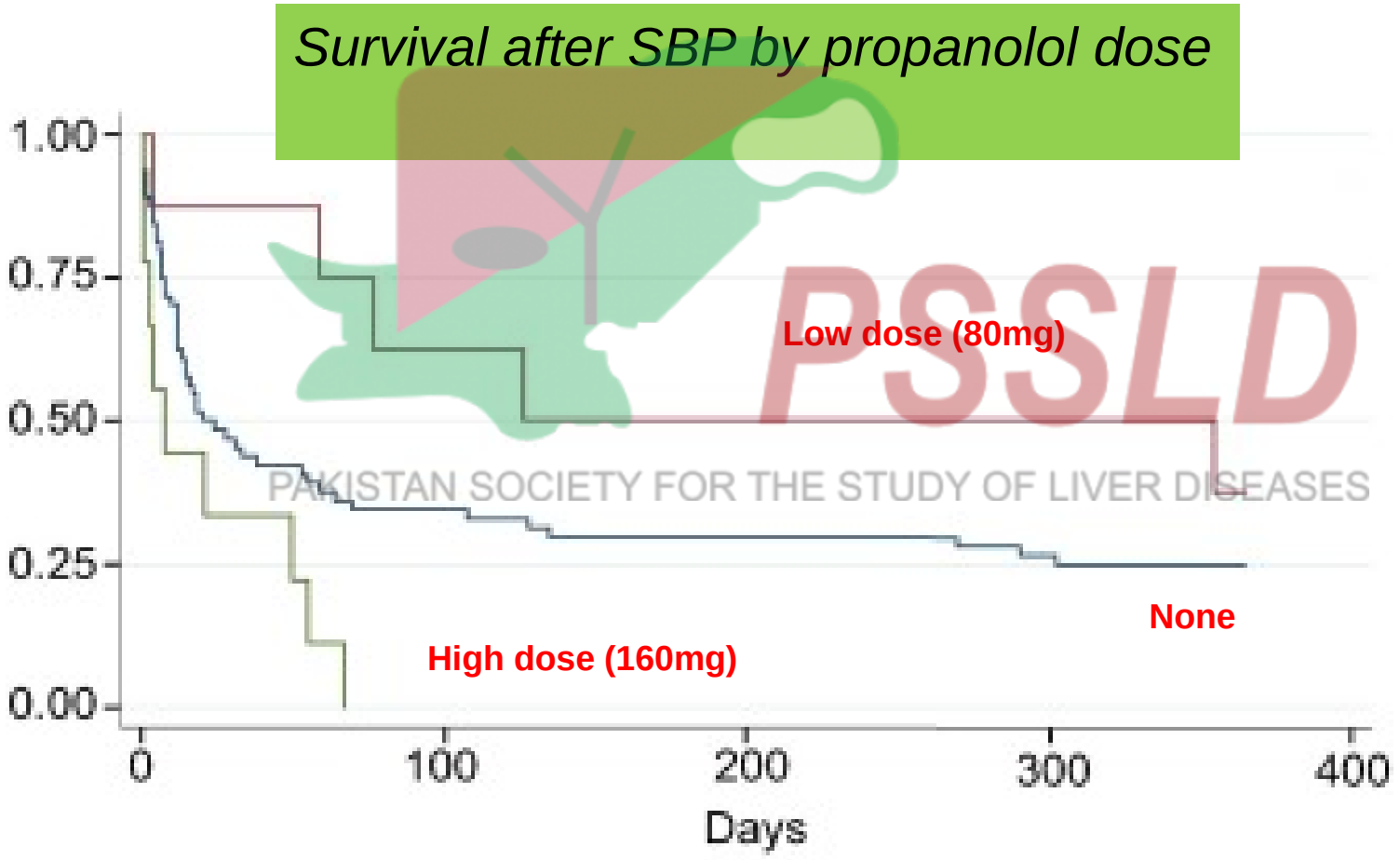


MAP reduced by propranolol: WMD -6.35 (-9.86 to -2.83)

MAP reduced by carvedilol: WMD -10.40 (-13.90 to -6.90)

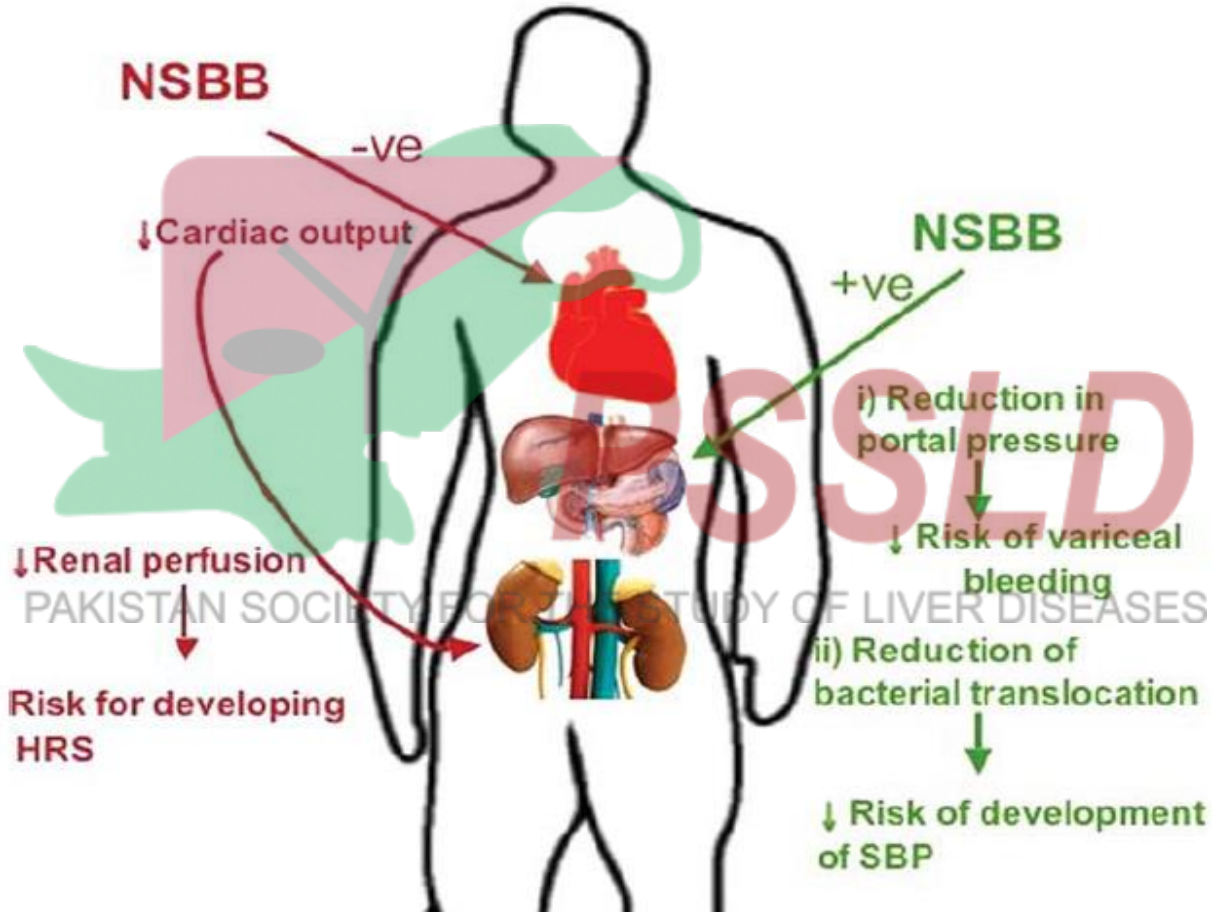
Sinaga E, et al. Aliment Pharmacol Ther 2014;39:557-68

Harms of Beta blockers may be dose related



Madsen et al., J of Hepatology, 2016

Proposed Mechanisms of Beneficial and Deleterious Effects of NSBB in Patients with Advanced Cirrhosis



Wong F, Salerno F. Hepatology 2010.

Statins effects in portal hypertension?

Improve endothelial dysfunction

↓

Decrease intrahepatic vascular tone

↓

Improve hepatic blood flow and liver function

+

Antifibrotic Properties!

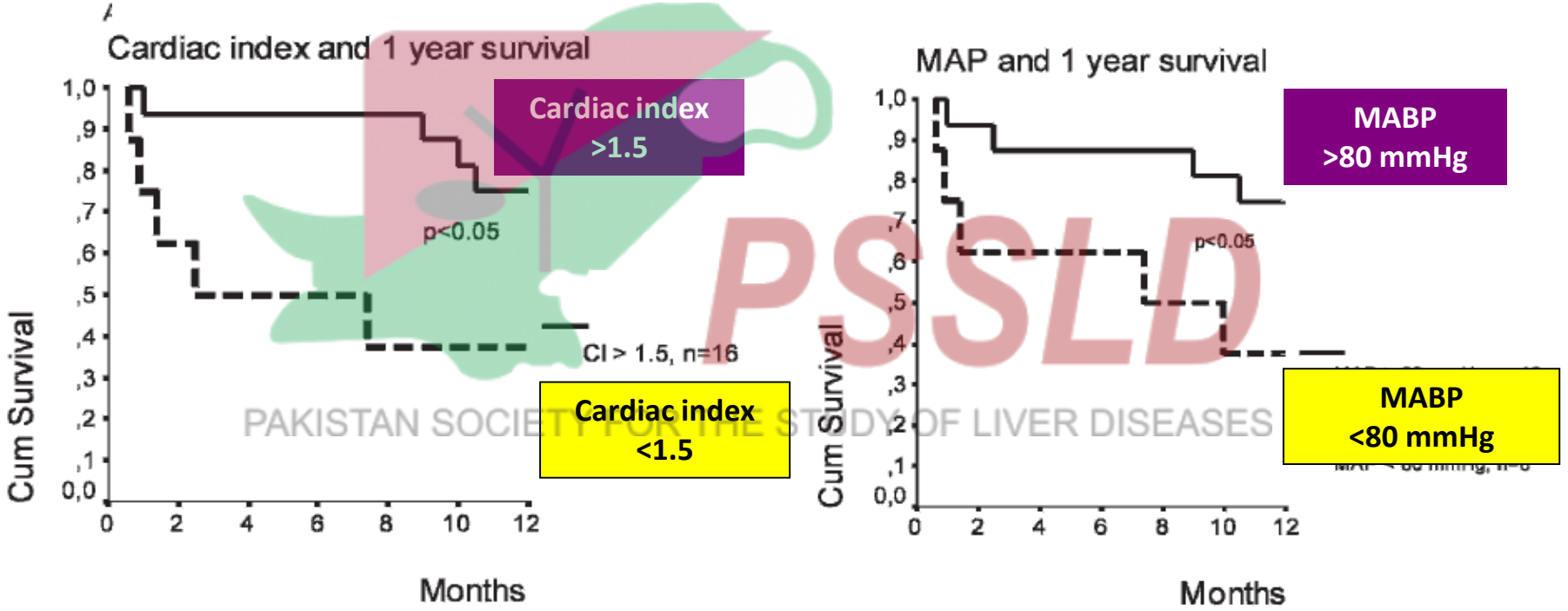
MORE TO COME ON BENEFITS OF STATINS IN PORTAL HYPERTENSION!

Antibiotics: Use caution or avoid in cirrhosis

Azithromycin and other macrolide antibiotics
Tetracycline
Chloramphenicol
Ketoconazole
Nitrofurantoin (chronic use)

Low cardiac output and MABP predicts development of HRS and survival in patients with cirrhosis and ascites

- 24 patients with alcoholic cirrhosis and ascites had FU



Krag A, et al. Gut 2010;59:105-10