TREATMENT WITH HMG-CoA REDUCTASE INHIBITORS (STATINS) IS ASSOCIATED WITH PRESERVATION OF HEPATIC FUNCTION IN ADVANCED CHRONIC LIVER DISEASE (CLD): RESULTS FROM THE SHUNT-V STUDY

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SHUNT-V Subjects, Investigators,
and Coordinators

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Disclosures

Robert Rahimi, MD

I have no financial relationship with a commercial interest

Steve M. Helmke, PhD: employee (CSO) HepQuant LLC; equity member HepQuant LLC; Intellectual property in HepQuant technology

Gregory T. Everson, MD: employee (CEO) HepQuant LLC; equity member HepQuant LLC; Intellectual property in HepQuant technology

The SHUNT-V Study was sponsored by HepQuant LLC

Aim

The primary aim of this analysis, was to identify factors in patients with advanced chronic liver disease that are associated with severity of:

- Impairment of liver function
- Portal-systemic shunting

Specifically, we used the dual cholate test (HepQuant) to quantify liver function (Disease Severity Index, DSI) and shunting (SHUNT%) and define the impact of:

- Disease Etiology – NASH versus Other
- Coexistent disease – Diabetes versus No Diabetes
- Drug treatment – Diabetic and Lipid-lowering drugs

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Background

- Etiology, coexistent disease, and concomitant drug therapy can influence the progression of chronic liver disease (CLD).
- With disease progression portal hypertension and portal-systemic shunting increase and liver function declines – leading to clinical complications, such as varices.
- The noninvasive DUAL CHOLATE test quantifies portal-systemic shunting (SHUNT%) and generates a Disease Severity Index (DSI) of global liver function.
- In the SHUNT-V Study, shunting (SHUNT%) and liver function (DSI) were characterized in subjects with suspected, compensated, or clinically-stable cirrhosis.
- SHUNT-V and other studies found that SHUNT% and DSI predicted likelihood for portal hypertension*, esophageal varices**, and risk for clinical outcome***.

*(*Clin Gastroenterol Hepatol 2021, doi: 10.1016/j.cgh.2021.04.030; **SHUNT-V and HALT-C data, Abstract #2126, AASLD 2021; ***Aliment Pharmacol Ther 2021; 53:928–938)*

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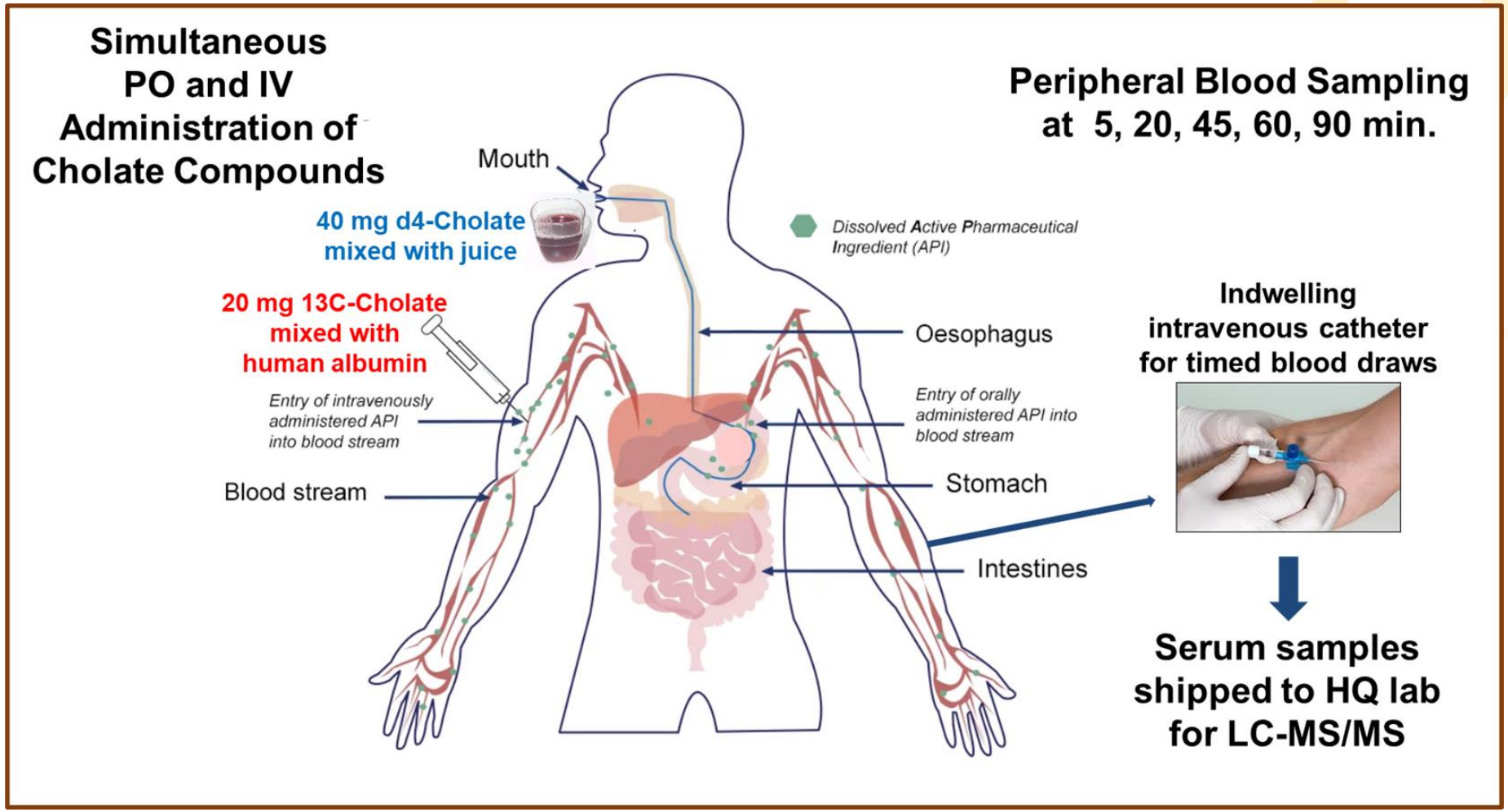
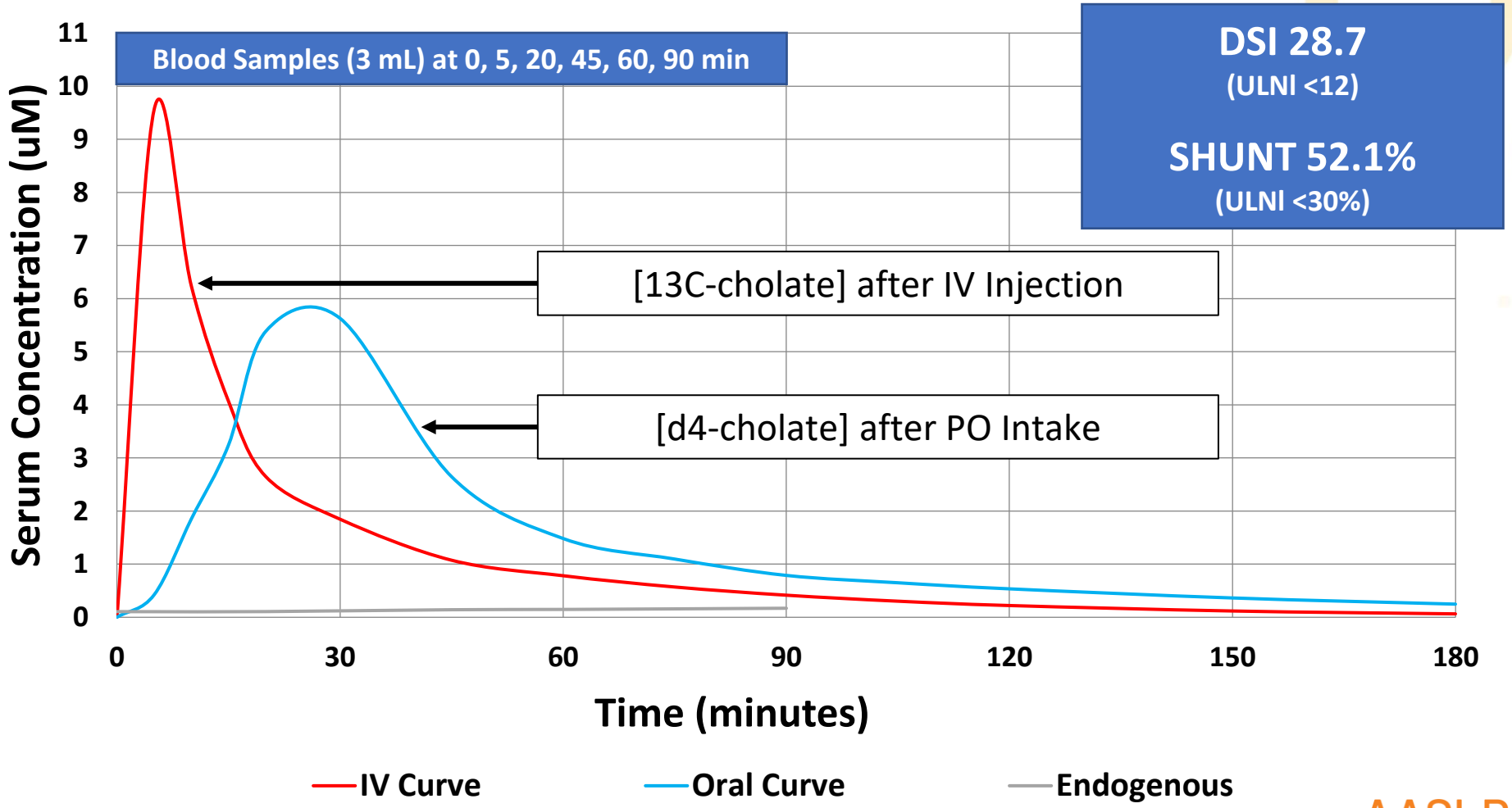
The SHUNT-V Study Enrollment Criteria

- 27 US clinical centers from Feb 2019 through Dec 2020
- Adults undergoing screening or surveillance EGD for varices
- Included suspected or definite cirrhosis as determined by:
  - Prior liver biopsy
  - Radiologic (including elastography) or clinical criteria
  - Chronically abnormal liver tests with low platelet count
- Exclusions included:
  - Child-Pugh C cirrhosis
  - Refractory ascites or encephalopathy
  - Prior variceal hemorrhage, known large varices, or treatment of varices

Dual Cholate Test Administration



Example of Dual Cholate Clearances in a Subject with Liver Disease



Results: NASH versus NON-NASH Subjects

Demographics by NASH Diagnosis

		Wt (kg)	Ht (cm)	BMI (kg m^{-2})	Obese (BMI >30)	Diabetes Mellitus	Age (yr)	Men	Hispanic	White	Black
NASH	N	123	123	123	96	82	123	51	13	122	1
	Mean (or %)	**98.5**	**167.1**	**35.1**	**78.0%**	**66.7%**	**62.9**	**41.5%**	**10.6%**	**99.2%**	**0.8%**
	SD	20.8	9.6	6.3			10.0				
Non-NASH	N	147	147	147	79	33	147	83	25	131	13
	Mean (or %)	**93.1**	**170.2**	**32.0**	**53.7%**	**22.4%**	**60.3**	**56.5%**	**17.0%**	**89.1%**	**8.8%**
	SD	25.2	10.6	7.6			10.7				
	p	0.06	**0.0130**	**0.0003**	**<0.0001**	**<0.0001**	**0.0466**	**0.0150**	0.16	**0.0006**	**0.0040**

NASH subjects were older, more likely to be obese, and 66.7% had diabetes – characteristics that would typically favor disease progression – and worse liver function.

Clinical Scores and Lab Tests by NASH Diagnosis

		CTP Score	MELD Score	MELD Na Score	Creatinine (mg/dL)	Bilirubin (mg/dL)	INR	Sodium (meq/L)
NASH	N	118	116	113	117	118	116	114
	Mean	**5.33**	**8.51**	**8.55**	**0.91**	**0.82**	**1.15**	**140**
	SD	0.73	3.02	4.08	0.27	0.60	0.30	3
Non-NASH	N	137	134	129	134	135	135	130
	Mean	**5.49**	**8.60**	**8.77**	**0.87**	**1.02**	**1.22**	**140**
	SD	0.95	2.91	3.85	0.32	0.95	0.91	3
t-test	p	0.14	0.81	0.67	0.27	0.06	0.43	0.59

NASH and NON-NASH subjects had similar clinical scores and standard laboratory tests.

Results of the Dual Cholate Test by NASH Diagnosis

		Systemic HFR	Portal HFR	SHUNT	DSI
		mL min^{-1} kg^{-1}	mL min^{-1} kg^{-1}	%	Score
NASH	N	123	123	123.00	123
	Mean	**3.29**	**10.90**	**39.0%**	**23.4**
	SD	0.98	6.49	18.2%	7.5
Non-NASH	N	147	147	147	147
	Mean	**3.16**	**9.38**	**44.1%**	**25.5**
	SD	1.10	6.76	18.8%	8.5
t-test	p	0.31	0.06	**0.0256**	**0.0375**

UNEXPECTED FINDING: Thus, it was surprising that NASH subjects had better liver function (lower DSI) and less portal-systemic shunting (lower SHUNT%).

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Results: Diabetic versus NON-Diabetic Subjects

Demographics by Diabetes Diagnosis

		Wt (kg)	Ht (cm)	BMI (kg m^{-2})	Obese (BMI >30)	NASH	Age (yr)	Men	Hispanic	White	Black
Diabetic	N	115	115	115	82	82	115	54	17	109	5
	Mean (or %)	**98.3**	**168.3**	**34.6**	**71.3%**	**71.3%**	**63.9**	**47.0%**	**14.8%**	**94.8%**	**4.3%**
	SD	20.6	9.1	6.3			8.1				
Non-Diabetic	N	155	155	155	93	41	155	80	21	144	9
	Mean (or %)	**93.5**	**169.2**	**32.5**	**60.0%**	**26.5%**	**59.7**	**51.6%**	**13.5%**	**92.9%**	**5.8%**
	SD	25.1	11.1	7.7			11.6				
	p	0.09	0.44	**0.0187**	0.07	**<0.0001**	**0.0012**	0.46	0.86	0.62	0.78

Diabetic subjects had higher BMI and were older; 71.3% had NASH.

Clinical Scores and Lab Tests by Diabetes Diagnosis

		CTP Score	MELD Score	MELD Na Score	Creatinine (mg/dL)	Bilirubin (mg/dL)	INR	Sodium (meq/L)
Diabetic	N	113	111	107	111	112	111	108
	Mean	**5.27**	**8.25**	**8.60**	**0.91**	**0.79**	**1.14**	**140**
	SD	0.65	3.04	3.97	0.27	0.68	0.35	3
Non-Diabetic	N	142	139	135	140	141	140	136
	Mean	**5.54**	**8.80**	**8.73**	**0.87**	**1.03**	**1.23**	**140**
	SD	0.97	2.88	3.96	0.32	0.89	0.88	3
t-test	p	**0.0121**	0.15	0.80	0.30	**0.0196**	0.30	0.17

Preserved function in diabetic subjects is suggested by the slightly lower CP score and mean bilirubin.

Results of the Dual Cholate Test by Diabetes Diagnosis

		Systemic HFR mL min-1 kg-1	Portal HFR mL min-1 kg-1	SHUNT %	DSI Score
DM	N	115	115	115	115
	Mean	**3.38**	**11.74**	**37.5%**	**22.63**
	SD	0.99	7.44	18.1%	7.46
No-DM	N	155	155	155	155
	Mean	**3.10**	**8.83**	**44.9%**	**26.0**
	SD	1.08	5.75	18.5%	8.3
	p	**0.0325**	**0.0004**	**0.0013**	**0.0008**

UNEXPECTED FINDING: Since diabetes is a risk factor for progression of liver disease, it was surprising that liver function was better (lower DSI) and Portal-Systemic Shunting Less (lower SHUNT%) in DIABETIC Subjects.

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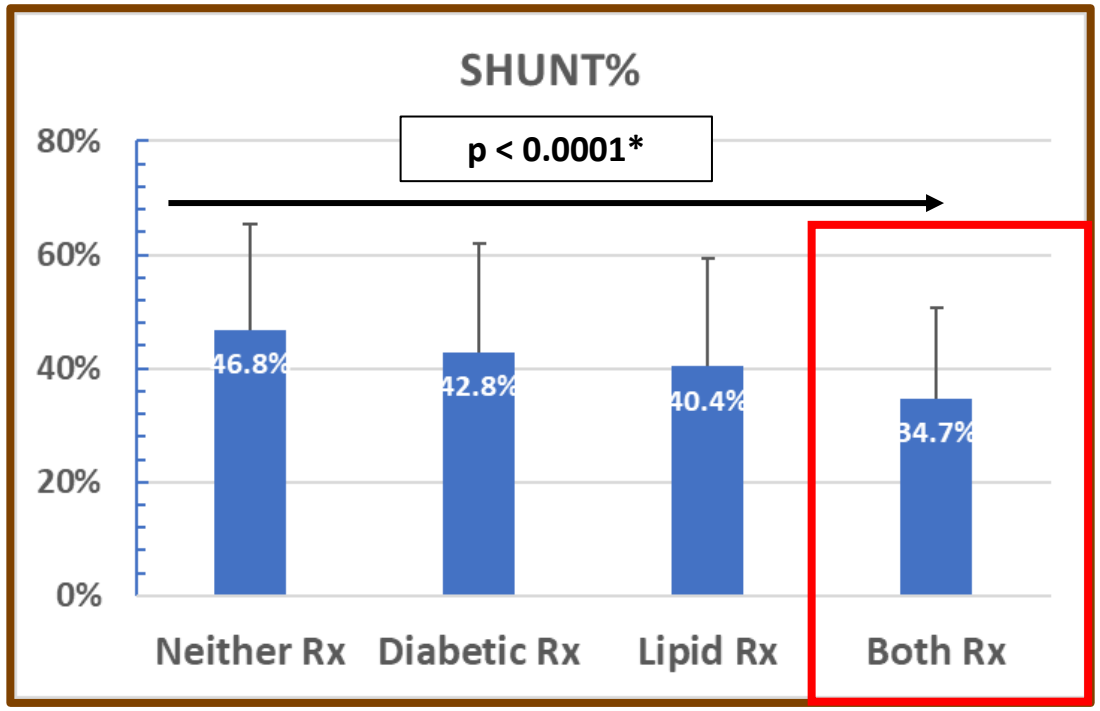
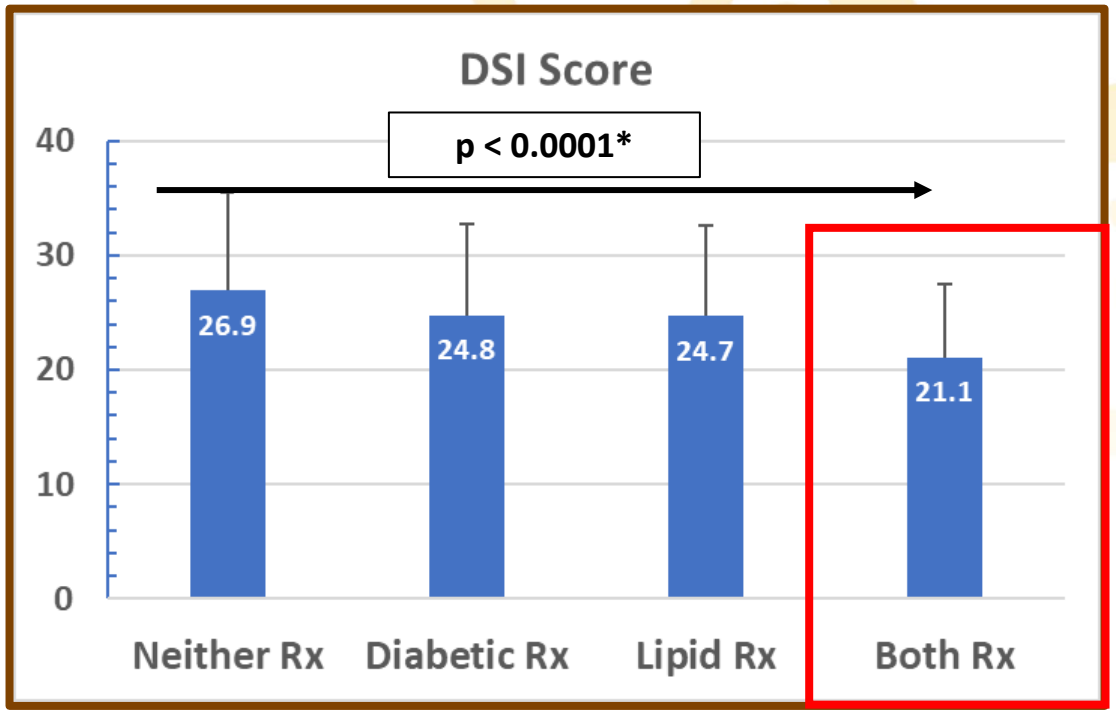
Results: Drug Treatment

Effect of Diabetic and Lipid-lowering Drugs





Diabetic and Lipid-lowering drug use is associated with less portal-systemic shunting (lower SHUNT%) and better liver function (lower DSI). *p value for change from treatment with neither to both classes of drug.

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In Multivariable Analysis the Use of STATINs or METFORMIN were Independently Associated with Lower SHUNT% and Lower DSI

	Impact on SHUNT%		Impact on DSI	
	Decline in SHUNT%	p	Decline in DSI	p
Statin	**-6.3%**	**0.0132**	**-3.3269**	**0.0025**
Metformin	**-5.9%**	**0.0475**	**-2.4337**	**0.0574**
Diabetes Diagnosis	-1.4%	0.64	-0.7239	0.5736
NASH Diagnosis	-1.3%	0.61	-0.2246	0.8343

The combined effect of the use of STATINs plus METFORMIN was 20% less portal-systemic shunting (lower SHUNT%) and 20% better function (lower DSI).

Summary

- This study highlights the potential utility of the sensitive and reliable dual cholate test of liver function for detecting treatment effects.

- STATINS and Metformin were independently associated with preserved hepatic function and reduced portal-systemic shunting.

- Improved liver function and reduced portal-systemic shunting should reduce risk for clinical outcome.

  ➢Follow-up of the SHUNT-V cohort is planned.

Key Takeaways

- STATIN and Metformin use may slow the progression of chronic liver disease.
- These results provide support for a clinical trial of STATIN and Metformin in the treatment of chronic liver disease.
- The dual cholate test may detect the effects of treatments on liver function and physiology, and potentially provide new endpoints for clinical trials.

SHUNT-V Investigators and Clinical Centers

Institution	Investigator Name	Investigator Title
Accel Research Sites	John M Hill, MD	Chair, Integrated Site Network
Arizona Liver Health	Anita Kohli, MD	Director of Research and Managing Partner
Baylor Scott and White	Robert Rahimi, MD	Transplant Hepatologist and Gastroenterologist
Bon Secours Liver Institute of Richmond	Mitchell Shiffman, MD	Director, Liver Institute of Virginia, Bon Secours Virginia Health System
California Liver Research Institute	Edward Mena, MD	Medical Director & CEO
Clinical Trials of Texas, Inc.	Douglas Denham, DO	Medical Director
Digestive Disease Associates	Natarajan Ravendhran, MD	Medical Director, Clinical Research Department
Gastroenterology Associates of Pensacola, PA	Frederic Newman, MD	Gastroenterologist
Gastroenterology Consultants of Southwest Virginia	Vishal Bhagat, MD	Director of Clinical Research
Gastroenterology Health Partners, PLLC	James Strobel, MD	Gastroenterologist
Inland Empire Liver Foundation	Zeid Kayali, MD	Medical Director
Intermountain Medical Center	Richard Gilroy, MD	Medical Director of Hepatology and Liver Transplantation
Lucas Research	Kathryn Lucas, MD	Endocrinologist & President
Mayo Clinic Florida	Andrew Keaveny, MD	Medical Director, Clinical and Transplant Hepatology
Mayo Clinic Rochester	Michael Leise, MD	Associate Professor of Medicine
McGuire VA	Michael Fuchs, MD	Professor of Medicine
Methodist Dallas Medical Center	Parvez Mantry, MD	Medical Director, Liver Institute Research
Nature Coast Clinical Research	Paul Hellstern, MD	Clinical Research Investigator Gastroenterology
Peak Gastroenterology Associates	Bhaktasharan Patel, MD	President & Founder
PMG Research	Brian Smith, MD	Clinical Investigator
Ralph H Johnson VAMC	Wing-Kin Syn, MBChB	Professor of Medicine & Associate Research Program Director
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St. Louis University	Kamran Qureshi, MD	Associate Professor
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Thank you!

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