Supplementary Tables

Supplementary table 1: Studies on primary and secondary prophylaxis in SBP, post Cochrane review 2009 (Cohen et al. 2009 Cochrane Database of Systematic Reviews)

Refid	Author	Title	Issue	Journal	Vol	Year	Study participants:	Comment
387	Flamm S.L., Sanyal A.J., Neff G.W., Rolleri R.L., Barrett A.C., Bortey E., Paterson C., Forbes W P (US) Abstract only.	Impact of liver disease status and treatment with rifaximin on complications of cirrhosis in a randomized, placebo-controlled trial	4 SUPPL. 1	Hepatology	58	2013	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	A post-hoc analysis with much stratification was done and the exact impact on SBP is not clear.
63	Felix Tellez-Avila, Jose Sifuentes-Osornio, Varenka Barbero-Becerra, Ada Franco-Guzman, Roberto Ruiz-Cordero, Roberto Alfaro-Lara, Angeles Hernandez-Ramirez, Florencia Vargas-Vorackova, F Téllez-Ávila, Jose Sifuentes-Osornio, Varenka Barbero-Becerra, A Franco-Guzmán, Roberto Ruiz-Cordero, Roberto Alfaro-Lara, A Hernández-Ramírez, F Vargas-Voráckova (Mexico)	Primary prophylaxis with ciprofloxacin in cirrhotic patients with ascites: a randomized, double blind study.	1	Annals of hepatology	13	2013	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline. Patients were excluded if previous SBP and if ascitic albumin <1.5g/dl.	n=49 ciprofloxacin n=46 placebo Both for 1 month. Conclusion: Primary prophylaxis without an accepted indication did not show a preventative effect on development of bacterial infections at 1-month follow up.
422	Abd-Elsalam S., Ali L.A., Soliman S., Ibrahim S., Elfert A , S Abd-Elsalam, La Ali, S Soliman, S Ibrahim, A Elfert (Egypt)	Randomized controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis	2 suppl. 1	Journal of Hepatology Later published in Eur J Gastroenterol Hepatol	64	2016	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	Rifaximin vs Norfloxacin for secondary prophylaxis. n=262. 6-month follow up. Recurrence of SBP significantly lower in the Rifaximin group.
225	Amr S Hanafy, Ahmad M Hassaneen (Egypt)	Rifaximin and midodrine improve	12	European journal of	28	2016	Cirrhosis with ascites, no gastrointestinal	Looked at Rifaximin and midodrine added to

		clinical outcome in refractory ascites including renal function, weight loss, and short-term survival.		gastroenterology & hepatology			bleeding, no obvious sign of infection at baseline	diuretic therapy compared to standard diuretic therapy and impact on diuresis and short term survival. SBP not an endpoint.
11	S Lontos, E Shelton, Pw Angus, R Vaughan, Sk Roberts, A Gordon, Pj Gow (Australia)	A randomized controlled study of trimethoprim-sulfamethoxazole versus norfloxacin for the prevention of infection in cirrhotic patients	5	Journal of digestive diseases	15	2014	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	RCT comparing trimetho-sufamethoxazole vs norfloxacin in patients at high risk of SBP. n=80. 12 month follow-up. No significant difference in infection between groups.
58	Markus Casper, Martin Mengel, Christine Fuhrmann, Eva Herrmann, Beate Appenrodt, Peter Schiedermaier, Matthias Reichert, Tony Bruns, Cornelius Engelmann, Frank Grunhage, Frank Lammert, INCA trial group (Germany)	The INCA trial (Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver Cirrhosis and Ascites): study protocol for a randomized controlled trial.		Trials	16	2015	Cirrhosis with ascites and gastrointestinal bleeding, no obvious sign of infection at baseline	Patients with NOD2 variants randomized to norfloxacin or placebo as primary prophylaxis. In progress.
59	Tarek Mostafa, Gamal Badra, Mahmoud Abdallah (Egypt)	The efficacy and immunomodulatory effect of rifaximin in prophylaxis of spontaneous bacterial peritonitis in cirrhotic Egyptian patients.	2	The Turkish journal of gastroenterology : the official journal of Turkish Society of	26	2015	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	Rifaximin vs Norfloxacin as secondary prophylaxis. 6-month treatment. n=70. Less recurrence of SBP in Rifaximin group.

				Gastroenterology				
398	Kimer N., Pedersen J.S., Moller S., Krag A., Bendtsen F (Denmark)	Randomized trial with rifaximin in liver cirrhosis. Effects on the haemodynamic and inflammatory state	SUPPL. 2	Journal of Hepatology	62	2015	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	Full text below
56	M Assem, M Elsabaawy, M Abdelrashed, S Elemam, S Khodeer, W Hamed, A Abdelaziz, G El-Azab (Egypt)	Efficacy and safety of alternating norfloxacin and rifaximin as primary prophylaxis for spontaneous bacterial peritonitis in cirrhotic ascites: a prospective randomized open-label comparative multicenter study.	2	Hepatology international	10	2016	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	Compared alternating norfloxacin/rifaximin vs norfloxacin alone vs rifaximin alone as primary prophylaxis in patients at high risk of developing SBP (ascitic protein <1.5 g/dL, CP>9). n=334. 6-month treatment. Alternating treatment showed higher efficacy compared to norfloxacin alone.
428	Hj Yim, Sj Suh, Yk Jung, Sy Yim, Ys Seo, Sy Park, Jy Jang, Ys Kim, Hs Kim, Bi Kim, Sh Um, Yim H.J., Suh S.J., Jung Y.K., Yim S.Y., Seo Y.S., Park S.Y., Jang J.Y., Kim Y.S., Kim H.S., Kim B.I., Um S H (South Korea)	Comparison of daily norfloxacin versus weekly ciprofloxacin for the prevention of spontaneous bacterial peritonitis in cirrhotic patients: A randomized controlled trial	2 suppl. 1	Journal of Hepatology Recently published in Am J Gastroenterol	64	2016	Cirrhosis with ascites and gastrointestinal bleeding, no obvious sign of infection at baseline	Daily norfloxacin vs weekly cipro in patients with previous SBP or deemed to be at high risk with ascitic protein of <1.5 g/dL. n=124. 12 month treatment and follow up. Once weekly ciprofloxacin as effective as daily norfloxacin.

449	Kimer N., Pedersen J.S., Busk T.M., Gluud L.L., Hobolth L., Krag A., Moller S., Bendtsen F , Nina Kimer, Julie Steen Pedersen, Troels Malte Busk, Lise Lotte Gluud, Lise Hobolth, Aleksander Krag, Soren Moller, Flemming Bendtsen, Copenhagen Rifaximin (CoRif) Study Group	Rifaximin has no effect on hemodynamics in decompensated cirrhosis: A randomized, double-blind, placebo-controlled trial.	2	Hepatology	65	2017	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	Haemodynamic effects of Rifaximin examined (n=45). SBP not an endpoint.
411	Praharaj D., Taneja S., Duseja A., Chawla Y.K., Dhiman R K (India)	Randomized control trial of rifaximin and norfloxacin in primary and secondary prophylaxis of spontaneous bacterial peritonitis (SBP) in cirrhotic patients	Supplement 2	Journal of Clinical and Experimental Hepatology	7	2017	Cirrhosis with ascites, no gastrointestinal bleeding, no obvious sign of infection at baseline	n=59 with previous SBP assigned to receive either norfloxacin or rifaximin. n=58 with ascites and CP>9, no past episode of SBP, assigned to receive either norfloxacin or rifaximin. 6-month treatment/follow up. Rifaximin more effective than norfloxacin in secondary prophylaxis of SBP.

Supplementary Table 2: Studies assessing salt restriction as a therapeutic intervention in controlling ascites in patients with cirrhosis

Author, sample size, study duration Outcome measures	**Study design, method of randomisation, patient, characteristics, study groups**	**Outcomes**
Reynolds T, 1978 N=201 8-27 days No outcome stated	RCT, randomisation method and sample size calculations not stated 90% ALD, non azotemic, no fluid restriction **Study 1** a. Sodium restriction 10 mmol/day + diuretics (ethacrynic acid/spironolactone) until ascites resolution b. Unrestricted sodium diet + diuretics until ascites resolution c. Unrestricted sodium diet + diuretics until partial ascites resolution **Study 2** Similar except furosemide used **Study 3** a. Sodium restriction (as above) + spironolactone and furosemide until ascites resolution b. Unrestricted sodium diet + spironolactone and furosemide until partial ascites resolution	Diuresis and weight loss similar in those with sodium restricted and sodium unrestricted diet. Greater natriuresis in sodium unrestricted diet. Serum sodium fell significantly in all three subgroups receiving a low sodium diet.
Descos L, 1983 N=328 5 days-1 month Outcome not stated	RCT, randomisation method and sample size calculations not stated ALD, 1L fluid blood urea > 8mmol/l excluded Groups 1. Sodium restricted to 500 mg/day + spironolactone 2. Sodium restriction as above + either spironolactone + furosemide or amiloride/hydrochlorothiazide 3. Unrestricted sodium + Spironolactone + furosemide /Moduretic 4. Sodium restriction as above + paracentesis with reinfusion of concentrated ascites 5. Sodium restriction as above + paracentesis with reinfusion of modified ascites 6. Sodium restriction as above + paracentesis	No difference between groups in body weight, abdominal girth, urine volume and partial/ complete regression of ascites. Treatment failure groups 1-6 16.6%, 26.2%,26.7%, 30.6%,21.7% and 38.7% (no difference in salt restricted and unrestricted diets) No differences in groups 1-3 as regards cirrhosis complications and mortality.

Gauthier A, 1986 N=140 90 days Non- azotemic Outcomes: day 14 and 90: ascites disappearance, wt change, nutritional status, cramps, and biochemical data.	RCT, randomisation method and sample size calculations not stated All ALD, blood urea > 8.3mmol/l excluded, fluid restriction 1L Groups 1. Sodium restricted to 21 mmol/day 2. Unrestricted sodium diet Both groups received diuretics (spironolactone or, if necessary, spironolactone + furosemide).	Day 14 Group 1 vs. 2 Day 14 Group 1 vs. 2: Ascites disappearance (complete 42% vs. 23% and partial 57% vs. 61% ns, failure 1% vs. 16% p<0.01), wt change (kg) 8 ± 4.3 vs. 5.4 ± 4 p<0.01, appetite improved 36% vs. 18% p<0.02, serum sodium difference +4 ± 4.3 vs. +2.4 ± 3.6, p=0.025) Day 90 Group 1 vs. 2: ascites disappearance complete 60% vs. 53%, partial 25% vs. 34%, failure 15% vs. 34%; wt change (kg) 5.9 ± 6.9 vs. 6.8 ± 5.6; appetite improved 52% vs. 50%, nutritional status improved 71% vs. 68%, difference in urea, sodium, potassium and albumin (p=ns for all) No actuarial survival difference at day 90 (p=0.15), except if previous GI bleed salt restricted diet favoured survival (p=0.02). Duration of hospitalisation and costs similar in both groups
Bernadi M, 1993 N=115 Study duration not stated Study aim: evaluate therapeutic effectiveness and complication rate of stepped up care including normal or low sodium diet.	RCT with sample size calculations, randomisation by sealed envelope About 50% Child B and 50% Child C, non azotemic, predominantly ALD, 20% had HCC Groups 1.Salt restricted diet (SRD), sodium 40 mmol/day 2. Salt unrestricted diet (SUD), sodium 120 mmol /day Both groups received increasing doses of potassium canrenoate. If no response, furosemide added	Group 1 vs. Group 2: no difference in spontaneous diuresis 10% vs. 8%, need for addition of furosemide 18% vs. 13%, drop outs (2% vs. 2%) and refractory ascites (5% vs. 6%). Univariate analysis showed that type of diet was not associated with differences in treatment response (Wilcoxon p=0.98). On multivariate analysis creatinine clearance and plasma aldosterone were independently predicted response to treatment.
Soulsby C, 1997 Abstract N=6 8 weeks Aim: compare energy and protein intake in low sodium and no added sodium diet	Cross over RCT, randomisation method and sample size calculations not stated Groups 1. SRD, sodium 40 mmol/day 2. No added salt diet, sodium 60-80 mmol /day	In Group 2 degree of ascites unchanged in 5 and increased in 1 patient . Group 1 vs. Group 2, mean energy intake kcal/day (1940 ± 284 vs. 2501 ± 138), protein intake (79 ± 13 g/d vs. 89 ± 13 g/day), weight loss (- 0.4 ± 1.7 kg vs. +1.7 ± 1.4 kg) and mid arm circumference (-0.5 ±1.5 cm vs. +1.0 ± 0.7cm) (p<0.05)
Gu X, 2012 N=200	RCT, no sample size calculations, randomisation by numerical tables	At day 10 Serum sodium (mmol/l)) higher in Group 2 (134 ± 4.03 vs. 137.6 ±

Duration not stated Aim: to compare blood and urine sodium, PRA, angiotensin II, aldosterone, RBF, renal impairment, diuretic effect, serum albumin and volume of ascites.	95% had HBV cirrhosis, 73% CPS C, fluid restriction implemented ? amount Groups 1. SRD, sodium < 85 mmol (<5g NACL) 2. SUD, sodium 85 mmol- 111mmol (5- 6.5g NACL) Both groups received silymarin, IV albumin and spironolactone 40 mg bd and furosemide 20 mg bd	2.24) and lower in Group 1 (134 ± 4.2 vs. 128.9 ± 2.28 (p<0.001) and higher at day 10 in Group 2 vs. Group 1 (p<0.001). Urine sodium (mmol/l) higher in Group 2 (269.2 ± 5.30 vs. 173.2 ± 5.87) with no change in Group 1 (183.1 ± 5.82 vs. 173.2 ± 4.88) (p<0.001) and higher at day 10 in Group 2 vs. Group 1) (p<0.001). PRA, angiotensin II, and aldosterone significantly reduced in Group 2 and significantly higher in Group 1 (p<0.001). RBF significantly increased in Group 2 (p<0.001), no change in Group 1. At day 30 serum albumin (g/L) increased in Group 2 (33.5 ± 1.86 vs. 31 ± 4.42) p<0.001 with no change in Group 1 (31.2 ± 3.31 vs. 30.6 ± 2.84) and higher at day 30 in Group 2 vs. Group 1 (p<0.001). Renal impairment 0% Group 2 vs. 13.8% (n=14) Group 1 (p<0.01), of whom 8 died Group 2 vs. Group 1: ascites disappearance 45% vs. 16% (p<0.001) and time to ascites disappearance shorter (days) (30.2 ± 3.12 vs. 47.2 ± 9.2 (p<0.001) Caloric intake at day 30 higher in Group 2 and no change in Group 1 (1043.15 ± 225.03 vs. 2081 ± 121.19, p<0.001) and 1044 ± 213.1 vs. 1529 ±113.96/), at day 30 higher intake in Group 2 vs. Group 1 (p<0.001).
Sorrentino P, 2012 N=120 One year Primary end points: transplant free survival. Secondary end points: liver related complications (HRS, GIB, HE).	RCT, Sample size calculations done, method of randomisation not stated Refractory ascites, HCV cirrhosis, excluded CPS >11 and serum creatinine <2 mg/dl Group A: Sodium 80 mmol/day + balanced oral diet + Post LVP TPN + late evening protein snack (BCAA) Group B: Sodium as above + balanced oral diet + late evening protein snack (BCAA) Group C: Sodium as above or sodium free diet	Group A vs. B vs. C Survival: 55% vs. 40% vs. 17.5% A vs. B p=0.048, A vs. C p<0.01, B vs. C p=0.046 Complications significantly lower in Groups A and B vs. C HE: 45% vs. 37.5% vs. 77.5% (p<0.01) GIB: 25% vs. 32.5% vs. 52.5% (p<0.01) HRS: 15% vs. 22.5% vs. .37.5% (p<0.01) SBP 17.5% vs. 22.5% vs. 47.5% (p<0.01 Mean LVP/month 1.1 (0.8–2.5) vs. 1.3 (1–2.9) vs., 2.1 (1.5–4) (p <0.01 and p =0.034).
Morando F, 2015 N=120	Non RCT. Interviews with a pre established questionnaire Patients with cirrhosis attending outpatients. Group 1 SRD Group 2 SUD	Group 1 vs. Group 2 mean daily sodium intake (mmol) 79.5 ± 5.5 vs. 205.9 ± 14.1 (p < 0.0001) 30.8% adherent to SRD 45% erroneously thought were on SRD

Aims: assess adherence of patients with cirrhosis and ascites to a moderately low-salt diet. Evaluate the impact of a low-salt diet on total calorie intake and serum sodium concentration.		24% not following SRD Group 1 vs. Group 2 mean daily caloric intake 20% lower (1382.5 vs. 1658.7) ($p<0.05$) with no difference in occurrence of hyponatremia.

ALD alcohol related liver disease; BCAA branched change amino acids; CPS Child-Pugh Score; GIB gastrointestinal bleed; HE hepatic encephalopathy; HBV hepatitis B virus; HCV hepatitis C virus; HCC hepatocellular cancer; HRS hepatorenal syndrome; PRA plasma renin activity; RCT randomised controlled trial; RBF renal blood flow; SRD salt restricted diet; SUD salt unrestricted diet; SBP spontaneous bacterial peritonitis; wt weight, RCT randomised controlled trial

Supplementary Table 3: Randomised controlled trials comparing sequential and combination diuretic therapy in patients with cirrhosis and ascites

Study	**Fogel M, 1981**	**Santos J, 2003**	**Angeli P et al, 2009**
Salt/fluid restriction	87mmol sodium and 2L fluid/day	50 mmol sodium/day	90 mmol sodium/day
Study groups	Sequential: spironolactone followed by furosemide Combination: spironolactone + furosemide Furosemide monotherapy	Sequential: spironolactone followed by furosemide Combination: spironolactone + furosemide	Sequential: potassium canrenoate followed by furosemide Combination: potassium canrenoate + furosemide
Maximum diuretic dose	Spironolactone 400mg and furosemide 400 mg	Spironolactone 400 mg and furosemide 160 mg	Potassium canrenoate 400 mg and furosemide 150 mg
Response definition	Dosage increased until a 0.4-0.8 kg daily diuresis	Decrease of ascites at least to grade 1(ultrasonography but not clinically detectable)	>700 gms weight loss every 3 days
Sample size (n)	90	100	100
Prior ascites	49%	41%	68%
Bilirubin (mg/dl)	6.4 $\pm$ 1.3 – 10.9 $\pm$ 1.9	2.1 $\pm$ 1.3 – 2.3 $\pm$ 1.6	1.9 $\pm$ 1.5 vs. 2.1 $\pm$ 1.2
Prothrombin time % activity	48 $\pm$ 3 - 49 $\pm$ 4	65 $\pm$ 6 - 68 $\pm$ 16	49 $\pm$ 19 - 50 $\pm$ 12
Albumin (gm/dl)	2.17 $\pm$ 0.1 – 3.0 + 0.1	2.63 $\pm$ 4.2- 2.74 $\pm$ 5.2	3.0 $\pm$ 3 - 3.2 $\pm$ 5
Creatinine mg/dl)	1.0 + 0.1 – 1.1 + 0.1	0.81 $\pm$ 0.2 - 0.84 $\pm$ 0.2	0.9 $\pm$ 0.2 - 0.9 $\pm$ 0.2
Child-Pugh Score	Majority Child C	8.9 $\pm$ 1.3 - 9.1 $\pm$ 1.5	50% Child B and 47% Child C
Response to spironolactone monotherapy	50%	91%	70%
Outcomes	Onset of diuresis faster and % body wt loss greater in combination/furosemide monotherapy vs. sequential group (9 $\pm$ 1 days vs. 13$\pm$ 1 days) and (17 $\pm$ 2 vs. 12 $\pm$ 2) (p <0.05).	Response combination vs. sequential 98% vs. 94% (p=ns) Median response time similar in combination vs. sequential: 9.8 days (4–35) vs.10.3 days (4–32)	In combined group - shorter time for ascites resolution (15.5 $\pm$ 5.6 vs. 20.7 $\pm$ 6.4) days, p < 0.001, - Treatment failures lower (24% vs. 44%, p<0.05)
Adverse events		Adverse reactions similar in both	Lower side effects in combined group (20% vs. 38%, p<0.05), especially hyperkalaemia (4% vs.

	Combination group: hyponatraemia and severe hyperkalaemia (p<0.01). Furosemide monotherapy frequent dose increases, need for potassium supplementation HE/marked electrolyte abnormality/HRS occurred in 33/90 (37%) patients	groups though serum potassium higher in sequential group (4.7±0.7 vs. 4.3±0.4 mmol/l, p=0.03. Need for diuretic dose reduction higher in combination group (68% vs. 34%, p=0.002)	18%, p<0.05)

Wt weight, HRS hepatorenal syndrome, HE hepatic encephalopathy

Supplementary table 4: Studies summarising impact of intravenous (IV) human albumin solution (HAS) on hyponatraemia in patients with cirrhosis and ascites (Group 1 received IV HAS vs. Group 2 no IV HAS)

Study characteristics and duration	Sample size and study duration	Child Pugh score (CPS)	Duration diuretics stopped before study	Baseline serum Na (mmol/L)	Salt/ fluid restriction	Impact of IV HAS on serum sodium (mmol/L) (Group 1 vs. Group 2)	Impact of IV HAS on other outcomes
Gines P, 1988 (RCT) Group 1 40 gms IV HAS after each LVP 4 weeks	n=105 with tense ascites, repeated LVP for 4 weeks	Mostly Child C	Six days, but continued after discharge	<135	Na 50 mmol/day If serum Na < 130, 500 ml fluids/day	133 ± 0.7 vs.133 ± 0.7 (ns) and 133 ± 0.9 vs. 131 ± 1.0 (p<0.01)	Group 2 increase in BUN, PRA, and PA (p<0.01)
McCormick P, (1990) Case series	n=4 with tense ascites, some undergoing LVP	Child C	Variable	122-141	Variable	Serum Na improved in 3 patients	NA
Garcia-Compean D, 1993 (RCT) 24 hours	n=35 with tense ascites undergoing LVP	54% Child C	3 days	<135	Na < 50 mmol/day	134 ± 4 vs. 133± 3.5 and 135±5 vs. 133±4 (p=ns)	Decrease in PRA and PA group 1 (p<0.05)
Luca A, 1995 (RCT) Group 1 mean IV HAS 68 ± 44 gms 24 hours	n=18 tense ascites undergoing LVP	Mean CPS 10.4	NA	>135	Na 40 mmol/day	137 ± 6 vs. 136 ± 7 (ns) and 137 ± 7 vs. 133 ± 10 (p=0.02)	Increase in PRA and PA after 24 hours in group 2 (p<0.05)
Jalan R, 2007 (RCT) Group 1 IV HAS 40 gms/day 7 days	n=24 with refractory ascites with last LVP 7 days ago	NA	> 7 days before	<130	Na < 80 mmol/day, fluids 1.5L/day	In group 1 serum sodium improved from 124 (2) to 133 (6)	Group 1 vs. group 2 serious culture positive infection 3/12 vs. 7/12, renal failure/severe HE/in-hospital mortality 1/12 vs. 5/12 (p=0.05)
Bajaj J, 2018 Retrospective cohort study Group 1 IV HAS 225 gms (IQR 100, 400)	n=1126 hospitalised cirrhotic patients,, HAS indications: AKI (52%), SBP (15%),	Mostly Child C	NA	Group 1 128.66 ± 4.69	NA	Group 1 vs. group 2 hyponatremia resolution 85.41% vs. 44.78%, OR: 1.50 (95% CI	Hyponatremia resolution independent predictor of 30 day mortality

16.80 ±18.60 days vs. 9.11 ± 9.67 days	LVP (33%), hyponatremia (29%)			Group 2 129.21 ± 10.50		1.13–2.00), p= 0.0057,	

BUN blood urea nitrogen, PRA plasma renin activity, PA plasma aldosterone, HE hepatic encephalopathy, IV intravenous, HAS human albumin solution, AKI acute kidney injury, LVP large volume paracentesis

Supplementary table 5: Effect of use of HAS on renal dysfunction in patients undergoing large volume paracentesis

Study	Albumin		Control		Weight	Risk Ratio
	Events (renal)	Total	Events (renal)	Total		[95% CI]
IV HAS versus no intervention						
Garcia-Compean et al. (1993)	1	17	2	18	6.3%	0.53 [0.05, 5.32]
Gines et al. (1988)	0	52	7	53	4.2%	0.07 [0.00, 1.16]
Subtotal	*1*	*69*	*9*	*71*	*10.5%*	*0.23 [0.03, 1.64]*
IV HAS versus alternative plasma expander						
Abdel-Khalek and Arif (2010)	1	68	1	67	4.5%	0.99 [0.06, 15.43]
Altman et al. (1998)	0	33	0	27	-	not estimable
Bertran et al. (1991)	1	8	0	9	3.6%	3.33 [0.15, 71.90]
Fassio and Kravetz (1992)	1	21	1	20	4.6%	0.95 [0.06, 14.22]
Garcia-Compean et al. (2002)	7	48	2	48	14.2%	3.50 [0.77, 16.00]
Perez and Silva (1995)	1	8	0	8	3.6%	3.00 [0.14, 64.26]
Moreau et al. (2006)	4	30	8	38	26.1%	0.63 [0.21, 1.90]
Planas et al. (1990)	1	43	1	45	4.5%	1.05 [0.07, 16.21]
Salerno and Incerti (1991)	1	27	1	27	4.6%	1.00 [0.11, 3.55]
Sola-Vera et al. (2003)	2	37	3	35	11.1%	0.63 [0.11, 3.55]
Subtotal	19	323	17	324	76.6%	1.11 [0.58, 2.14]
IV HAS versus vasoconstrictor						
Appenrodt et al. (2008)	0	13	2	11	3.9%	0.17 [0.01, 3.23]
Bari et al. (2012)	0	13	0	12	-	not estimable
Hamdy and MD (2014)	0	25	9	25	4.3%	0.05 [0.00, 0.86]
Moreau et al. (2002)	0	10	0	10	-	not estimable
Singh et al. (2006b) a	1	20	1	20	4.6%	1.00 [0.07, 14.90]
Singh et al. (2006a) b	0	20	0	20	-	not estimable
Singh et al. (2008)	0	20	0	20	-	not estimable
Subtotal	1	121	12	118	12.9%	0.22 [0.04, 1.20]
TOTAL	**21**	**513**	**38**	**513**	**100%**	**0.77 [0.43, 1.38]**

Supplementary table 6: Effect of use of HAS mortality in patients undergoing large volume paracentesis.

Study	Albumin		Control		Weight	Risk Ratio
	Events (death)	Total	Events (death)	Total		[95% CI]
IV HAS versus no intervention						
Arora et al. (2018)	8	30	21	29	13.6%	0.37 [0.20, 0.69]
Garcia-Compean et al. (1993)	0	17	0	18	-	not estimable
Gines et al. (1988)	20	52	16	53	17.8%	1.27 [0.75, 2.17]
Subtotal	*28*	*99*	*37*	*100*	*31.5%*	*0.69 [0.21, 2.34]*
IV HAS versus alternative plasma expander						
Abdel-Khalek and Arif (2010)	7	68	8	67	6.7%	0.86 [0.33, 2.24]
Bertran et al. (1991)	1	8	0	9	0.7%	3.33 [0.15, 71.90]
Fassio and Kravetz (1992)	6	21	7	20	7.4%	0.82 [0.33, 2.01]
Garcia-Compean et al. (2002)	11	48	18	48	13.6%	0.61 [0.32, 1.15]
Moreau et al. (2006)	1	30	3	38	1.3%	0.42 [0.05, 3.86]
Planas et al. (1990)	13	43	17	45	15.4%	0.80 [0.44, 1.44]
Sola-Vera et al. (2003)	1	37	1	35	0.9%	0.95 [0.06, 14.55]
Zhao and LI (2000)	14	36	11	32	13.8%	1.13 [0.60, 2.12]
Subtotal	*54*	*291*	*65*	*294*	*59.8%*	*0.83 [0.61, 1.12]*
IV HAS versus vasoconstrictor						
Appenrodt et al. (2008)	0	13	1	11	0.7%	0.29 [0.01, 6.38]
Bari et al. (2012)	4	13	5	12	5.6%	0.74 [0.26, 2.12]
Hamdy and MD (2014)	0	25	7	25	0.8%	0.07 [0.00, 1.11]
Moreau et al. (2002)	1	10	1	10	1.0%	1.00 [0.07, 13.87]
Singh et al. (2008)	0	20	1	20	0.7%	0.33 [0.01, 7.72]
Subtotal	*5*	*81*	*15*	*78*	*8.7%*	*0.54 [0.23, 1.26]*
TOTAL	**87**	**471**	**117**	**472**	**100.0%**	**0.77 [0.59, 1.00]**

Supplementary Table 7: Effect of use of HAS on renal dysfunction in patients with SBP

Study	Albumin		Control		Weight	Risk Ratio [95% CI]
	Events (renal)	Total	Events (renal)	Total		
IV HAS versus no intervention						
XUE et al. (2002)	5	56	19	56	40.7%	0.26 [0.11, 0.66]
Sort P (1999)	6	63	21	63	48.4%	0.29 [0.12, 0.66]
Chen et al. (2009)	1	15	3	15	7.4%	0.33 [0.04, 2.85]
Subtotal	*12*	*134*	*43*	*134*	*96.4%*	*0.28 [0.15, 0.51]*
IV HAS versus alternative plasma expander						
Fernandez et al. (2005)	0	10	1	10	3.6%	0.33 [0.02, 7.32]
Subtotal	*0*	*10*	*1*	*10*	*3.6%*	*0.33 [0.02, 7.32]*
TOTAL	**12**	**144**	**44**	**144**	**100.0%**	**0.28 [0.16, 0.50]**

Supplementary Table 8: Effect of use of HAS on mortality in SBP

Study	Albumin		Control		Weight	Risk Ratio [95% CI]
	Events (death)	Total	Events (death)	Total		
IV HAS versus no intervention						
Chen et al. (2009)	4	15	6	15	14.0%	0.67 [0.23, 1.89]
Lone (2015)	6	32	8	34	17.2%	0.80 [0.31, 2.04]
Sort P (1999)	14	63	26	63	50.9%	0.54 [0.31, 0.93]
XUE et al. (2002)	5	56	17	56	17.8%	0.29 [0.12, 0.74]
TOTAL	**29**	**166**	**57**	**168**	**100.0%**	**0.53 [0.36, 0.79]**

Supplementary Table 9: Effect of use of outpatient HAS infusions in patients with liver cirrhosis and ascites

Reference	Patients	Intervention (I)	Comparison (C)	Outcomes	Follow up
Gentilini and Laffi [1] Randomised, single centre, non-blinded. Italy	Cirrhosis & 1st onset clinical ascites. Mostly viral hepatitis. Excluded CKD, HF, HCC, Grade 2-4 HE, infection, GI bleeding	n=43 25g albumin/week for 1 year then 25g albumin fortnightly in years 2-3 PLUS diuretics	n=38 Diuretics only	<table><tr><td></td><td>I (n=43)</td><td>C (n=38)</td></tr><tr><td>Ascites recurrence</td><td>21</td><td>31</td></tr><tr><td>Episodes of ascites</td><td>26</td><td>36</td></tr><tr><td>SBP</td><td>1</td><td>3</td></tr><tr><td>Admitted to hospital</td><td>22</td><td>28</td></tr><tr><td>Admission episodes</td><td>32</td><td>40</td></tr><tr><td>Mortality</td><td>11</td><td>9</td></tr><tr><td>Liver transplant</td><td>3</td><td>1</td></tr></table>	I: 19.5 +/- 1.8 months C: 20.4 +/- 1.5 months Total range 6-36 months
Vizzutti, et al. [2] *Abstract only* Randomised, single centre, non-blinded, Italy	Cirrhosis and ascites Total 175 patients (?numbers in each group)	Albumin infusions, infusion protocol unclear PLUS diuretics	Diuretics alone	<table><tr><td></td><td>I (n=?)</td><td>C (n=?)</td></tr><tr><td>Admission</td><td>92%</td><td>62%</td></tr><tr><td>Ascites recurrence</td><td>94%</td><td>51%</td></tr><tr><td>Total episodes of ascites</td><td>113</td><td>65</td></tr></table>	I: 20.07 months C: 21.24 months
Romanelli and Giorgio La Villa [3] Randomised, single centre, non-blinded, Italy	Cirrhosis and 1st onset clinical ascites. Aged 35-70years Nearly all HCV Excluded active ETOH, renal failure, refractory ascites, HCC, HE, infection and GI bleeding at baseline	n=54 25g albumin/week for 1 year then 25g albumin fortnightly in years 2-3 PLUS diuretics	n=46 Diuretics only	<table><tr><td></td><td>I (n=54)</td><td>C (n=46)</td></tr><tr><td>Early loss of f/u</td><td>9</td><td>2</td></tr><tr><td>Cumulative survival</td><td>108 months</td><td>36 months</td></tr><tr><td>Survival (2yrs)</td><td>31</td><td>11</td></tr><tr><td>Liver transplant</td><td>1</td><td>3</td></tr><tr><td>Ascites recurrence</td><td>21 (31 episodes)</td><td>39 (54 episodes)</td></tr><tr><td></td><td></td><td></td></tr></table>	Median follow-up was 84 (2-120) months *(not reported between groups)*
Caraceni, et al. [4] Randomised, multi centre, non-blinded, Italy	Cirrhosis and uncomplicated ascites. All treated with >200mg/day antialdosterone and	n=213 40g albumin twice a week for 2 weeks then	n=218 standard medical care	<table><tr><td></td><td>I (n=213)</td><td>C (n=218)</td></tr><tr><td>Death (total)</td><td>38</td><td>46</td></tr><tr><td>Liver transplant</td><td>19</td><td>18</td></tr><tr><td>TIPS</td><td>6</td><td>8</td></tr><tr><td>>3 LVP/month</td><td>18</td><td>42</td></tr></table>	I: median 17.6 months C: median 11.5 months

<table>
<tr>
<td></td>
<td>>25mg/day furosemide.
Aetiology: around 1/3 viral, around 1/3 ETOH

Excluded: refractory ascites, TIPS, HCC, previous transplant, active ETOH, extrahepatic organ failure

Mean MELD 12-13</td>
<td>40g albumin weekly for up to 18 months</td>
<td></td>
<td>
<table>
<tr><td>Any LVP</td><td>71</td><td>116</td></tr>
<tr><td colspan="3">Evaluation according to time spent in study</td></tr>
<tr><td>Mortality (deaths per person per 18months)</td><td>0.27</td><td>0.44</td></tr>
<tr><td>Probability of survival</td><td>77%</td><td>66%</td></tr>
<tr><td>IRR (I vs C)</td><td colspan="2"></td></tr>
<tr><td>SBP</td><td colspan="2">0·33 (0·19–0·55)</td></tr>
<tr><td>non SBP inf</td><td colspan="2">0·70 (0·54–0·90)</td></tr>
<tr><td>HE (G3-4)</td><td colspan="2">0·48 (0·37–0·63)</td></tr>
<tr><td>renal dysfunct</td><td colspan="2">0·50 (0·39–0·64)</td></tr>
<tr><td>low Na</td><td colspan="2">0·51 (0·40–0·67)</td></tr>
</table>
Hospital admissions decreased by 35% in intervention arm.
Serum albumin higher in treatment arm.
</td>
<td>Loss of follow up similar in both arms</td>
</tr>
<tr>
<td>Sola, et al. [5]

Randomised, multi centre, blinded, Spain</td>
<td>Cirrhosis and ascites active on the liver transplant waiting list

Aetiology: 40% ETOH, 30% HCV. MELD 16-17

Excluded patients treated with DAAs</td>
<td>n=87

Midodrine 15-30mg/day (according to BP) PLUS 40g albumin every 15days</td>
<td>n=86

Dual placebo (encapsulated tablet plus infusion of saline in covered bag every 15 days)</td>
<td>
<table>
<tr><td></td><td>I (n=87)</td><td>C (n=86)</td></tr>
<tr><td>Any complication (renalfailure/hyponatraemia/ infection/HE/GI bleed)</td><td>32</td><td>37</td></tr>
<tr><td>Time to 1st complication</td><td>16 days</td><td>26 days</td></tr>
<tr><td>Death</td><td>6</td><td>4</td></tr>
<tr><td>Transplant</td><td>59</td><td>47</td></tr>
</table>
No difference in number of LVP. No effect of post transplant outcome. No difference in serum albumin.
</td>
<td>Median treatment length 80 days
I: median 63 days
C: median 103 days
10% of treatment arm and 23% of control arm completed 1 year study follow up</td>
</tr>
<tr>
<td>Di Pascoli, et al. [6]

Non randomised (patient choice to be part of intervention arm), single centre, non-blinded, Italy</td>
<td>Cirrhosis with refractory ascites undergoing regular LVP.

Aetiology: ≈ 50% viral.

Excluded: HCC beyond Milan criteria</td>
<td>n=45
Patients who accepted the intervention

20g albumin twice weekly plus diuretics and sodium restriction</td>
<td>n=25
Patients who did not accept the intervention

Standard of care</td>
<td>
<table>
<tr><td></td><td>I (n=45)</td><td>C (n=25)</td></tr>
<tr><td>Mortality (at 2 years)</td><td>15</td><td>15</td></tr>
<tr><td>Cumalative incidence of mortality</td><td>41.6%</td><td>65.5%</td></tr>
<tr><td>Liver transplant</td><td>5</td><td>2</td></tr>
<tr><td>No admission during follow up</td><td>100%</td><td>66%</td></tr>
<tr><td>SBP</td><td>1</td><td>1</td></tr>
</table>
Lower probability of hospitalization in treatment group
No difference in the number or volume of LVP
</td>
<td>I: 400 days

C: 318 days

Loss of follow up not reported</td>
</tr>
</table>

Supplementary Table 10: RCTs comparing TIPS with LVP in patients with refractory ascites and cirrhosis

		Patients enrolled (N)		Ascites improved, %		Survival, %		HE, %		Stent failure	Notes
	Exclusions	TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP		
Lebrec 1996	Age >70 HE Severe other. Disease Pulmonary hypertension HCC Sepsis SBP Severe alcoholic hepatitis PV/HV/HA obstruction Biliary obstruction Cr >150	13	12	38	0	29	60	23	0	TIPS was not successful in 3 patients. 3 patients (30%) who had TIPS developed shunt obstruction.	All beta-blockers were stopped. 32% Child C patients. Following TIPS, IV heparin given for 3 days and Ofloxacin 400mg/day for 3 days
				4 months		2-year (p=0.03)					
				23	8						
				1 year							
Rossle 2000	HE Bilirubin >86 μmol/L Creatinine >265 μmol/L PV thrombus Hepatic hydrothorax Advanced cancer Failure of LVP (ascites persisting after LVP or need more than 1 LVP/week)	29	31	61	18	69	52	58	48	13 (45%) patients had shunt insufficiency, 11 patients underwent shunt reestablishment.	30% Child C patients. Following TIPS, IV heparin for 1 week followed by LMWH for 4 weeks. 45% recidivant ascites
				3 months		1-year					
				79	24	58	32	Shunt flow reduced in 3 patients with debilitating HE.			
				6 months		2-year (p=0.11)					

Gines 2002	Age <18, >75 Bilirubin >171 μmol/L INR >2.5 Platelet <40,000/mm^3 Creatinine >265 μmol/L HCC PV thrombus Cardiac/respiratory failure Organic renal failure Bacterial infection Chronic HE	35	35	51	17	41	35	Moderate		TIPS unsuccessful in 1 patient. After shunt insertion, complete obstruction occurred in1 patient and could not be repermeablised.	40% Child C patients. TIPS was done to reduce portocaval pressure gradient (PPG) below 12 mmHg.
				Approx 10 months		1-year		51	40		
						26	30	Severe (p=0.03)			
						2-year (p=0.51)		60	34		
Sanyal 2003	Other causes of ascites than cirrhosis Incurable cancer Non-hepatic systemic disease with life expectancy <1 year	52	57	58	16	58	65	42	23	1 patient shunt thrombosis – treated with thrombolysis and anticoagulation.	

	Bilirubin >85 μmol/L INR >2 Congestive cardiac failure Acute renal failure Parenchymal renal disease PV thrombosis Active sepsis Active HE Florid alcoholic hepatitis HCC GI haemorrhage within 6 weeks of randomisation			1-year		2-year (p=0.8)				Shunt stenosis – 53% at 6 months and 70% at 12 months.	
Salerno 2004	Age >72 Recurrent HE Bilirubin >103 μmol/L Creatinine >265 μmol/L Child Pugh >11 PV thrombosis HCC Recent GI bleeding Serious cardiorespiratory dysfunction Ongoing bacterial infection SAAG <11g/L	33	33	79	43	77	52	61	39	Shunt insufficiency 23% at 1 year and 66% at 2 years. Complete TIPS obstruction in 2 patients.	76% Child C (but no CP>11) Included recidivant ascites (32%)
						1-year					
						59	29	One patient required reduction of stent size.			
						2-year (p=0.021)					
Narahara 2011	Age >70 Child Pugh >11 Bilirubin > 51 μmol/L	30	30	87	9	97	77	67	17	86% (26 patients) developed shunt dysfuntion.	Japanese study TIPS done to achieve portosystemic gradient of below 12mmHg

	Creatinine >168 μmol/L HCC PV thrombosis Chronic HE Active infection Cardiorespiratory disease Organic renal disease			3 months		3 months			More than 2 revisions required in 20 patients.	33% Childs C Patients with good hepatic and renal function.
				80	27	87	60			
				6 months		6 months				
				67	27	70	37	No shunt reversal carried out for HE		
				1-year		1-year				
				40	17	40	20			
				2-year		2-year (p<0.005)				
Covered stent										

Bureau 2017	Age >70 More than 6 LVPs in 3 months OLT expected in the next 6 months or on waiting list CCF Pulmonary hypertension PV thrombosis Recurrent HE HCC Bilirubin>100 μmol/L Child Pugh >12 Creatinine >250 μmol/L Sepsis	29	33	52	0	93	52	34	33	1 patient (3%) developed stent thrombosis	34% Child C
				1-year P<0.05		1-year P=0.003		1 patient had TIPS reduction for recurrent OHE			

Supplementary Table 11: Impact of beta-blockers on clinical outcomes in patients with ascites.

Impact of beta-blockers on survival in patients with ascites:							
Paper	Year	Journal	Country	Description	Nos	Outcomes	Comments
Borroni G	2002	J Hep	Italy	RCT nadolol vs ISMN for prevention of variceal haemorrhage in patients with ascites.	27 vs 27	Nadolol was associated with a reduced variceal bleeding rate, but similar survival to ISMN arm.	Mean 23 months FU. CPS 8. No difference at baseline. Refractory ascitics excluded. 6 nadolol and 4 ISMN patients stopped treatment due to adverse effects within median 4 weeks.
Serste T	2010	Hepatology	France	Prospective observational study of patients hospitalised with refractory ascites. Of the 77 patients on NSBB (100% propranolol), 50% 160mg per day.	151	NSBB patients had a lower probability of survival at 1 year on univariate analysis and after adjusting for CP class, HCC and "aetiology of refractory ascites".	Not matched at baseline – NSBB group were more likely to have OV and had a higher bilirubin; and had a trend towards a higher CP grade, lower Na and greater % of HCC. Lack of consecutive patients. 26 patients transplanted and 13 had HCC – no competing risk analysis No diff in HVPG NSBB vs no NSBB, in the subgroup of patients with measurements (n=50). Causes of death not clearly stated for the NSBB and non NSBB groups.

Galbois A	2011	Hepatology (letter)	France	68 patients with cirrhosis admitted to ITU with severe sepsis/septic shock.	68	Mortality rate in ICU similar for NSBB and non NSBB at 60%. 6 month mortality rate of survivors of ITU was higher in the NSBB group.	Patients on beta-blockers preadmission (not specified NSBB) had a trend towards a higher baseline serum Na, higher MAP and lower HR. (Not clear that they were discharged on NSBB!) Small nos not allowing adjusted analysis.
Mandorfer M	2014	Gastroe -nterology	Austria	Retrospective review of consecutive patients admitted for first LVP. 245 on NSBB – >70% propranolol (70% 60mg or less); most 6.25-12.5 carvedilol. FU largely to ~ 3 years.	607	No difference in variceal bleed rate during FU. NSBB - higher adjusted transplant free survival. But once a patient developed SBP – NSBB associated with a lower transplant free survival (n=182) – but higher bilirubin. NSBB patients were more likely to develop HRS during the 90 days after SBP diagnosis.	No competing risk analysis (censored at transplant – 10%). Higher baseline bilirubin level (and trend towards greater proportion of CPC) in the SBP patients on NSBB vs noNSBB. And during survival analysis adjusted for CPB/C (binary) and varices – but not bilirubin, which would have made sense. Not clear if patients were on NSBB at discharge.
Leithead	2015	Gut	Brum, UK	Retrospective, patients listed for liver transplantation. 117 RA.	322	Overall in all ascitics NSBB had similar mortality to NSBB. In PRS matched ascitics, NSBB were less likely to die on list and more likely to reach transplantation; and in RA, NSBB reduced associated with less wait list death.	Competing risk and PRS matched. Matched on PRS.

				119 prop, 40 carv			
Aday AW	2016	Am J Med Sciences	USA	Retrospective, hospitalised patients with cirrhosis. 43% on NSBB at admission. Primary outcome measure – all cause inhospital mortality	1500 with asci -tes	After adjusting for MELD, NSBB use had a massively reduced HR for inhospital mortality for all commers including non ascitic (ie upper limit of range <0.5, lower limit not visible on diagram). On univariate analysis of patients with any ascites, and then mild and severe ascites, NSBB associated with reduced inhospital mortality.	Only 12% inhospital mortality rate – lower than expected? Unusual way of presenting data. Multivariate analysis included MELD plus components of MELD separately (bilirubin, INR, creat)…. Baseline data not adequately provided. Similar results in subgroup analysis of all commers including only PRS matched. Data not provided.
Bang	2016	Liver Int	Danish	Retrospective study of patients with ascites. Ultimately 3719 patients with decompensated cirrhosis (ie had been treated with paracentesis) identified via the Danish National Patient Register.		For both mildly decompensated and severely decompensated patients, NSBB use was associated with reduced mortality during FU (in the whole cohort adjusted for PRS, and in PRS matched cohort only). In severely decompensated only, NSBB use was associated with a lower incidence of "peritonitis". Apparent dose dependent effect – if propranolol dose >160mg per day any benefit was lost (ie survival was comparable to no NSBB). But no matching for this	National register data with typical data limitations. PRS matched cohort. But even after matching not similar at baseline – NSBB group were more likely to be on diuretics and were less likely to have had a variceal bleed. Lots of subgroup analysis without baseline data and issues with timing of prescription of NSBB in relation to events.

				Mildly decompensated = 1st paracentesis. Severely decompensated = 4th paracentesis. Propranolol users (20%) – minimum of 2 issues of prescription for >1 month. Median dose 100mg per day. FU limited to 2 years.		cohort and no baseline data provided for the subgroups. No impact on incidence of HRS. Amongst the patients who developed peritonitis, those on NSBB had reduced long term mortality (median time from peritonitis to first prescription collection 50 days). Propranolol use prior to peritonitis had no impact on mortality thereafter.	Difficult to interpret.
Njei B	2016	Gut	USA	Letter – metaanalysis of 9 observational studies of patients with ascites that documented NSBB subtype		6 studies including propranolol (dose 40-320), 2 nadolol (60-120) and 2 carvedilol (6.25-12.5) Overall NSBB had no impact on mortality. Propranolol/nad no incease; but carvedilol increase	No individual patient data and simple stats.
Bossen L	2016	Hepatology	Danish	Post hoc analysis of 3 satavaptan RCTs. Diuretic controlled to refractory.	1198	All cause and cirrhosis-related mortality similar for NSBB and non NSBB based on at trial inclusion both for all ascites – and the subgroup of refractory ascitics. (patients who stopped the NSBB had high mortality thereafter and reason for stopping was deterioration)	Reasonably matched at baseline – but slightly less likely to have hyponatraemia or ascites.

				Info not provided on NSBB subtype.			
R Mookerjee	2016	J Hep	EASL-CLIF	Data from CANIONIC study – prospectively collected, 1349 cirrhotic patients. 47% on NSBBs – 68% of whom propranolol, median dose 40mg then mixture for the rest. 95% had ascites – but main defining factor – ACLF.	349 with ACLF	The "NSBB" patients (1/2 of whom had stopped the NSBB pre study inclusion i.e. had been on NSBB within 3 months of diagnosis of ACLF) were less likely to evolve to a more severe grade of ACLF, and had superior 28 day survival on univariate analysis. No multivariate analysis – but for similar CLIF-C ACLF scores, patients on NSBB had a lower probability of death. NSBB was found to be linked with reduced 28 day mortality after LR analysis adjusted for age, presence of previous decompensations and active alcohol consumptions (just). CLIF score, MELD etc not included. 28-day and 3-month mortality was significantly higher in patients who stopped NSBBs vs those that continued.	NSBB group older, were more likely to have had previous decompensations including bleeding, were less likely to have cerebral or coagulation organ failure (with a trend towards less renal failure), had a trend towards a lower MELD (but only just 29 vs 27), had a lower bilirubin, WCC and higher Na, and a lower ACLF grade. **78/164 NSBB patients had the drug stopped prior to inclusion in the study**, and 8 had the dose reduced. But the baseline data and analyses includes these patients (ie who were no longer on NSBB). Presumably patients stopped NSBBs because they were sicker… - the patients who stopped NSBBs were more likely to have circulatory or lung failure and had a higher CLIF-C ACLF score. Low dose propranolol.
Madsen BS	2016	J Hep (letter)	Denmark	Retrospective, first dose SBP and with 12 months FU.	81	Low dose NSBB (80mg) associated with improved survival on adjusted analysis after diagnosis of SBP; high dose NSBB no difference from patients on no NSBB.	Not disclosed how many had active ascites. Minimal stats provided, and median survival for the non NSBB group was only 20 days,

							and for the high dose NSBB group 8 days. Does not add to literature.
Chirapong -sathorn S	2016	Clin Gastroent -terol Hepatol	USA	Metaanalysis of 3 RCTs and 8 observational studies focusing on impact of NSBB on mortality in patients with refractory ascites.	3145 any, 443 RA	NSBBs not associated with increased all-cause mortality. Results were consistent between RCTs and observational studies. And no increase in either RA or non RA groups.	Significant heterogeneity. One of the RCTs had RA as an exclusion criteria.
Sinha R	2017	J Hep	RIE, UK	Retrospective, hospitalised patients with cirrhoisis and ascites. 132 on carvedilol, median dose 12.5mg. 24% severe ascites.	325, 264 PRS	Overall cohort – NSBB patietns had superior survival. In severe ascites NSBB and non NSBB patients had similar survival. Conclusion long term carvedilol not detrimental in decompensated patients with ascites.	Median FU > 2 years. PRS matching – matched at baseline. 50% ALD – no info on abstinence.
Onali S	2017	Liver Int	RFH, UK	Retrospective, cirrhosis with ascites undergoing liver transplant assessment. 92% propranolol (median dose 80mg), 8% carv (6.25mg).	316, 124 RA	In whole cohort – NSBB associated with reduced HR death (adj cox regression competing risk) (but not when analysis repeated in PRS matched patietns where no assocation), and in those with RA when only PRS matched patients included (but not when unmatched, all patietns with RA).	Competing risk analysis and PRS. 17 TIPSS patients included in the PRS cohort. After matching – not quite matched. Sig difference in varices and TIPSS, with a trend towards increased CP grade in nonNSBB patients.

				After PRS matching 106:106			
Bhutta AQ	2017	AP&T	USA	Subanalysis of NACSELD database – patients hospitalised with cirrhosis. 43% on NSBB, 51% refractory ascites.	716	NSBB did not impact on survival (Cox regression) in the whole cohort or the RA group. BB stopped 49% - sicker patients, infection, AKI. Stopping NSBB had no impact on short term survival. BB reinitiated in 40%.	Acutely unwell. Followed up to death or hospital discharge. 62/307 patients classified as being on a betablocker were actually on a selective BB! And still included in the analysis. Not matched at baseline in particular re comorbidity and HCC. BB patients with RA had a lower creat and MELD. Multicentre – different practice between units. Bottom line, low quality.
Albillos A	2017	Hepatology	Spain	Meta-analysis of 6RCTs of patients receiving secondary prophylaxis. 3 studies propranolol 50-120mg/day +/- ISMN; 5 studies nadolol.	800	416 patients VBL/BB vs VBL (as opposed to VBL/BB vs BB). 312 of these patients were CPB/C. Addition of BB to VBL in CPB/C patients resulted in reduced rebleeding and mortality.	One RCT excluded RA. FU 14-23 months.
Facciorusso A	2018	Dig Dis Sci	Multiple led by Italy	Metaanalysis of 16 studies, including 3 RCTs (vs VBL/TIPSS) – patients with	8279	No difference in survival overall, or inpatients with refractory ascites specifically. No difference in SBP or HRS rates.	Marked heterogeneity of studies. RCTs:

				cirrhosis and ascites. 3604 on NSBB, 1994-2015. Mixed NSBB. 6 studies with info on refractory ascites.			Escorsell 2002 – TIPSS vs propranolol for preventing variceal rebleeding (RA not reported); Lo 2004 – VBL vs nadolol for primary prophylaxis (RA excluded); Shah 2014 carvedilol vs VBL for primary prophylaxis (RA not reported); and then the Bossen pulled vaptan trials as above.
Wong RJ	2019	Liver Int	USA	Metaanalysis of 8 observational studies – NSBB vs not in patients with ascites. Primary outcome all cause mortality 1630 NSBB, 1997 not.	3627	No diff in survival for NSBB vs no NSBB groups, including in the subgroup of patients with refractory ascites ie no harm.	"However, significant heterogeneity between studies was observed and our overall GRADE assessment rating of the certainty of the evi- dence was 'very low'"
Tergast	2019	AP&T	Germ	Retrospective, patients hospitalised with ascites requiring paracentesis, 45% refractory Prop/carv – n=255	624	28 day liver transplant free survival greater in patients already on NSBB (including in in SBP and ACLF subgroups). The superior survival benefit was not seen in patients with a MAP<65 where no difference (including in SBP and ACLF subgroups. Notably not detrimental).	NSBB arm had a lower bil at baseline (and were more likely to have varices). Patients had been acutely admitted to hospital – low MAP will have been representative of acute illness. (30% had AKI)

				Median dose propranolol (n=147) 30mg/day; carvedilol (n=108) 12.5mg/d.		In patients with SBP and MAP<65, NSBB was associated with a rise in serum creat from baseline (not seen in no NSBB arm).	Competing risk Short term FU
Ngwa T	2020	BMC Gastro	USA	Retrospective; patients referred for liver transplant 65 on NSBB (prop/carv/nad) – median propranolol dose 20mg od. 25% no ascites, 23% refractory 157/245 nadolol, 65 prop, 23 carv.	170	NSBB arm – lower 90 day mortality. NSBB independently associated with better 90/7 survival on competing risk analysis	NSBB patients were more likely to develop AKI within 90 days but not matched and sicker at baseline. Why was 90 day outcome selected
Yoo JJ	2020	Medicine (Baltimore)	Korea	Retrospective; CPB/C with ascites. PRS analysis. Gd 1/2/3 varices – primary prophlaxis VBL/Propranolol (176) vs VBL alone (95) 80% gd 2 ascites, 20% gd 3 70% propranolol <80mg per day	271	The VBL/propranolol arm had increased mortality secondary to "hepatic failure" – despite similar rates of bleeding, HRS, SBP. Dose of NSBB not relevant.	Only removed 20 patients with PRS matching despite the 2 unmatched cohorts being sig different at baseline. And not 1:1 matched as stated in methods.
Impact of betablockers on variceal bleeding in patients with ascites:							

Paper	Year	Journal	Country	Description	Nos	Outcomes	Comments
Poynard T	1991	NEJM	France Italy	Meta-analysis of 4 RCTs of NSBB for primary prophylaxis. 2 propranolol; 2 nadolol. ~50% no ascites, ~30% mild ascites, and <20% severe ascites. (Undefined).	589	Patients with ascites who were randomised to the NSBB arm were less likely to have a variceal bleed during 2 years FU.	Individual patient data. 3 of the 4 RCTs excluded patients with intractable ascites; and 1 excluded CPS >13.
Bernard B	1997	Hepatology	France	Meta-analysis of 12 RCTs of NSBB for secondary prophylaxis	~800	Ascites not mentioned – but 20-90% CP B/C. Overall, NSBB reduced the rebleeding rate, mortality rate and bleeding related mortality.	Difficult to draw conclusions given ascites not mentioned.
Borroni G	2002	J Hep	Italy	RCT nadolol vs ISMN for prevention of variceal haemorrhage in patients with ascites	27 vs 27	Nadolol was associated with a reduced variceal bleeding rate, but similar survival to ISMN arm.	Mean 23 months FU. CPS 8. No difference at baseline. Refractory ascitics excluded. 6 nadolol and 4 ISMN patients stopped treatment due to adverse effects within median 4 weeks.
Albillos A	2017	Hepatology	Spain	Meta-analysis of 6RCTs of patients receiving secondary prophylaxis.	800	416 patients VBL/BB vs VBL (as opposed to VBL/BB vs BB). 312 of these patients were CPB/C.	One RCT excluded RA. FU 14-23 months.

				3 studies propranolol 50-120mg/day +/- ISMN; 5 studies nadolol.		Addition of BB to VBL in CPB/C patients resulted in reduced rebleeding and mortality.	
Yoo JJ	2020	Medicine (Baltimore)	Korea	Retrospective; CPB/C with ascites. PRS analysis. Gd 1/2/3 varices – primary prophylaxis VBL/Propranolol (176) vs VBL alone (95) 80% gd 2 ascites, 20% gd 3 70% propranolol <80mg per day	271	The VBL/propranolol arm had increased mortality secondary to "hepatic failure" – despite similar rates of bleeding, HRS, SBP. Dose of NSBB not relevant.	Only removed 20 patients with PRS matching despite the 2 unmatched cohorts being sig different at baseline. And not 1:1 matched as stated in methods.
Impact of beta-blockers on SBP in patients with ascites:							
Paper	Year	Journal	Country	Description	Nos	Outcomes	Comments
Soylu AR	2003	Am J Gastro (letter)	Turkey	Retrospective study of patients with ascites. 36 propranolol – mean dose 28mg/day.	73	Incidence of SBP no different between NSBB and no NSBB.	Small no (36 on NSBB), low dose and relatively short FU for mean 6 months. Relatively high rate of SBP Crude stats – univariate analysis of primary outcome measure only and no adjustment for FU (chi square!).

Villaneuva C	2004	J Hep	Spain	Prospective long term study of patients receiving nadololol and ISMN as secondary prophylaxis of variceal haemorrhage. Response defined as HVPG<12 or >20% reduction from baseline	132	The probability of developing ascites, HRS or SBP was less in the responders. The haemodynamic response was maintained to 12-18 months in 81%.	Crude stats – minimal adjustment for duration of FU/confounders. Response may reflect earlier in disease spectrum hence less development of complications.
Senzolo M	2009	Liver Int	UK, RFH	Metaanalysis of primary and secondary prophylaxis of variceal haemorrhage trials looking at impact of NSBB on SBP incidence. Included 3 RCTs and 2 retrospective where SBP as outcome reported. RCTs – 30-60% patients had ascites at entry. Retrospective studies 100% had ascites. 257 propranolol – 94 haemodynamic responders.	644 (374 in RCT)	NSBB reduced the incidence of SBP – including when only RCTs reviewed. Effect also seen in haemodynamic response vs not.	FU 23-76 months; 112 SBP episodes. Not all had ascites, and no subgroup analysis of ascites patients.

				Dose NSBB not given.			
Reiberger T	2013	J Hep	Austria/ Germ	Prospective study of impact of starting NSBB on intestinal permeability.	50	High portal pressure was associated with increased markers of intestinal permeability and bacterial translocation (LPS and IL-6); and NSBB resulted in reduced intestinal permeability and bacterial translocation (not limited to haemodynamic responders).	18% had ascites. Largely CPA but 70% HVPG >20.
Gimenez P	2018	Liver Int	Spain	Prospective, cirrhotics with acute ascites decompensation. Not randomised – 30 already on NSBB. 10/30 propranolol <60mg/day, 2 higher than 80mg/day.	63	No difference in bacterial DNA in blood NSBB vs noNSBB. Concluded "in patients with cirrhosis, chronic treatment with beta-blockers is associated with a higher unstimulated production of serum cytokines and an increased phagocytic activity in the presence of bacterial DNA."	Not matched at baseline. NSBB patients – younger, were more likely to have varices, had a trend towards a higher albumin. Note higher LPS in NSBB patients who did not have bacterial DNA detected – ie difficult to read too much into this study.
Yoo JJ	2020	Medicine (Baltimore)	Korea	Retrospective; CPB/C with ascites. PRS analysis. Gd 1/2/3 varices – primary prophylaxis VBL/Propranolol (176) vs VBL alone (95) 80% gd 2 ascites, 20% gd 3	271	The VBL/propranolol arm had increased mortality secondary to "hepatic failure" – despite similar rates of bleeding, HRS, SBP. Dose of NSBB not relevant.	Only removed 20 patients with PRS matching despite the 2 unmatched cohorts being sig different at baseline. And not 1:1 matched as stated in methods.

				70% propranolol <80mg per day			
Impact of betablockers on kidneys in patients with ascites:							
Villaneuva C	2004	J Hep	Spain	Prospective long term study of patients receiving nadololol and ISMN as secondary prophylaxis of variceal haemorrhage. Response defined as HVPG<12 or >20% reduction from baseline	132	The probability of developing ascites, HRS or SBP was less in the responders. The haemodynamic response was maintained to 12-18 months in 81%.	Crude stats – minimal adjustment for duration of FU/confounders. Response may reflect earlier in disease spectrum hence less development of complications.
Serste T	2011	J Hep	France	Prospective study of impact of NSBB withdrawal on development of PICD in patients with refractory ascites. Patients acted as their own controls. PICD defined as increase in PRA by >50% 1 week after LVP. NSBB = propranolol – 7/10 160mg per day.	10	Whilst on NSBB, paracentesis associated with no change in HR (increased in 9/10 but not sig), but immediate sig drop in systolic BP that returned to baseline by 1 week and 8/10 fulfilled criteria for PICD. Off NSBB, paracentesis resulted also in drop in SBP that returned to baseline but also sig increase in HR. Only 1/10 PICD. No long term data.	Delay between the 2 evaluations mean 3.4 months, but up to 5 – progressive liver disease could have influenced results (?? blunted PRA response on later disease - systolic BP did not seem to bounce back to baseline post paracentesis after NSBB withdrawal compared to when on NSBB; BP still dropped when off NSBB despite HR response). NB sig rise in prothrombin time. 4 patients did not undergo large volume paracentesis during the second study (ie off NSBB). PICD development did not seem to correlate with baseline PRA.

							And baseline PRA did not change with stopping NSBB. Small nos. No patient fulfilled criteria for type 2 HRS or had hypotension at time of paracentesis. No control group who did not change NSBB status but underwent 2 paracenteses.
Mandorfer M	2014	Gastroenterology	Austria	Retrospective review of consecutive patients admitted for first LVP. 245 on NSBB – >70% propranolol (70% 60mg or less); most 6.25-12.5 carvedilol. FU largely to ~ 3 years.	607	No difference in variceal bleed rate during FU. NSBB - higher adjusted transplant free survival. But once a patient developed SBP – NSBB associated with a lower transplant free survival (n=182) – but higher bilirubin. NSBB patients were more likely to develop HRS during the 90 days after SBP diagnosis.	No competing risk analysis (censored at transplant – 10%). Higher baseline bilirubin level (and trend towards greater proportion of CPC) in the SBP patients on NSBB vs noNSBB. And during survival analysis adjusted for CPB/C (binary) and varices – but not bilirubin, which would have made sense. Not clear if patients were on NSBB at discharge.
Serste T	2015	Liver Int	France	Retrospective study of patients with AAH. 60% ascites (no mention of severity). 48/139 NSBB (propranolol, 80%	139	NSBB patients had increased probability of the development of AKI during the subsequent ~30 days (including after adjusted for MELD), but no sig increase in mortality.	NSBB arm had a trend towards a higher baseline serum creatinine, and were more likely to have varices and a previous variceal haemorrhage/severe AAH (potential significant of pre-existing more severe portal hypertension). AKI was 50% increase from baseline in preceding 6 months….

				80mg or less per 24hrs).			
Kim SG	2017	Liver transplant	USA	Retrospective – nested case control, on liver transplant waiting list. 205:205 (NSBB 170). 268 ascites, not documented how many refractory. Propranolol/nadolol 81 (median 40mg)/89.	2361	Patients with ascites on a NSBB were more likely to develop AKI during FU than patients with ascites not on a NSBB or patients without ascites. (NSBB with no ascites were less likely to develop AKI on MV analysis??) Lots of problems with this study….	Long study period back to 1990 Primary outcome – development of AKI during median FU of 18 months. Not clear how many were transplanted – and no competing risk analysis NSBB at baseline ie not known if continued during FU. No info given on NSBB vs non NSBB ie differences??
Tergast	2020	AP&T	Germ	Retrospective, patients hospitalised with ascites requiring paracentesis, 45% refractory Prop/carv – n=255 Median dose propranolol (n=147) 30mg/day; carvedilol (n=108) 12.5mg/d.	624	In patients with SBP and MAP<65, NSBB was associated with a rise in serum creat from baseline (not seen in no NSBB arm).	NSBB arm had a lower bil at baseline (and were more likely to have varices). Patients had been acutely admitted to hospital – low MAP will have been representative of acute illness. (30% had AKI) Competing risk Short term FU

Impact of betablockers on reducing development ascites							
Villaneuva C	2004	J Hep	Spain	Prospective long term study of patients receiving nadololol and ISMN as secondary prophylaxis of variceal haemorrhage. Response defined as HVPG<12 or >20% reduction from baseline	132	The probability of developing ascites, HRS or SBP was less in the responders. The haemodynamic response was maintained to 12-18 months in 81%.	Crude stats – minimal adjustment for duration of FU/confounders. Response may reflect earlier in disease spectrum hence less development of complications.
Villaneuva C	2009	Gastroe- terology	Spain	Prospective observational study of response to acute iv propranolol and impact on longer term outcomes	105	Acute haemodynamic response to propranolol (HVPG <12 or >=10% reduction from baseline) associated with reduced variceal bleeding rate during FU and reduced onset of ascites	50% ascites at baseline. 75/105 responders.
Hernandez-Gea	2012	Am J Gastro		Prospective compensated cirrhotics with varices and HVPG>12. Nadolol – 50% haemodynamic responders.	83	Haemodynamic responders had a lower probability of ascites, refractory ascites and HRS during FU.	Trend towards higher CPS and MELD score in non responders. ? non response a surrogate marker of more advanced liver disease.
Villanueva	2019	Lancet	Spain	RCT of NSBB vs not in compensated cirrhosis with HVPG >=10..	201	NSBB associated with reduced primary outcome measure – due to a reduced rate of ascites development.	Short term FU

				101:100. Depending on HVPG response – propranolol or carvedilol. Primary outcome measure – decompensation (development of ascites, bleeding, enceph) or death.			
Turco L	2020	Clin Gastro Hepat	Spain	Metaanalysis of studies of primary/secondary prophylaxis of varices. 5x RCTs and 10 observational.	452	Amongst the 452 patients with ascites, haemodynamic responders had a lower rate of clinical events (variceal haemorrhage, refractory ascites, SBP, HRS or encephalopathy) than non responders	Rate of HVPG responders lower in ascites than non ascites patients ie same concern that non response may reflect more advanced disease.

Supplementary Table 12: Reported survival rates and reversal of hepatorenal syndrome (HRS) in randomised controlled studies involving terlipressin among patients with HRS in cirrhosis. (Reproduced with permission from Palaniyappan, N. and Aithal, G.P. (2020), Editorial: treating hepatorenal syndrome—a window and the views. Aliment Pharmacol Ther, 52: 895-896. doi:10.1111/apt.15943)

		Survival			Reversal of HRS	
		Terlipressin	**Comparator**		**Terlipressin**	**Comparator**
Terlipressin vs placebo	Solanki 2003 (n=24)	42%	0%	*15-day survival*	42%	0%
	Sanyal 2008 (n=112)	43%	38%	*6-month survival*	34%	13%
	Neri 2008 (n=52)	54%	19%	*6-month survival*	81%	19%
	Martín-Llahí 2008 (n=46)	26%	17%	*3-month survival*	35%	11%
	Zafar 2012 (n=50)	24%	20%	*3-month survival*	40%	8%
	Boyer 2016 (n=196)	57%	55%	*3-month survival*	20%	13%
	Wong 2019 (n=300)	27%	29%	*3-month survival*	29%	16%
Terlipressin vs Noradrenaline	Alessandria 2007 (n=22)	67%	70%	*3-month survival*	83%	70%
	Sharma 2008 (n=49)	55%	55%	*30-day survival*	50%	50%
	Singh 2012 (n=46)	30%	35%	*30-day survival*	39%	43%
	Indrabi 2013 (n=60)	7%	3%	*3-month survival*	57%	53%

	Badawy 2013 (n=51)	54%	48%	*30-day survival*	46%	40%
	Ghosh 2013 (n=46)	61%	65%	*3-month survival*	74%	74%
	Goyal 2016 (n=41)	45%	48%	*2-week survival*	50%	48%
	Arora 2020 (n=120)	48%	20%	*28-day survival*	40%	17%
Terlipressin vs Octreotide & Midodrine	Cavallin 2015 (n=49)	59%	43%	*3-month survival*	56%	5%
Terlipressin vs Dopamine & Furosemine	Srivastava 2015 (n=80)	23%	20%	*30-day survival*	*Not reported*	*Not reported*
		Terlipressin Bolus	**Terlipressin Infusion**		**Terlipressin Bolus**	**Terlipressin Infusion**
Terlipressin bolus vs Terlipressin infusion	Cavallin 2016 (n=71)	69%	53%	*3-month survival*	65%	76%