Accuracy of FibroScan®Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Non-alcoholic Fatty Liver Disease

Eddowes PJ, *et al.*, Gastroenterology 2019;156(6):1717-1730

Objectives	• To evaluate the diagnostic accuracy of CAP™ & LSM by VCTE™ in assessing steatosis & fibrosis in patients with suspected NAFLD
Method	• **Adults who underwent liver biopsy analysis for suspected NAFLD at 7 centers in the United Kingdom** - Liver biopsy was conducted within 2 weeks of FibroScan®examination - FibroScan®examination performed with either M or XL probe according to embedded automatic probe selection tool
Patients analyzed	• 450 patients with suspicion of NAFLD
Results	**Applicability of FibroScan®(VCTE™)** • Applicability rate 97% (404 examinations with 10 valid measurements out of 415 performed) • M probe 136 (34%) and XL probe 268 (66%) **Performance of CAP™ to grade steatosis** • AUROC of 0.87 for >=S1; Youden cutoff value was 302 dB/m • AUROC of 0.77 for >=S2; Youden cutoff value was 331 dB/m • AUROC of 0.70 for S3; Youden cutoff value was 337 dB/m • CAP™ performance was not better in patients with an IQR of CAP™<30 or <40 dB/m **Performance of LSM by VCTE™ to stage fibrosis** • AUROC of 0.77 for >=F2; Youden cutoff value was 8.2 kPa • AUROC of 0.80 for >=F3; Youden cutoff value was 9.7 kPa • AUROC of 0.89 for F4; Youden cutoff value was 13.6 kPa • On multivariate analysis, the only parameter that significantly affect LSMs was fibrosis stage, no association with steatosis or probe type **(cf Fig. 1 and 2)**

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • CAP™: Controlled Attenuation Parameter • NAFLD: Non-alcoholic Fatty Liver Disease • AUROC: Area Under Receiving Operator Characteristics Curve • BMI: Body Mass Index

Key points

- CAP™ and LSM by VCTE™ are accurate non-invasive methods for assessing liver steatosis and fibrosis in patients with NAFLD, respectively.
- High applicability rate of VCTE™ (97%) in a large UK NAFLD cohort with BMI up to 53.2 kg/m^2
- Amount of hepatic steatosis did not influence liver stiffness
- Probe type (M, XL) did not influence liver stiffness, indicating that the same diagnostic thresholds can be used for M & XL probes
- Previously proposed CAP™ reliability criteria based on CAP™ IQR are not validated in this cohort

FIGURE 1 **Box plot of probe type as function of liver stiffness (kPa). Patients were scanned either with M or XL probe based on the automatic probe selection tool**

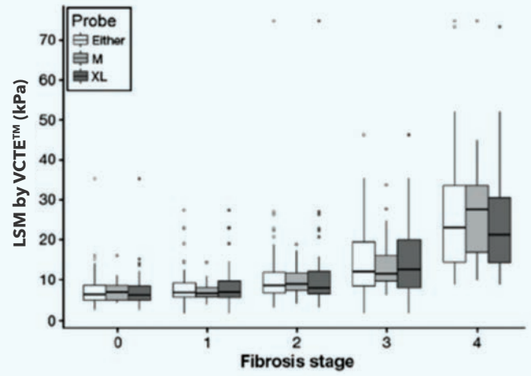
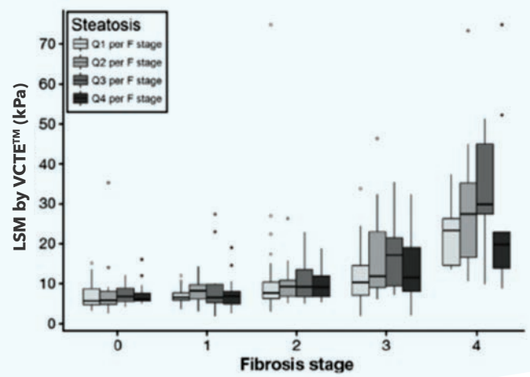


FIGURE 2 **Box plot of liver stiffness (kPa) vs fibrosis stage, stratified by steatosis amount. For each fibrosis stage, patients are stratified by steatosis quartile in the fibrosis stage**



LSM by VCTE™
CAP™
Fast™

FibroScan®-AST (FAST™) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study

Newsome PN, *et al.*, The Lancet Gastroenterology and Hepatology 2020;5(4):362-373

Objectives	• To develop and validate a score to identify patients with NASH, elevated NAFLD activity score (NAS>=4), and advanced fibrosis (stage 2 or higher [F>=2])
Method	• **A derivation cohort before validation in multiple international cohorts at 7 study sites** • **Subjects scheduled to have a liver biopsy for suspicion of NAFLD**
Patients analyzed	• 350 patients with suspected NAFLD (derivation cohort) • 1026 patients (validation cohort)
Results	**Derivation cohort** • AST was determined to be the best parameter (among AST, ALT, and AST/ALT ratio) to be combined in a score with LSM by VCTE™ & CAP™ to predict active fibrotic NASH -> FAST™ score • Diagnostic performance of FAST™ Score indicated an AUROC of 0.80 in the derivation cohort to detect presence of active fibrotic NASH • Cut-offs for sensitivity and specificity of >=0.90 were 0.35 and 0.67, respectively in the derivation cohort, allowing to rule out or rule in active fibrotic NASH in 61% of patients. 39% of the patients fall between the two cut-offs (indeterminate results) and would need further investigation or testing **(cf Fig. 1 & 2)** **Validation cohort** • Performances (AUROCs) of FAST™ in the external validation cohorts ranged from 0.74 to 0.95 with 0.85 in the pooled external validation cohort • When applying the derived cut-offs in the pooled validation cohort, active fibrotic NASH was ruled out or ruled-in in 70% of patients, and 30% of patients have indeterminate results **(cf Fig. 2)** **Proposed Application of Patient Eligibility for NASH Drug Clinical Trials** • In the context of patient screening in drug trials for NASH, the screen failure rate would decrease from 174 (50%) of 350 patients with increasing FAST™ score cutoffs **(cf Fig. 3)** • At given FAST™ score cutoffs, it is possible to graphically access the screen failure rate & missed cases rate together with the proportion of patients above the FAST™ score who would be given liver biopsy **(cf Fig. 3)**

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • CAP™: Controlled Attenuation Parameter • FAST™: FibroScan-AST • NASH: Non-alcoholic Steatohepatitis • NAFLD: Non-alcoholic Fatty Liver Disease • AST: Aspartate Aminotransferase • ALT: Alanine Aminotransferase • NAS: NAFLD Activity Score • AUROC: Area Under Receiving Operator Characteristics Curve • Se: Sensitivity • Sp: Specificity

Key points

- A new simple non-proprietary FibroScan®based FAST™ score (combining LSM by VCTE™, CAP™ and AST) allows identification of patients with active fibrotic NASH (NASH, NAS>=4, F>=2), and has been validated in multiple large global cohorts
- FAST™ score will allow for the ready identification of at-risk patients with active fibrotic NASH that merit consideration for further treatment
- FAST™ score will be an important adjunct in identifying patients for clinical trials or commencement of pharmacotherapies
- FAST™ sore is freely available on the myFibroScan App

FIGURE 1 **FAST™ score cut-offs for identification of active fibrotic NASH with associated Sensitivity (Se) and Specificity (Sp)**

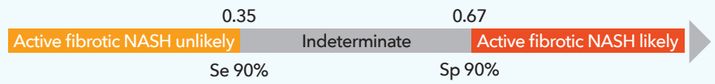


FIGURE 2 **Percentage of patients ruled-in and ruled-out in derivation & validation cohorts**

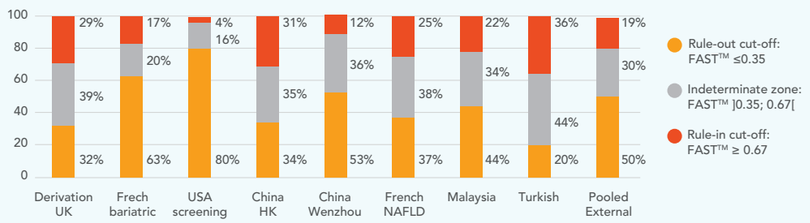
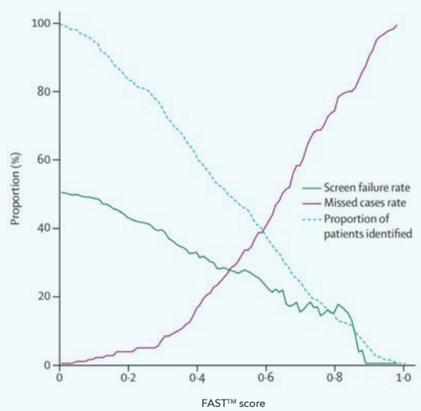


FIGURE 3 **Screen failure rate, missed cases rate, & proportion of patients identified, versus FAST™ score values**

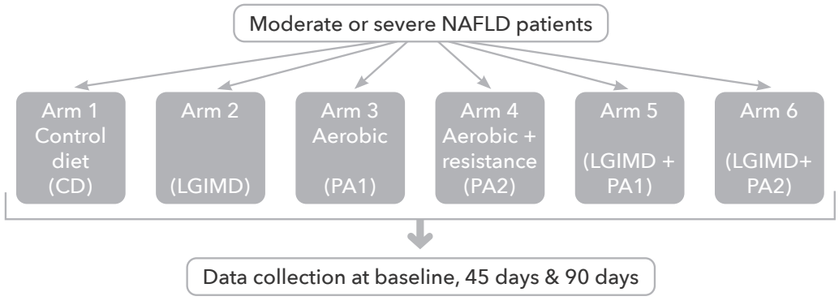


Screen failure rate – proportion of screened participants having liver biopsy that would not meet the histological target

Missed cases rate – proportion of patients identified as false negatives for the histological target

Physical Activity and Low Glycemic Index Mediterranean Diet: Main and Modification Effects on NAFLD Score. Results from a Randomized Clinical Trial

Franco I, *et al.,* Nutrients 2020;13(1):66

Objectives	• To estimate the effect of the following life-style interventions on liver fat assessed by CAP™ - two different physical activity (PA) programs – PA1 and PA2 - one Low Glycemic Index Mediterranean Diet – LGIMD - combination of PA & LGIMD – LGIMD plus PA1 and LGIMD plus PA2
Method	
Patients analyzed	• 144 moderate or severe NAFLD patients
Results	• There was a statistically significant reduction in CAP™ value after 45 days of treatment in every working arms except for Arm1 (control diet) • After 90 days, the best results were shown by the intervention arms in which LGIMD was associated with PA: LGIMD plus PA1 (-61.56 dB/m) and LGIMD plus PA2 (-38.15 dB/m) • The changes in CAP™ value by intervention arms, time (at 90 days) & NAFLD severity was shown in Table 1 • The relative decrease of CAP™ values was more relevant among severe NAFLD subjects • The most intense effect in decreasing CAP™ values was observed among severe NAFLD subjects who underwent LGIMD plus PA1 (Arm 5)

CAP™: Controlled Attenuation Parameter • NAFLD: Non-alcoholic Fatty Liver Disease • PA: Physical Activity • LGIMD: Low Glycemic Index Mediterranean Diet

Key points

- The use of FibroScan®with CAP™ as the NAFLD assessment method can help detect severe steatosis more frequently & monitor the effect of non-therapeutic intervention on the amount of intra-hepatic fat
- A multidisciplinary team including dietitians, psychologists & physical activity supervisors is needed to ensure the best management of NAFLD patients

TABLE 1 **Effect of treatments on NAFLD score (assessed by CAP™ value) by time & NAFLD severity**

	Moderate NAFLD	Severe NAFLD
	Contrast in CAP™ (90 days vs base)	Contrast in CAP™ (90 days vs base)
Arm 1	-29.00	-21.82
Arm 2	-22.65	-39.13*
Arm 3	10.67	-72.77**
Arm 4	18.40	-77.70**
Arm 5	-23.09	-83.27**
Arm 6	-46.31*	-32.57

* p-Value <0.05; ** p-value <0.001

FibroScan®liver stiffness after anti-viral treatment for hepatitis C is independently associated with adverse outcomes

Vutien P, *et al.,* Alimentary Pharmacology & Therapeutics, 2020;52(11-12):1717-1727

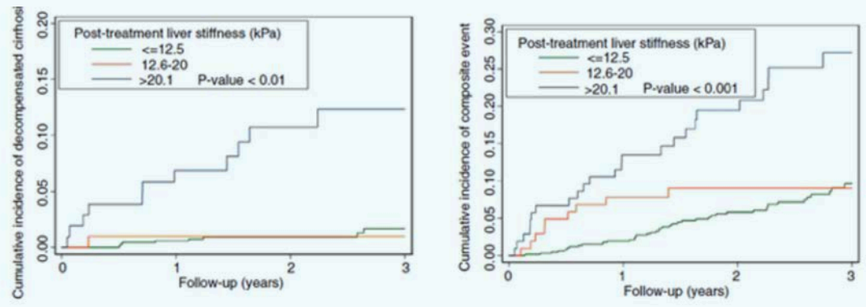
Objectives	• To assess whether LSM by VCTE™ pre- or post-anti-viral treatment was associated with the development of decompensated cirrhosis, HCC or death
Method	• It was a retrospective study, identifying subjects who initiated HCV treatment and had at least one LSM before (pretreatment LSM group) or after HCV therapy (posttreatment LSM group) • LSM cut-off of 12.5 kPa was recommended for the diagnosis of cirrhosis based on systematic review & meta-analysis conducted by the American Gastroenterology Association (AGA) • LSM cut-off of 20kPa was chosen as this was the LSM above which studies have reported higher rates of clinically significant portal hypertension • Composite outcome defined by the development of hepatocellular carcinoma (HCC), decompensated cirrhosis, death or liver transplant
Patients analyzed	• 492 patients (pretreatment LSM); 877 patients (posttreatment LSM)
Results	• LSM by VCTE™ tended to decrease during antiviral therapy (mean difference of -3.94 kPa) • In the post-treatment cohort, when comparing patients with post-treatment LSM<=12.5 kPa, those with post-treatment LSM>20 kPa had **(cf. Fig. 1)**: - Higher risks of developing decompensated cirrhosis (adjusted hazard ratio 3.85) - Higher risks of developing composite outcome (adjusted hazard ratio 1.95) • When post-treatment LSM was higher than the pre-treatment value, patients had higher risk of death or liver transplant (hazard ratio of 7.93), and of occurrence of composite outcome (hazard ratio of 4.83)

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • HCV: Hepatitis C Virus • AGA: American Gastroenterology Association • HCC: Hepatocellular Carcinoma

Key points

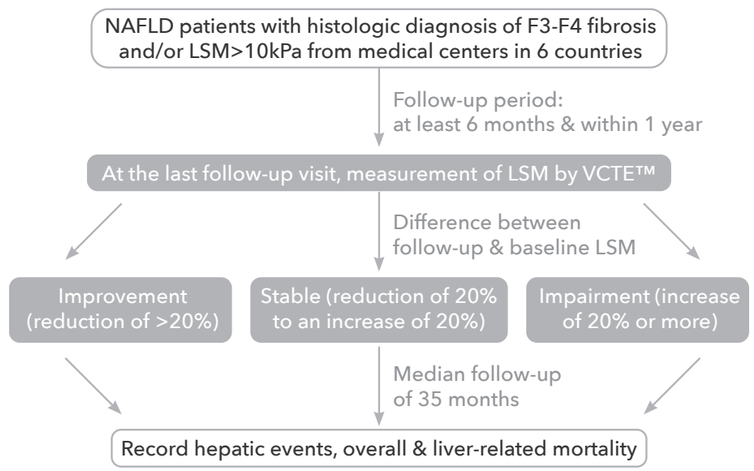
- Post-treatment LSM by VCTE™ >20 kPa was independently associated with the development of decompensated cirrhosis and liver related outcome or death
  ➜ This further supports professional guidelines recommending the use of LSM by VCTE™ values above 20kPa to identify clinically significant portal hypertension
- Measuring LSM by VCTE™ should also be considered after HCV anti-viral treatment because it predicts adverse outcomes even beyond routinely available clinical predictors

FIGURE 1 **Cumulative incidence rate of cirrhosis decompensation (left) and liver related event (right) as function of the post treatment liver stiffness measurement (kPa) during follow up (mean follow up of 27.3 months)**



Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver disease

Petta S, *et al.*, Clinical Gastroenterology & Hepatology, 2021;19(4):806-815

Objectives	• To investigate whether baseline liver stiffness measurements (LSM by VCTE™) and their changes over time can be used to identify patients at risk of liver-related and extrahepatic events, in a large cohort of patients with NAFLD and compensated advanced chronic liver disease
Method	
Patients analyzed	• 1039 NAFLD patients with F3 & F4
Results	• Baseline LSM was - Independently associated with occurrence of hepatic decompensation (hazard ratio = 1.03) - Independently associated with occurrence of HCC (hazard ratio = 1.03) - Independently associated with occurrence of liver-related death (hazard ratio = 1.02) • 533 patients with available LSMs at follow-up, change of LSM was - Independently associated with hepatic decompensation (hazard ratio = 1.56) - Independently associated with HCC (hazard ratio = 1.72) - Independently associated with overall mortality (hazard ratio = 1.73) - Independently associated with liver-related mortality (hazard ratio = 1.96)

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • NAFLD: Non-alcoholic Fatty Liver Disease

Key points

- In patients with NAFLD & compensated advanced chronic liver disease, baseline LSM & change in LSM are associated with risk of liver-related events and mortality
- LSM by VCTE™ should be made at multiple timepoints in patients with NAFLD and compensated cirrhosis to monitor disease progression

A novel spleen-dedicated stiffness measurement by FibroScan® improves the screening of high-risk oesophageal varices

Stefanescu H, *et al.*, Liver International 2020;40(1):175-185

Objectives	• To evaluate the new spleen stiffness measurement algorithm (SSM@100Hz) by VCTE™ as a surrogate non-invasive marker for the presence of esophageal varices (EV), large EV and high risk varices (HRV) in patients with chronic liver disease • To test whether SSM@100Hz by VCTE™ might improve the Baveno VI criteria to better select patients with HRV screening by esophagogastroduodenoscopy (EGD)
Method	**Examinations performed for each subject** • Ultrasound examination • Blood examination • EGD within 6 months of LSM and SSM by VCTE™ **VCTE™ examination** • LSM@50 Hz with M or XL probe according to automatic probe selection tool • SSM@50Hz and SSM@100Hz with M probe
Patients analyzed	• 260 patients with chronic liver disease (60% HCV and 30% of ALD patients)
Results	**New SSM@100Hz** • SSM@100Hz showed a significantly higher examination success rate (92.5%) than SSM@50Hz (76%) **(cf. Fig. 1)** • Diagnostic accuracy of SSM@100Hz for EV (AUC=0.728), large EV (AUC=0.767) & HRV presence (AUC=0.756) was signficantly higher than most other non-invasive tests (NITs) • SSM@100Hz accuracy (AUC=0.782) was significantly higher than SSM@50Hz (AUC=0.72) to diagnose large EV (grade>=2) • SSM@100Hz was more closely correlated to HVPG than SSM@50Hz • SSM@100Hz with cut-off of 34.15 kPa detected patients with clinically signficant portal hypertension (CSPH) with AUC of 0.811 **(cf. Table 1)** • SSM@100Hz with cut-off of 44.95 kPa detected patients with hepatic venous pressure gradient (HVPG)>=12mmHg with AUC of 0.782 **(cf. Table 1)** • A new sequential diagnositc algorithm combining Baveno VI criteria & SSM@100Hz (with a cut-off of 41.3 kPa) for the diangosis of HRV allowed to almost triple the spared EGD rate (38.9%), compared to Baveno VI criteria alone (8.1%). The missed HRV rate was 4.7%. **(cf. Fig. 2)**

VCTE™: Vibration Controlled Transient Elastography • SSM: Spleen Stiffness Measurement • LSM: Liver Stiffness Measurement • EV: Esophageal Varices • HRV: High Risk Varices • EGD: Esophagogastroduodenoscopy • HCV: Hepatitis C Virus • ALD: Alcoholic Liver Disease • AUC: Area Under Receiving Operator Characteristics Curve • NIT: Non-invasive Test • CSPH: Clinically Signficant Portal Hypertension • HVPG: Hepatic Venous Pressure Gradient

Key points

- A novel spleen-dedicated examination (SSM@100Hz) has recently been developed and found to have a better accuracy in detecting EV & large EV
- A sequential algorithm to rule out HRV, starting with Baveno VI criteria and followed by SSM@100Hz, allowed to spare more EGD compared to Baveno VI criteria alone or combined with standard SSM@50Hz

FIGURE 1 Examination success rate of SSM@100Hz & SSM@50Hz

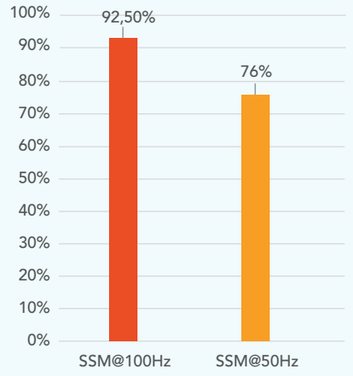
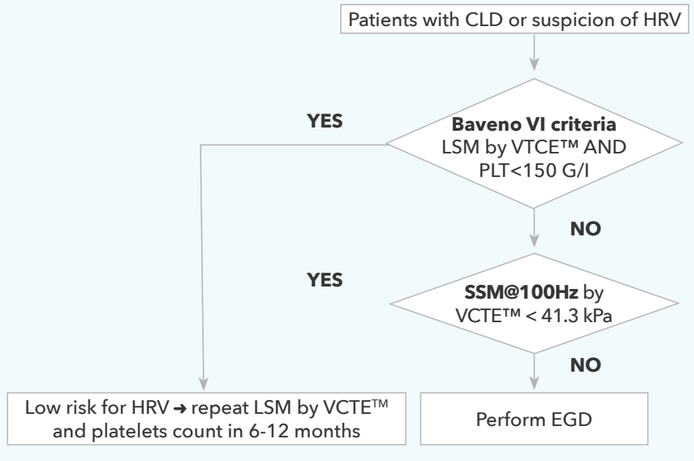


TABLE 1 Diagnostic performance and respective cut-off value of SSM@100Hz to detect HVPG >=10mmHg and >=12mmHg

	AUROC	Cut-off
SSM@100Hz (HVPG>=10mmHg)	0.811	34.15 kPa
SSM@100Hz (HVPG>=12mmHg)	0.782	44.95 kPa

FIGURE 2 New alogrithm combining Baveno VI and SSM@100Hz for ruling-out patients at risk of HRV



LSM by VCTE™
CAP™

The Effect of Laparoscopic Sleeve Gastrectomy on Nonalcoholic Fatty Liver Disease

Batman B, *et al.*, Surgical Laparoscopy, Endoscopy & Percutaneous Techniques, 2019;29(6):509-512

Objectives	• To demonstrate the effect of Laparoscopic sleeve gastrectomy (LSG) on liver steatosis & fibrosis assessed by CAP™ and LSM by VCTE™, respectively
Method	Patients fulfilling criteria for bariatric surgery → FibroScan®examination → Laparoscopic sleeve gastrectomy → FibroScan®exam at 3rd & 6th month post-operation
Patients analyzed	• 72 patients with an indication of bariatric surgery
Results	• Significant decrease in CAP™ & LSM by VCTE™ mean values after 6 months' follow-up after surgery **(cf. Table 1)**

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • CAP™: Controlled Attenuation Parameter • LSG: Laparoscopic sleeve gastrectomy

Key points

- Laparoscopic sleeve gastrectomy is associated with significant improvement in liver steatosis and fibrosis assessed by CAP™ and LSM by VCTE™, respectively
- Evaluation of fibrosis in morbid obese patients is crucial since a significant number of patients who undergo bariatric surgery may develop fibrosis or cirrhosis
- FibroScan®might be a useful adjunct to evaluate the effects of bariatric surgery on liver steatosis and fibrosis

TABLE 1 Mean preoperative & postoperative CAP™ & LSM by VCTE™ values

	Pre-operation	Post-operation (6th month)	P value
LSM by VCTE™	7.5 ± 5.0 kPa	5.6 ± 2.5 kPa	0.013
CAP™	309.2 ± 68.7 dB/m	217.4 ± 56.4 dB/m	0.001