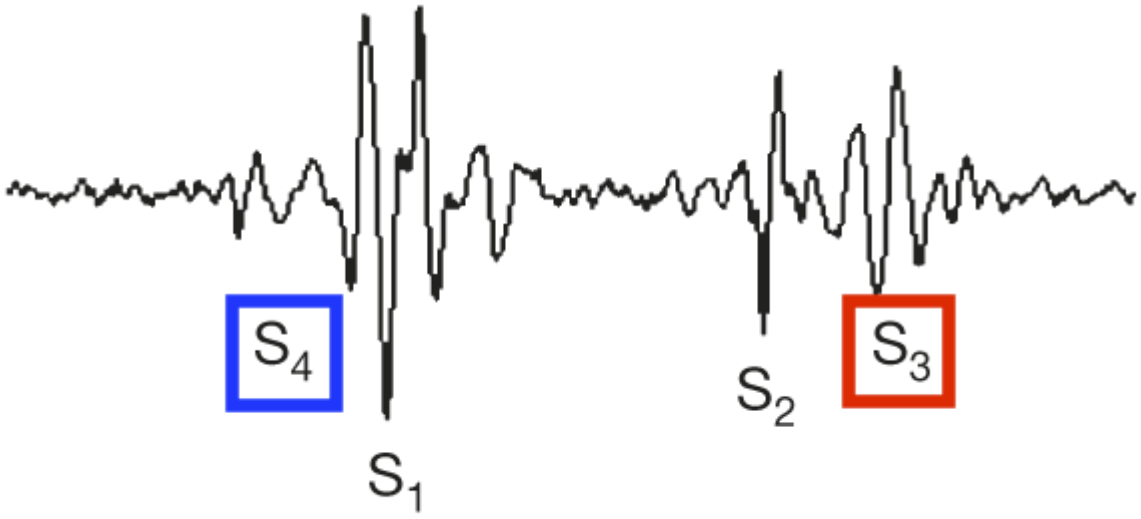
Twitter Thread by Alexander Hajduczok, MD

Alexander Hajduczok, MD
@AHajduczok

Q: Why do we use a stethoscope?
A: For many reasons, and here's one of them that I will argue is undervalued. And is still at the heart (hint hint) of some ongoing research…

First described by Potain in 1880, the gallop rhythm refers to the presence and cadence of abnormal diastolic cardiac sounds, namely S3 and S4.



In 1989, Stevenson and Perloff described the previously unestablished relationship between physical exam signs, increased ventricular filling pressures, and decreased cardiac output in chronic HF patients. Stevenson et al. JAMA. 1989. https://t.co/Fjpx1MQLTX

An excellent point is made in this paper: "While the relationship between physical signs and hemodynamic profile has a firm basis for acute congestive heart failure, the chronic state is characterized by a host of compensatory mechanisms that may cause disparities, …"

"…such as the absence of rales and peripheral edema despite symptomatic elevation of ventricular filling pressures."

This cohort had quite the notable med regimen: digoxin (84%), furosemide (84%), vasodilators (56%), and milrinone (4%);

39/50 were being evaluated for transplant

Interestingly, S3 was not specific for identifying high filling pressures in this cohort – possibly given that it was graded on a binary scale (presence vs. absence). Could it be more useful if somehow represented as a continuous variable??

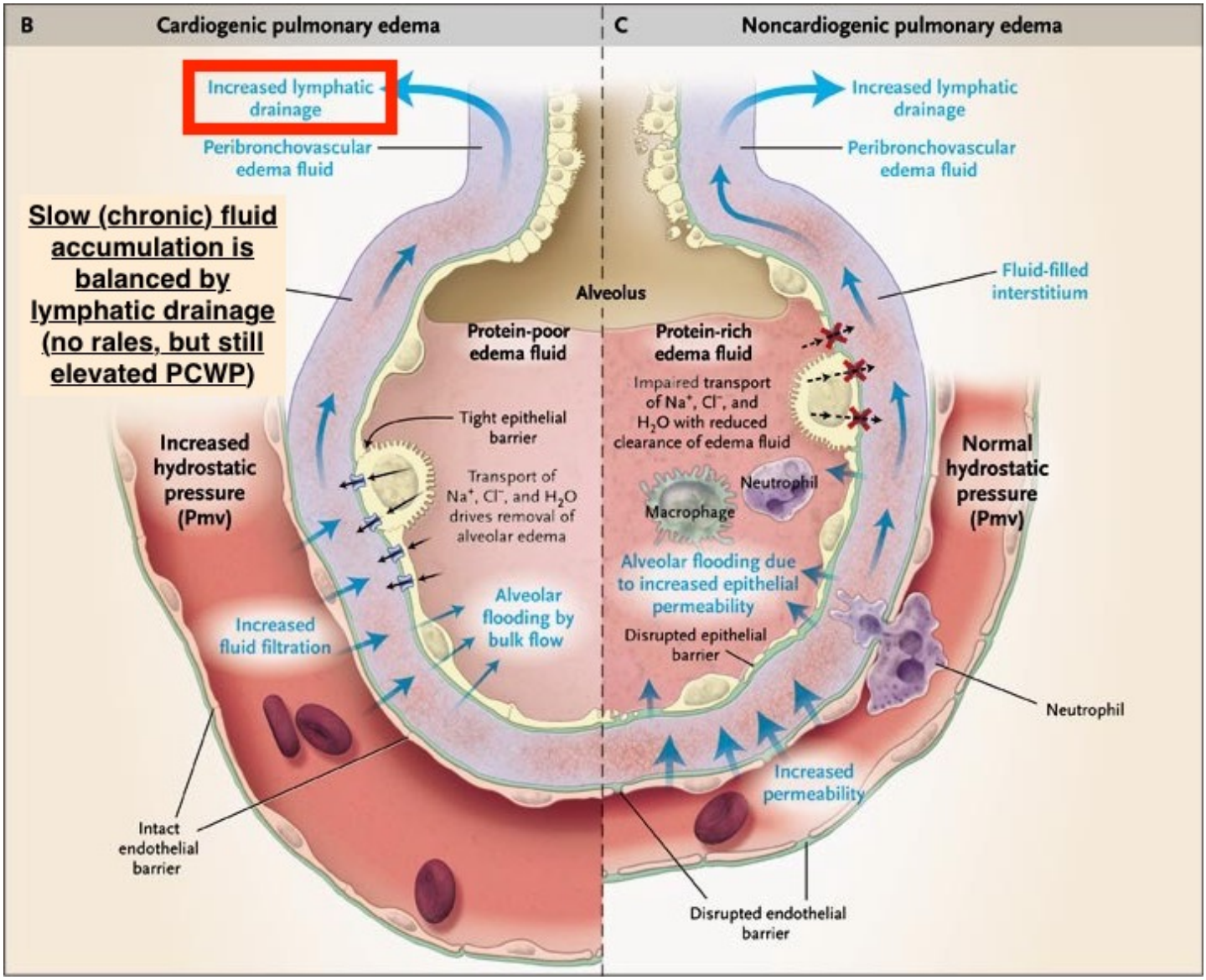
Table 1.—Clinical Characteristics and Physical Findings in 50 Patients With Chronic Heart Failure

Characteristic/Finding	Present	Absent
Coronary artery disease	16	34
Male gender	37	13
Rales	8	42
Third heart sound	48	2
Increased jugular venous pressure	25	25
Peripheral edema	10	40
Orthopnea	39	11

Similarly, presence of rales was non-specific, only found in 19% of patients with PCWP > 22.

A plausible explanation for this observation in chronic (as opposed to acute HF):

In chronic HF - a sudden elevation of pulmonary venous pressure causes rales due to extravasation of fluid into the alveoli, but chronic exudation of fluid is associated with an increase in lymphatic drainage so that the alveoli remain relatively dry and rales are absent.

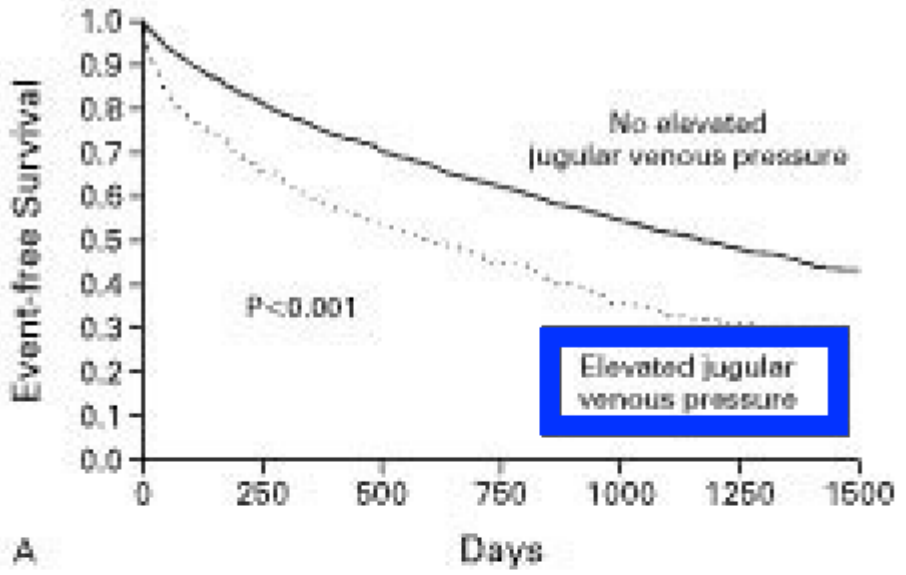


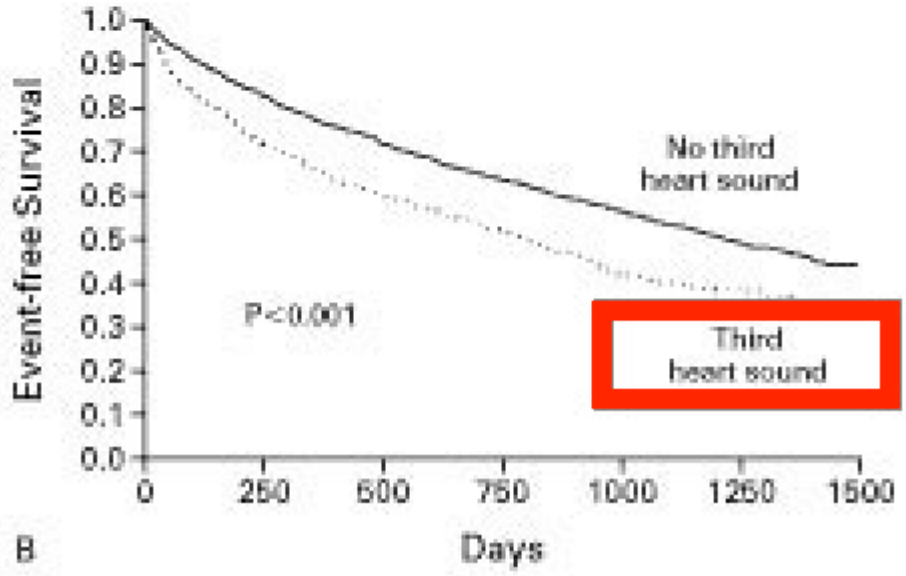
Last, elevated JVP correlated tightly with other physical signs of congestion but was not particularly specific for detection of elevated filling pressures.

Taken together, this study suggested that marked to severe elevations of left ventricular filling pressure frequently are undetected and recommend more judicious use of invasive hemodynamic monitoring in this population.

Over a decade later, the prognostic value of the third heart sound and elevated JVP was further explored by Drazner et al. (NEJM, 2001), in a retrospective analysis of 2569 HF patients enrolled in the SOLVD trial (enalapril vs placebo for HFrEF). https://t.co/UKT9XDf0mc

On univariate analysis, patients with an S3 were at significantly higher risk of death from all causes (RR 1.35 [1.17-1.55], P<0.001) and hospitalization for heart failure (RR 1.70 [1.46-1.97], P<0.001) than those without an S3.





A strength of this study was the addition of multivariate analysis to adjust for markers of HF severity (LVEF, NYHA class, medications, serum Na, etc). Contrary to what was seen in other observational studies (such as above), S3 and elevated JVP had a strong prognostic value.

TABLE 3. RESULTS OF THE MULTIVARIATE ANALYSIS.*

END POINT	ELEVATED JUGULAR VENOUS PRESSURE (N=280)	THIRD HEART SOUND (N=597)	ELEVATED JUGULAR VENOUS PRESSURE, THIRD HEART SOUND, OR BOTH (N=706)
	relative risk (95% confidence interval)		
Death from all causes	1.15 (0.95–1.38)	1.15 (0.99–1.33)	1.17 (1.02–1.35)†
Hospitalization for heart failure	1.32 (1.08–1.62)‡	1.42 (1.21–1.66)§	1.43 (1.23–1.66)¶
Death or hospitalization for heart failure	1.30 (1.11–1.53)‖	1.22 (1.08–1.38)**	1.28 (1.14–1.45)¶
Death from pump failure	1.37 (1.07–1.75)††	1.40 (1.14–1.71)**	1.47 (1.21–1.79)¶
Death from arrhythmia	0.96 (0.62–1.49)	1.13 (0.82–1.54)	1.08 (0.80–1.46)

*Each model also included age, left ventricular ejection fraction, New York Heart Association class, treatment assignment (enalapril or placebo), sex, cause of left ventricular systolic dysfunction (ischemic or nonischemic), black race (yes or no), electrocardiographic evidence of atrial fibrillation at base line (yes or no), serum sodium level, serum creatinine level, presence or absence of a history of diabetes mellitus or hypertension, and presence or absence of base-line use of a beta-blocker, digoxin, or a diuretic.

†$P<0.05$ for the comparison with patients with neither elevated jugular venous pressure nor a third heart sound.

‡$P<0.01$ for the comparison with patients without elevated jugular venous pressure.

§$P<0.001$ for the comparison with patients without a third heart sound.

¶$P<0.001$ for the comparison with patients with neither elevated jugular venous pressure nor a third heart sound.

‖$P<0.005$ for the comparison with patients without elevated jugular venous pressure.

**$P<0.005$ for the comparison with patients without a third heart sound.

††$P<0.05$ for the comparison with patients without elevated jugular venous pressure.

In summary, presence of S3 and elevated JVP was associated with subsequent HF hospitalization, increased risk of HF progression and all-cause mortality. An association that persisted even with adjustment for markers of disease severity.

One may ask whether there is a “better” or more objective/standardized way to assess these signs, namely S3. Marcus et al. (JAMA. 2005) aimed to test this using phonocardiographic measurements to detect abnormal LV function. https://t.co/xWeIhzZ93b

Neither the device-measured S3 nor the S4 was a sensitive marker of left ventricular dysfunction, however, phonocardiographic S3 is specific for left ventricular dysfunction and appears to be superior to the moderate specificity of the S4.

Table 3. Test Characteristics for Computerized Heart Sound Detection*

		LVEDP >15 mm Hg	LVEF <50%	BNP >100 pg/mL
S_3				
	Sensitivity	41 (26-58)	52 (31-73)	32 (20-46)
	Specificity	92 (80-98)	87 (76-94)	92 (78-98)
	Positive predictive value	81 (58-95)	57 (34-78)	85 (62-97)
	Negative predictive value	65 (53-76)	84 (73-92)	48 (36-60)
	Accuracy	69 (58-78)	78 (68-86)	56 (45-67)
S_4				
	Sensitivity	46 (31-63)	43 (23-66)	40 (26-54)
	Specificity	80 (66-90)	72 (59-82)	78 (61-90)
	Positive predictive value	66 (46-82)	34 (18-54)	72 (52-87)
	Negative predictive value	64 (51-76)	79 (66-88)	47 (34-60)
	Accuracy	64 (54-74)	64 (54-74)	55 (44-66)
S_3 and/or S_4				
	Sensitivity	68 (52-82)	74 (52-90)	57 (42-70)
	Specificity	73 (59-85)	64 (52-76)	72 (55-86)
	Positive predictive value	68 (52-82)	42 (26-58)	75 (59-87)
	Negative predictive value	73 (59-85)	88 (75-95)	53 (38-67)
	Accuracy	71 (61-80)	67 (56-76)	63 (52-73)

Abbreviations: BNP, B-type natriuretic peptide; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction.
*Data are presented as percentage (95% confidence interval).

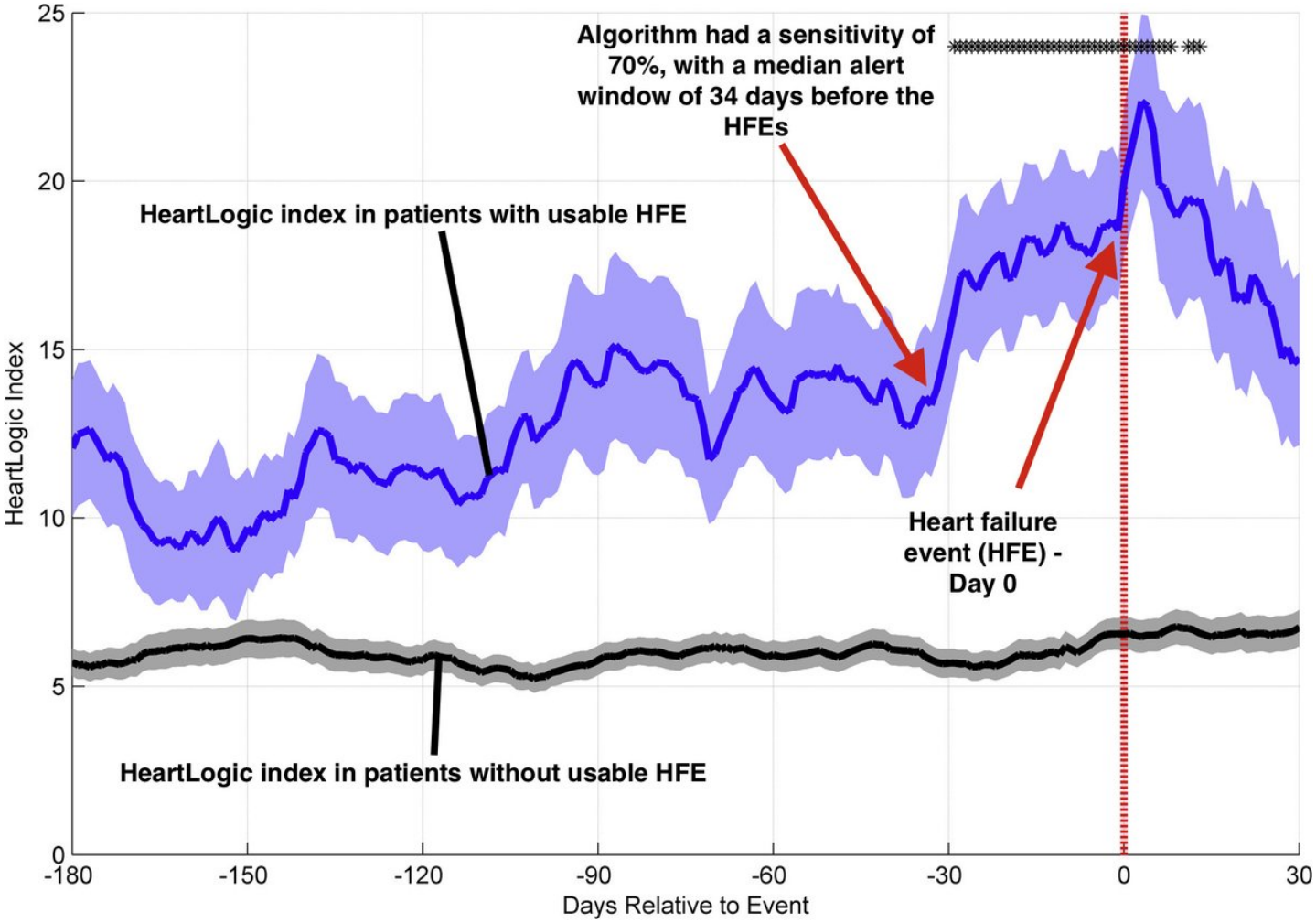
Moving forward now – we have shown that certain parameters are good prognostic factors for HF, based on how they tie into the pathophysiology of HF itself. Can we add additional measures with high clinical relevance to create a model for prediction of impending HF exacerbation?

Table 1. Physiological Variables and Their Clinical Relevance

Physiological Variable	Clinical Relevance
Heart sounds	
First heart sound	Associated with ventricular contraction status
Third heart sound	Associated with early diastolic filling
Thoracic impedance	Associated with fluid accumulation and pulmonary edema
Respiration	
Respiration rate	Rapid shallow breathing patterns associated with shortness of breath
Ratio of respiration rate to tidal volume	
Heart rate	Indicator of cardiac status
Activity	Global patient status and fatigue

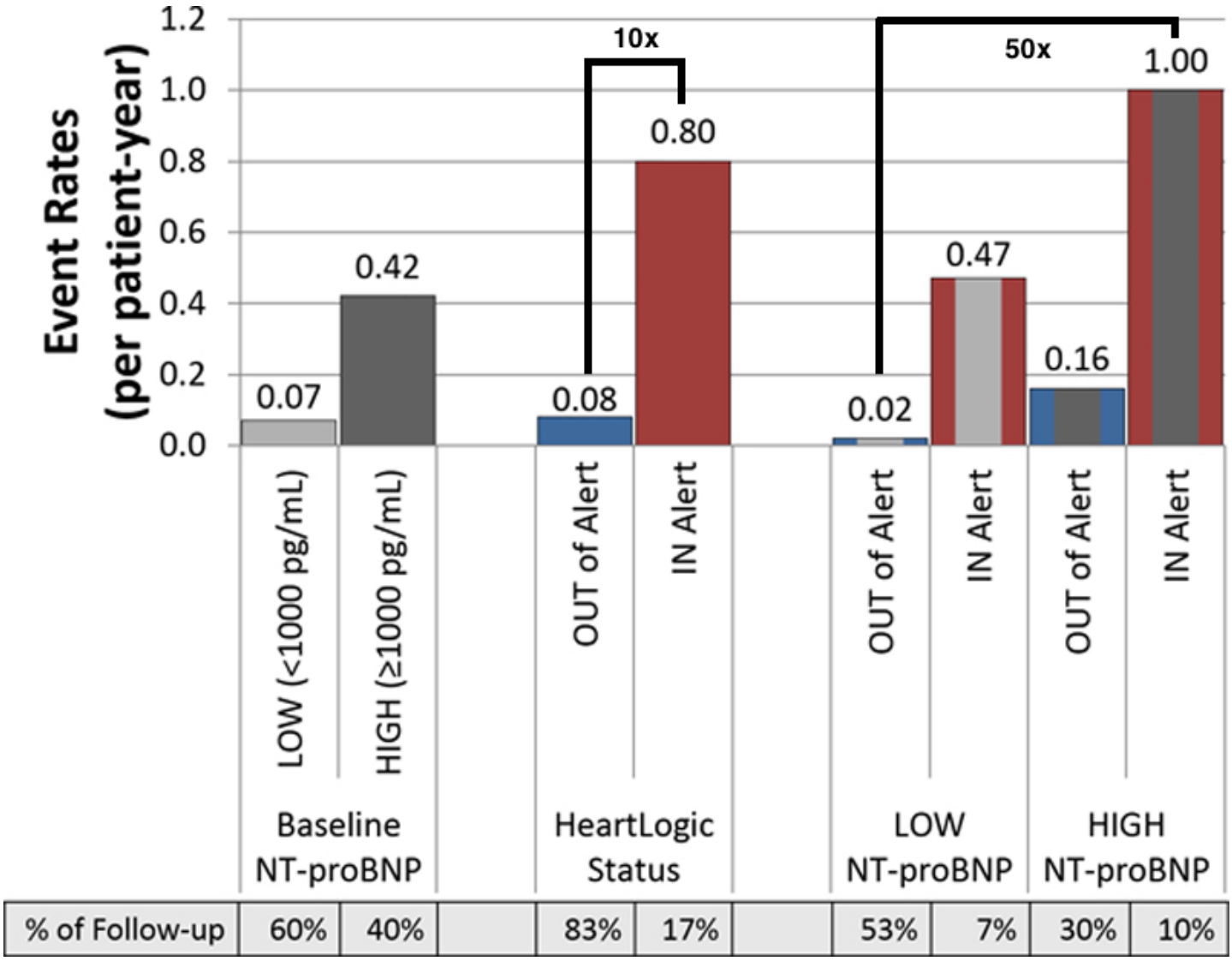
The above parameters form the HeartLogic Index used in the MultiSENSE trial - incorporated into ICD/CRT-Ds allowing for automated daily HF status eval and early awareness of impending decompensation with high sensitivity of 70% (Boehmer, JACC:HF, 2017) https://t.co/6IWfheQhdd

This algorithm was designed to detect gradual worsening of HF over days to weeks. The median early warning (alert window) was 34 days before a heart failure event, which is critical in order to provide actionable care to a patient early in the decompensation spectrum.



Further analysis of MultiSENSE (Gardner, Circ HF, 2018) showed the risk of a heart failure event while “in-alert” was 10x higher then when “out of alert” by HeartLogic Index (0.80 vs 0.08/pt-year)
https://t.co/Plaev6fe4q

What about biomarkers?
Substratification showed that the lowest risk group (low NT-proBNP and not in alert status) vs. the highest risk group (high NT-proBNP levels and being in alert status), had a 50-fold increased risk of an HF event (1.00/pt-year vs 0.02/pt-year).



Although NT-proBNP levels had independent predictive power for HF events, it was significantly lower than that of the HeartLogic alert algorithm alone (event rates: 0.42 vs 0.80/pt-year).

Furthermore, the risk for a HF event was greater in patients with low NT-proBNP levels but in HeartLogic alert status than in subjects with high NT-proBNP levels but out of device alert status (event rates: 0.47 vs 0.16/pt-year).

If you made it this far, you must also love heart failure remote monitoring (!!)

Look how far we've come from simply placing a stethoscope on a patient - although this is still not obsolete, it has led to some excellent advances over the years.

Next, we will look at some other monitoring systems – implantable hemodynamic sensors along with wearable monitoring (a taste below). And discuss some the recent work in the field, and where things may go in the future. Until next time. https://t.co/6jyS3lhfE5

> Next exciting thing on the agenda @PennStHershey - using @nanowearinc\u2019s wearable vest with nano-fiber ECG pads and a very sensitive microphone to quantify S3 heart sounds in the inaudible range, to predict HF exacerbations. pic.twitter.com/kmxpRL6a0Y

— Alexander Hajduczok, MD (@AHajduczok) December 19, 2020

Some folks who might like this: @JeffHsuMD @FudimMarat @DrNasrien @JJheart_doc @AndrewJSauer @RyanTedfordMD @JagSinghMD @MarkDrazner @NMHheartdoc @gcfmd @HFpEF @Cardiobro @TJHeartFellows @HanCardiomd @JavedButler1 @JonathanDavisHF @MKIttlesonMD @DavidLBrownMD @CMichaelGibson etc

And our recent review article on this topic:
Ali, O., Hajduczok, A.G. & Boehmer, J.P. Remote Physiologic Monitoring for Heart Failure. Curr Cardiol Rep 22, 68 (2020). https://t.co/1bmFVDU4Ij