CHEST

Low Prognostic Value of Novel Nocturnal Metrics in Patients With OSA and High Cardiovascular Event Risk

Post Hoc Analyses of the SAVE Study

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BACKGROUND: Traditional methods for the quantification of OSA severity may not encapsulate potential relationships between hypoxemia in OSA and cardiovascular risk.

RESEARCH QUESTION: Do novel nocturnal oxygen saturation (Spo_2) metrics have prognostic value in patients with OSA and high cardiovascular event risk?

STUDY DESIGN AND METHODS: We conducted post hoc analyses of the Sleep Apnea Cardiovascular Endpoints (SAVE) trial. In 2687 individuals, Cox proportional hazards models that were stratified for treatment allocation were used to determine the associations between clinical characteristics, pulse oximetry-derived metrics that were designed to quantify sustained and episodic features of hypoxemia, and cardiovascular outcomes. Metrics included oxygen desaturation index, time <90% Spo_2, average Spo_2 for the entire recording (mean Spo_2), average Spo_2 during desaturation events (desaturation Spo_2), average baseline Spo_2 interpolated across episodic desaturation events (baseline Spo_2), episodic desaturation event duration and desaturation/resaturation-time ratio, and mean and SD of pulse rate.

RESULTS: Neither apnea-hypopnea index, oxygen desaturation index, nor any of the novel Spo_2 metrics were associated with the primary SAVE composite cardiovascular outcome. Mean and baseline Spo_2 were associated with heart failure (hazard ratio [HR], 0.81; 95% CI, 0.69-0.95; $P = .009$; and HR, 0.78; 95% CI, 0.67-0.90; $P = .001$, respectively) and myocardial infarction (HR, 0.86; 95% CI, 0.77-0.95; $P = .003$; and HR, 0.81; 95% CI, 0.73-0.90; $P < .001$, respectively). Desaturation duration and desaturation/resaturation time ratio, with established risk factors, predicted future heart failure (area under the curve, 0.86; 95% CI, 0.79-0.93).

INTERPRETATION: Apnea-hypopnea index and oxygen desaturation index were not associated with cardiovascular outcomes. In contrast, the pattern of oxygen desaturation was associated with heart failure and myocardial infarction. However, concomitant risk factors remained the predominant determinants for secondary cardiovascular events and thus deserve the most intensive management.

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ABBREVIATIONS: AHI = apnea-hypopnea index; ODI = oxygen desaturation index; SAVE = Sleep Apnea Cardiovascular Endpoints; Spo_2 = oxygen saturation

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Sleep-disordered breathing, particularly OSA, is common in patients with cardiovascular disease, and is associated with significant morbidity and death.[1,2] CPAP treatment is the main therapy for OSA, effectively reducing hypopneas and apneas when used appropriately. Despite a clear association between CPAP treatment and reduced cardiovascular event rates and mortality rates in nonrandomized studies,[1] CPAP therapy did not prevent secondary cardiovascular events in the randomized Sleep Apnea Cardiovascular Endpoints (SAVE) study[3] or a subsequent meta-analysis.[4]

Various theories have been advanced to explain discrepancies between epidemiologic and randomized controlled study findings, which included the theories that residual confounding factors caused observational studies to overestimate OSA-associated cardiovascular risk and that low CPAP adherence contributed to neutral findings in randomized studies.[5] Alternatively, current sleep study metrics, namely frequency of respiratory or desaturation episodes, may be less informative for cardiovascular disease risk than other pathophysiologic features of OSA.[6] Recent retrospective analyses of data from cohort studies have identified new candidate markers of OSA-associated cardiovascular risk, which include degree of daytime sleepiness,[7] length of obstructive events,[8] and cumulative extent of oxygen desaturation.[9-17]

In practice, a disturbance in oxygen saturation (Spo_2) generally is quantified as the oxygen desaturation index (ODI) (ie, the number of desaturation episodes ≥3% to 4% per hour of sleep. The apnea-hypopnea index (AHI) (ie, number of hypopneas and apneas per hour of sleep) provides similar information because it requires that hypopnea events are accompanied by ≥3% to 4% Spo_2 or arousal.[18] Neither of these event-based metrics capture features of episodic or sustained changes in Spo_2, such as severity of episodic desaturations and the baseline Spo_2 level from which they occur, for which cumulative effects may be clinically important.[6,19] The clinical utility of other measures of nocturnal hypoxemia compared with conventional indexes of sleep apnea severity is unclear. Thus, to help clarify potential impacts of different patterns of hypoxemia on cardiovascular outcomes, this study aimed to examine overnight pulse oximetry data from participants in the SAVE study to compare the predictive value of conventional and novel metrics of nocturnal Spo_2 and patterns of episodic and sustained episodic desaturations and pulse rate data to predict longer term cardiovascular outcomes that include stroke, myocardial infarction, and heart failure. We hypothesized that oximetry-derived metrics of nocturnal hypoxemic burden have predictive utility for future cardiovascular events.

Methods

Study Design

This is an ancillary study of the SAVE trial. This study used existing data from the SAVE clinical trial (NCT00738179/ACTRN 126080000409370) to assess new methods, but it is not itself a clinical trial. SAVE was an international, multicenter, prospective, randomized, open-label, blinded outcome event assessed (PROBE) trial of CPAP treatment for secondary prevention of cardiovascular events in patients with co-occurring moderate or severe OSA and cardiovascular disease. For this analysis, all individuals, irrespective of CPAP treatment allocation, were included to examine the association of novel oximetry metrics at baseline with longitudinal outcomes. Details are outlined elsewhere.[3,20-22] SAVE was conducted in accordance with the amended Declaration of Helsinki. The protocol of the SAVE clinical trial was approved by regulatory authorities and ethics committees at participating centers; participants provided written informed consent (e-Table 1).

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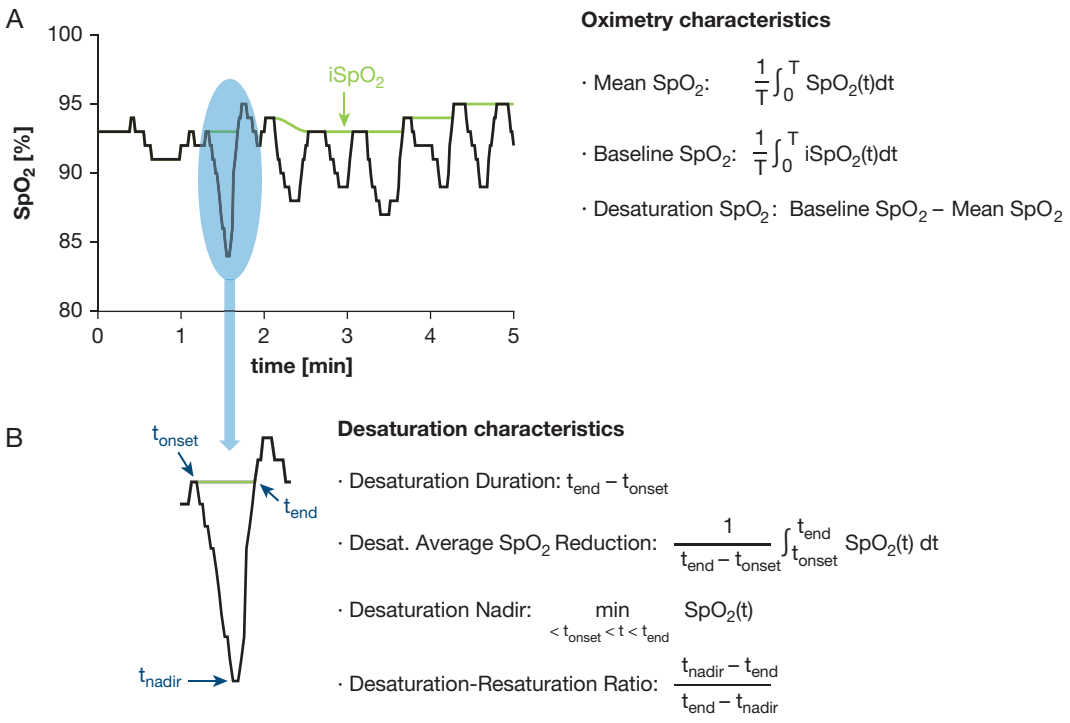

Figure 1 – *A-B, Descriptive diagram and definition of oximetry measures (A) and desaturation characteristics (B) obtained from raw oximetry data (recorded by ApneaLink [ResMed, San Diego, CA]) with the use of a custom MATLAB software algorithm (MathWorks). dt = integrated with respect to time; iSpo$_2$ = Spo$_2$ signal with desaturation periods interpolated; Spo$_2$ = oxygen saturation; T = total recording duration.*

Data Collection

Screening for participants involved overnight home use of an ApneaLink device (ResMed) to record nasal pressure (a surrogate of airflow) and fingertip oximetry (Nonin 8000AA-Adult; Nonin Medical Inc). Eligibility for SAVE required an ODI of ≥12 events/h, defined by ≥4% Spo$_2$ drops. Participants who showed a predominantly Cheyne-Stokes respiration pattern of central sleep apnea were excluded, as were those who had very severe oxygen desaturation (resting awake Spo$_2$ of ≤90% or >10% of recording time with Spo$_2$ of ≤80%). Clinically significant heart failure (New York Heart Association categories III-IV) was also excluded. Eligible participants were assigned randomly to receive either CPAP treatment plus usual cardiovascular care (CPAP group) or usual cardiovascular care alone (usual care group). Medical history, demographic, and anthropometric information was collected at baseline and follow-up appointments (1, 3, 6, and 12 months, and annually thereafter). Clinical outcomes and serious adverse events were recorded according to Medical Dictionary for Regulatory Activities classifications (MedDRA version 14). The primary end point for the SAVE study was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure, acute ischemic cardiac event (unstable angina), or cerebral event (transient ischemic event).[23] For nonfatal events, participants could continue in the trial, and any subsequent events of the same or other types could be recorded.

Oximetry Analyses

Novel metrics calculated to characterize oximetry features included (1) average Spo$_2$ across the recording (mean Spo$_2$), (2) average baseline Spo$_2$ interpolated across acute desaturation events (baseline Spo$_2$), and (3) average Spo$_2$ desaturation below the interpolated baseline Spo$_2$ during acute events (desaturation Spo$_2$) (Fig 1). Acute desaturations were defined as episodic, monotonic drops in Spo$_2$ that reach a peak amplitude of ≥4%, followed by resaturation of at least two-thirds of the preceding drop, within 150 seconds from desaturation onset.[10,23] ODI was calculated as the number of such events per hour. Total accumulated time spent at <90% Spo$_2$ (T90) was also calculated.

To further characterize acute episodic desaturations, we determined (1) median event duration (from onset of deoxygenation to completion of resaturation), (2) median of the average reduction in Spo$_2$ over the duration of identified events, (3) median nadir of all desaturation events, and (4) median desaturation/resaturation time ratio.

Using pulse rate traces from ApneaLink software output, we calculated the average pulse rate and its SD as surrogate measures of mean heart rate and heart rate variability. Methods information and artefact detection have been published[10,23] (e-Fig 1).

Statistical Analyses

Statistical analyses used SPSS software (version 23; IBM). Given the number of comparisons and the exploratory nature of the analyses, a probability value of <.01 was considered statistically significant.

Relationships between standard and novel metrics and outcome events were investigated with the use of Cox proportional hazards regression. Outcomes that were assessed were the primary composite as described in the main SAVE trial[3] and each component event type. Each variable was first assessed individually with only a stratification for treatment allocation (CPAP vs usual care), which permitted different baseline hazard according to treatment arm but a single estimate of the regression coefficient for the variable of interest. For multivariable Cox regression analyses, two stages (blocks) were used to generate predictive equations. Block 1 included common exposures that are also associated with OSA-related outcomes recorded at baseline as

predictor variables: diabetes mellitus and hypertension diagnoses, age, waist:hip ratio, smoking status (never/past/current), ODI, ethnicity category (Caucasian/European, Asian, other), treatment allocation (CPAP/usual care), cardiovascular disease history (coronary/cerebrovascular/both), and total number of prescribed cardiovascular and diabetes mellitus medications. Block 2 included oximetry and pulse metrics:pulse mean and SD, desaturation/resaturation time ratio, desaturation average Spo_2 reduction and duration, and baseline Spo_2. For the composite outcome and separately for each component event type, block 1 was assessed first, and variables were retained after stepwise assessment proceeded to the second stage, in which block 2 variables were added and a second round of stepwise assessment was carried out to generate a final model. Regression coefficients that were generated from block 1 in the first phase alone, and from both blocks 1 and 2 in the second phase, were applied as predictive equations to assess the relative contribution of known and novel variables and presented as receiver-operating characteristic curves.

Results

General Characteristics

Of 2687 participants who were included in the SAVE follow up,[3] 38 participants could not be included due to technical problems with their recording files, which left 2649 participants with complete overnight oximetry raw data for analysis. Table 1 and e-Table 2 outline their general characteristics. Most were middle-aged, overweight men, with median follow up of 3.54 years (range, 1 day to 6.89 years). There were no significant differences between treatment allocation groups in pulse or oximetry metrics (e-Table 3).

TABLE 1] Baseline Demographic and Anthropometric Features of Participants Included in the Study

Patient Characteristics	CPAP (n = 1,329)	Usual Care (n = 1,320)	Total (N=2,649)
Sex: female, No. (%)	250 (18.8)	254 (19.2)	504 (19.0)
Ethnicity, No. (%)			
Causcasian/European	326 (24.5)	332 (25.2)	658 (24.8)
Asian	851 (64.0)	831 (63.0)	1,682 (63.5)
Other	152 (11.4)	157 (11.9)	309 (11.7)
Country, No. (%)			
Australia	104 (7.8)	117 (8.9)	221 (8.3)
Brazil	139 (10.5)	140 (10.6)	279 (10.5)
China	845 (63.6)	823 (62.3)	1,668 (63.0)
India	59 (4.4)	58 (4.4)	117 (4.4)
New Zealand	53 (4.0)	45 (3.4)	98 (3.7)
Spain	128 (9.6)	134 (10.2)	262 (9.9)
United States	1 (0.1)	3 (0.2)	4 (0.2)
Smoking status,[a] No. (%)			
Never	580 (43.7)	595 (45.2)	1175 (44.5)
Past	536 (40.4)	528 (40.1)	1,064 (40.3)
Current	210 (15.8)	194 (14.7)	404 (15.3)
Age at randomization, median (IQR), y	61.4 (55.6-67.2)	61.6 (55.3-67.6)	61.4 (55.4-67.4)
Height, median (IQR), cm	168 (163-173)	168 (162-173)	168 (162-173)
Weight, median (IQR), kg	80 (70-89)	79 (70-88)	80 (70-89)
BMI, median (IQR), kg/m^2	28.2 (25.8-31.0)	28.0 (25.7-30.9)	28.1 (25.7-30.9)
Waist, median (IQR), cm	100 (93-108)	100 (93-107)	100 (93-108)
Hip, median (IQR), cm	105 (100-110)	105 (100-111)	105 (100-110)
Waist:hip ratio, median (IQR)	0.96 (0.91-1.00)	0.95 (0.91-1.00)	0.95 (0.91-1.00)
Neck circumference, median (IQR), cm	41 (38-43)	41 (38-43)	41 (38-43)
Systolic BP, median (IQR), mm Hg	130 (120.5-140)	130 (120-140)	130 (120-140)
Diastolic BP, median (IQR), mm Hg	80 (72.5-87)	80 (71.5-86)	80 (72-86.5)
Heart rate, median (IQR), beats/min	70 (63-78)	71 (64-79)	71 (64-78)

[a]Information missing for six participants (three in each treatment group). IQR = interquartile range.

TABLE 2] Summary of Unadjusted Univariate Cox Regression Analyses for the Primary Composite End Point of the Sleep Apnea Cardioascular Endpoints (SAVE) Study

Variable	Hazard Ratio[a]	95% CI[a]	*P* Value
Apnea-hypopnea index, events/h	0.99	0.98-1.00	.066
Patterns of nocturnal hypoxemia (custom MATLAB [MathWorks] algorithm)			
Oxygen desaturation index, events/h	0.99	0.98-1.00	.072
T<90%, min (log transformed)	1.00	0.94-1.07	.988
Mean Spo_2, %	0.99	0.94-1.04	.652
Baseline Spo_2, %	0.96	0.91-1.01	.141
Desaturation Spo_2, % (log transformed)	0.93	0.81-1.06	.262
Desaturation duration, s	1.01	1.00-1.02	.039
Desaturation/resaturation time ratio	0.93	0.80-1.08	.329
Desaturation average Spo_2 reduction, %	0.94	0.86-1.03	.166
Desaturation nadir, %	1.00	0.97-1.04	.886
Pulse mean, beats/min	0.99	0.99-1.01	.774
Pulse SD, beats/min	1.00	0.95-1.05	.987

[a]From crude (univariate) Cox regressions for the primary composite end point of SAVE, with the use of individual measures as univariate continuous covariates. Regression analyses were stratified according to CPAP treatment allocation, with no other adjustments. Spo_2 = oxygen saturation.

Predictive Value of Measures for the Composite Endpoint and Its Component Cardiovascular Outcomes

Unadjusted Cox proportional hazard models stratified by treatment allocation (CPAP vs usual care) showed no significant predictive value of AHI, ODI, or T90 for the primary composite outcome (Table 2) or any component cardiovascular outcomes (Table 3).

With the use of the same approach to assess novel Spo_2 metrics and acute episodic desaturation patterns, none were strongly predictive of the SAVE composite outcome (Table 2). However, lower mean Spo_2 and baseline Spo_2, but not desaturation Spo_2, were associated with increased risk of heart failure and myocardial infarction (Table 3). The hazard ratio for desaturation/resaturation time ratio indicated an inverse relationship with heart failure risk (0.35 [0.17-0.74]; $P = .005$), which indicates a higher risk with lower desaturation/resaturation ratios, as would be expected in central rather than OSA (Table 3). Pulse rate SD, which is indicative of high heart rate variability, was associated with a higher risk of cardiovascular death and stroke but showed a protective relationship with angina (Table 3).

Multivariable Cox regression analysis adjusted for demographic, clinical, and anthropometric risk variables was used to generate a predictive equation for the composite outcome (Table 4). The resultant receiver-operating characteristic curve showed statistically significant (area under the curve, 0.61; 95% CI, 0.58-0.65; $P < .001$) but poor predictive utility for the primary composite outcome at 2 years (sensitivity, 70%; specificity, 41% at threshold value of 2.95) (Fig 2).

Stepwise backwards conditional multivariable Cox regression analyses indicated distinctive patterns that were associated with each component outcome type (e-Table 4). Several novel oximetry metrics were predictive of cardiovascular death. None of the novel oximetry metrics retained independent significance as predictors of stroke or myocardial infarction. Receiver-operating characteristic curves that were derived from these multivariable regression equations for component cardiovascular outcomes are shown in e-Figure 2; except for heart failure, these were poorly predictive.

Desaturation/resaturation time ratio, desaturation duration, and mean pulse rate were retained as predictors of heart failure risk in multivariable analyses. The regression formula that was produced by stepwise conditional multivariable Cox regression analysis for heart failure (e-Table 5) was significant and strongly predictive of outcomes at 2 years (area under the curve, 0.84; 95% CI, 0.76-0.91; $P < .001$; sensitivity, 75%; specificity, 70% at threshold value of 11.18) (Fig 2).

The 2-year heart failure outcome was reanalyzed in a second backwards stepwise conditional analysis, in which the general category of cardiovascular disease history in block 1 was replaced with a variable specific for history of heart failure (e-Table 5). Although a

TABLE 3] Summary of Unadjusted Univariate Cox Regression Analyses for Component Outcomes of the Sleep Apnea Cardioascular Endpoints (SAVE) Study

Variable	Hazard Ratio (95% CI)[a]; *P* Value					
	Cardiovascular Death (n = 44)	Myocardial Infarction (n = 81)	Stroke (n = 132)	Heart Failure (n = 32)	Angina (n = 187)	Transient Ischemic Event (n = 25)
Apnea-hypopnea index, events/h	0.98 (0.96-1.00); .085	0.99 (0.97-1.00); .057	1.00 (0.99-1.01); .970	0.99 (0.97-1.01); .476	0.99 (0.98-1.00); .108	0.99 (0.97-1.02); .632
Oxygen desaturation index, events/h	0.99 (0.97-1.01); .293	0.99 (0.97-1.00); .137	0.99 (0.99-1.01); .840	1.00 (0.98-1.03); .729	0.99 (0.98-1.00); .131	0.98 (0.96-1.01); .286
T<90%, min (log transformed)	0.81 (0.67-0.99); .035	1.17 (0.99-1.37); .066	0.98 (0.89-1.10); .717	1.27 (0.97-1.66); .081	0.98 (0.89-1.09); .722	0.89 (0.68-1.16); .374
Mean Spo_2, %	1.15 (0.97-1.36); .119	0.86 (0.77-0.95); **.003**	1.09 (1.00-1.20); .065	0.81 (0.69-0.95); **.009**	0.97 (0.90-1.05); .456	1.13 (0.90-1.41); .295
Baseline Spo_2, %	1.05 (0.88-1.26); .563	0.81 (0.73-0.90); **.001**	1.13 (1.02-1.26); .020	0.78 (0.67-0.90); **.001**	0.94 (0.87-1.01); .092	1.07 (0.85-1.34); .583
Desaturation Spo_2 (log transformed), %	0.73 (0.48-1.12); .145	0.81 (0.59-1.10); .178	1.08 (0.86-1.37); .509	0.89 (0.55-1.45); .657	0.87 (0.71-1.07); .191	0.86 (0.49-1.49); .581
Desaturation duration, s	1.02 (0.99-1.06); .124	1.01 (0.98-1.03); .595	1.01 (0.99-1.02); .565	1.03 (1.00-1.07); .059	1.00 (0.99-1.02); .931	1.05 (1.01-1.08); .011
Desaturation/resaturation time ratio	0.81 (0.50-1.01); .397	0.65 (0.44-0.96); .032	1.13 (0.88-1.45); .352	0.35 (0.17-0.74); **.005**	0.94 (0.75-1.18); .609	0.87 (0.46-1.64); .658
Desaturation average Spo_2 Reduction, %	0.71 (0.50-1.01); .055	0.82 (0.65-1.03); .094	1.06 (0.92-1.23); .410	0.78 (0.53-1.14); .202	0.94 (0.82-1.08); .390	0.77 (0.50-1.19); .243
Desaturation nadir, %	1.16 (1.01-1.34); .033	0.97 (0.89-1.05); .430	1.02 (0.95-1.09); .622	0.93 (0.82-1.06); .279	0.99 (0.93-1.04); .631	1.16 (0.97-1.40); .104
Pulse mean, beats/min	1.02 (0.99-1.05); .249	1.00 (0.98-1.03); .890	1.02 (1.00-1.04); .035	1.01 (0.98-1.05); .472	0.99 (0.97-1.00); .087	0.98 (0.94-1.03); .375
Pulse SD, beats/min	1.08 (1.04-1.12); **.001**	0.90 (0.79-1.04); .161	1.06 (1.02-1.09); **.001**	0.95 (0.76-1.18); .625	0.85 (0.78-0.94); **.001**	0.98 (0.78-1.23); .847

P values < .01 indicating comparisons considered significant are in bold.

[a]From crude (univariate) Cox regressions for component outcomes of SAVE, with the use of individual measures as univariate continuous covariates. Regression analyses were stratified according to CPAP treatment allocation, with no other adjustments. Spo_2 = oxygen saturation.

TABLE 4] Final Model From Two Block Backwards Stepwise (Conditional) Multivariable Cox Regression Analysis for Predictors of the Primary Composite End Point of the Sleep Apnea Cardioascular Endpoints (SAVE) Study Outcome at 2 Years

Variable	Hazard Ratio (95% CI)	Hazard Ratio, Z-Normalized Value for Scale Variables (95% CI)	*P* Value
Diabetes mellitus	1.50 (1.23-1.83)	…	< .001
Ethnicity (simplified)			
White/European	Reference	…	.092
Asian	1.23 (0.95-1.59)	…	.111
Other	0.85 (0.56-1.28)	…	.436
Hypertension	1.43 (1.10-1.86)	…	.008
Cardiovascular disease history			
Cardiac only	Reference	…	< .001
Cerebrovascular only	0.78 (0.63-0.97)	…	.028
Both	2.74 (1.98-3.79)	…	< .001
Age at baseline	1.01 (1.00-1.02)	1.07 (0.97-1.18)	.167
Waist:hip ratio	5.73 (1.69-19.45)	1.15 (1.04-1.26)	.005
Oxygen desaturation index	1.00 (0.99-1.00)	0.92 (0.82-1.02)	.125
Median desaturation duration, s	1.01 (1.00-1.02)	1.09 (0.99-1.21)	.073

Regression formula for the primary composite outcome: 0.003 + 0.405*1(if diabetic, 0 if not) + 0.209*1(if Asian, 0 if not) + 0.355*1(if hypertension, 0 if no) + 1.746*waist:hip ratio + -0.005*ODI + 1.008*1(if both cardiac and cerebrovascular disease history, 0 if not) + 0.009*median desaturation duration.

history of heart failure was important, desaturation duration and desaturation/resaturation time ratio retained predictive value in this second model; the resultant equation was similarly strongly predictive of heart failure outcomes at 2 years (area under the curve, 0.86; 95% CI, 0.79-0.93; $P < .001$; sensitivity 90%, specificity 70% at threshold value of 7.39) (Fig 2).

Discussion

In this ancillary study of the SAVE trial, conventional metrics such as AHI and ODI predicted neither the primary composite cardiovascular outcome nor its components in individuals with moderate-to-severe OSA and high cardiovascular risk. Novel oximetry-derived Spo_2 metrics had some prognostic value, but concomitant risk factors, which are highly prevalent in patients with OSA, remain the predominant determinants for secondary cardiovascular events.

Other features of nocturnal hypoxemic burden, such as the degree of sustained hypoxemia and/or the severity of intermittent desaturation events, may provide additional prognostic information. Punjabi et al[24] first showed that prevalent cardiovascular disease was related to the extent of hypopnea-associated oxygen desaturation during sleep. More recently, T90 was shown to be an independent predictor of all-cause death in patients with stable chronic heart failure[9] and was associated with increased incidence of cardiovascular death[11] and fatal stroke in older men.[10] Another recent study showed that hypoxemic burden due to sleep apnea is strongly predictive of cardiovascular death.[12] In contrast, in this SAVE study cohort, neither T90 nor the component of hypoxemic burden due to acute desaturation events (desaturation Spo_2) were associated with the primary end point and were associated only weakly with risk of myocardial infarction and heart failure risk. There are several potential reasons for these disparate findings. First, follow up in SAVE was shorter, with relatively few deaths. Second, because SAVE included only participants with moderate-to-severe OSA, the mean T90 in SAVE was 3- to 4-times higher than other cohort studies that investigated the association between T90 and mortality rates in individuals who were not preselected for OSA status.[10-12] Although nocturnal hypoxemia may be a key variable that affects cardiovascular death and morbidity,[9-17] it may be less evident in the SAVE population that is preselected by OSA diagnosis because of the narrower range of T90 values. Instead, other cardiovascular risk factors, which were prevalent in the population recruited to SAVE, appear to predominate.

The contribution of acute desaturation events (desaturation Spo_2) to overall hypoxemia, with the incorporation of cumulative severity of desaturation events, did not determine cardiovascular risk in SAVE participants. Mean Spo_2, and baseline Spo_2 comprising

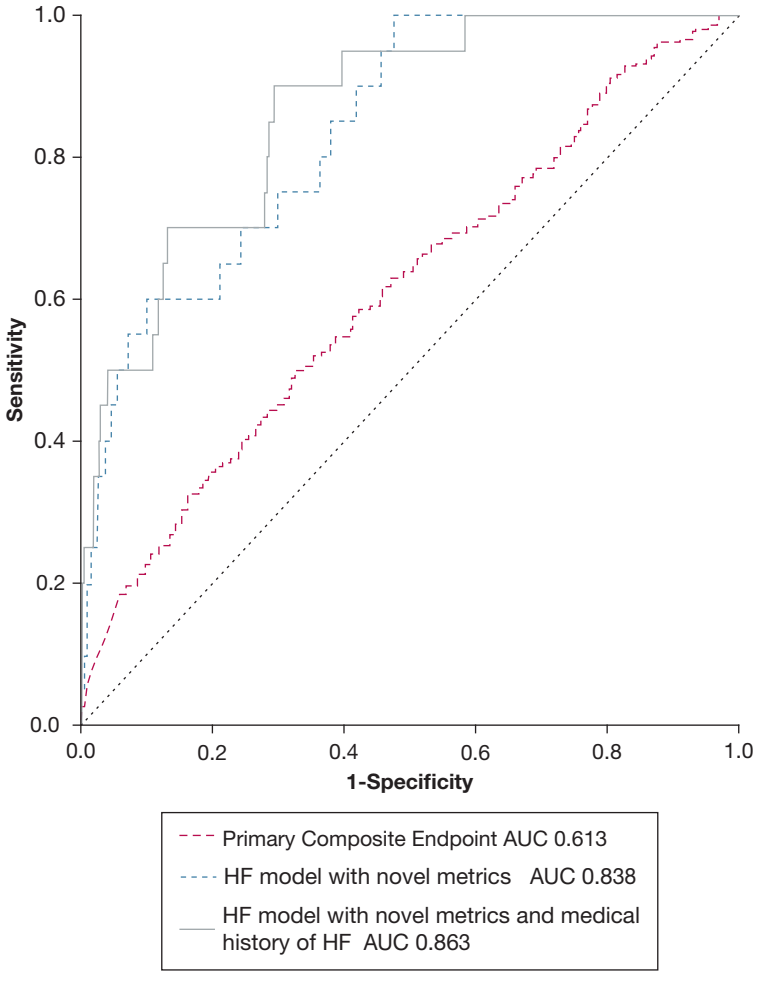

Figure 2 – *Receiver-operator characteristic curves that use regression formulae from stepwise multivariable Cox regression analyses applied to 2-year outcomes for the primary composite end point (Table 4) and the heart failure component (for the regression formulae see e-Tables 5, 6).*

sustained changes in Spo_2 independent of episodic desaturation events failed to predict the primary composite outcome in SAVE but were associated with myocardial infarction and heart failure in univariate analyses; hazard ratios of <1 indicated worse prognosis with lower mean Spo_2 and baseline Spo_2. Baseline Spo_2 was retained in predictive models for some outcome components. Although patients with clinical lung disease, awake $Spo_{2\ of} \leq 90\%$ or very severe nocturnal hypoxemia were excluded from the SAVE study, alterations in mean and baseline Spo_2 may reflect mild subclinical lung disease, pulmonary congestion, or V/Q mismatches. Additionally, some individuals with severe sleep apnea may be at risk of "micro" lung injury due to OSA-related mechanical or oxidative stressors.[25]

We cannot exclude a potential bidirectional cause-effect relationship for which not only hypoxemic burden may contribute to component cardiovascular outcomes, but also additional mechanisms that involve pulmonary congestion, prolonged circulation time, and subclinical lung disease in patients with cardiovascular disease may also increase hypoxemic burden. Pooling pathophysiologically distinct end points such as strokes and myocardial infarction with different cause-effect relationships into one composite outcome may partially mask the effects of a specific exposure such as hypoxemia on individual outcomes. This has important implications for interventions that target or are being guided by a specific variable that may be associated heterogeneously with a component of the composite outcome. It also affects the selection of components in composite outcomes and sample size requirements in future clinical studies.

The duration of respiratory events and cycle length of hypopneas have been studied previously in central sleep apnea and Cheyne-Stokes respiration.[26-28] Our study examined additional features of episodic desaturation events to determine amplitudes and durations of desaturation and reoxygenation phases. The desaturation/reoxygenation relationship may provide

important information about hemodynamics and cardiac performance. Increased sensitivity of peripheral and central chemoreceptors and prolonged circulation time may contribute to dysregulation of respiratory control and prolong respiratory events.[29-31] Obstructive respiratory events typically show a slower desaturation phase followed by steeper resaturation, although central apneas show a more symmetric pattern.[6] In this study, a lower desaturation/resaturation time ratio, which is suggestive of a more central pattern of breathing instability, potentially indicates preexisting subclinical or emerging cardiac dysfunction despite exclusion of participants with frank heart failure and predicted high risk of heart failure during follow up. Subclinical heart failure in some study participants may have escaped the SAVE exclusion criteria and have contributed to a central sleep apnea component in some of the participants with predominant OSA in SAVE. Theoretically, the desaturation/resaturation time ratio may be helpful to separate the cause of desaturations by detecting subtle "central-like" events in overnight oximetry recordings.

Heart (or pulse) rate provided little additional predictive information about future cardiovascular risk. However, heart (pulse) rate variability, which is an indicator of autonomic regulation,[32] did provide predictive value in multivariable prediction of some of the component outcomes of SAVE.

Although broad inclusion criteria were used, SAVE was a clinical trial that purposefully recruited patients in stable condition with comorbid cardiovascular disease and untreated OSA with a relatively short follow-up time and excluded those with very severe hypoxemia (ie, >10% overnight recording with Spo_2 of <80%). As such, we were unable to assess outcomes in a broader range of individuals with OSA or to undertake comparisons with individuals without OSA. Moreover, we do not have detailed information about participants' lung function or lung volume. Because the regression models often involved small numbers of events, our data are mainly hypothesis-generating and need cautious interpretation. Given the large number of comparisons made in our analyses, some statistically significant findings may reflect chance. However, particularly strong predictive utility in patients with heart failure clearly warrants validation in an independent sample and with larger numbers of participants.

Interpretation

Conventional metrics such as AHI and ODI had limited value for the prediction of future cardiovascular events in our population with moderate-to-severe OSA and preexisting cardiovascular disease. Novel oximetry-derived Spo_2 metrics and shapes of episodic desaturation events had some prognostic value, but concomitant risk factors, which are highly prevalent in patients with OSA, remain the predominant determinants for secondary cardiovascular events and thus deserve intensive management. Future studies that will measure and target alternative measures of OSA severity should clarify whether nocturnal hypoxemic burden metrics represent meaningful risk markers or modifiable cardiovascular risk factors.

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***SAVE (Sleep Apnea Cardiovascular Endpoints) Investigators:** For list of investigators, see e-Appendix 1.

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