SUPPLEMENTARY MATERIAL

Hypoxic Burden to Guide CPAP Treatment Allocation in Patients with Obstructive Sleep Apnoea: A *Post-hoc* Study of the ISAACC Trial

Figure S1. Cardiovascular response to CPAP treatment according to the baseline HB level and the mean adherence to the treatment. Unadjusted Kaplan–Meier curves showing the cumulative incidence of cardiovascular events in the Usual Care group, the lower CPAP adherence group, and the higher CPAP adherence group, for **(A)** all participants, **(B)** participants with low HB, and **(C)** participants with high HB. The pre-intervention HB was categorized as "low" and "high" when ≤ or > the median value (73.1 %min/h), respectively. The adherence to CPAP treatment was categorized as "lower" and "higher" when < or ≥ the median value of daily use (2.3 h/day), respectively. Definitions of abbreviations: CPAP = continuous positive airway pressure; HB = hypoxic burden.
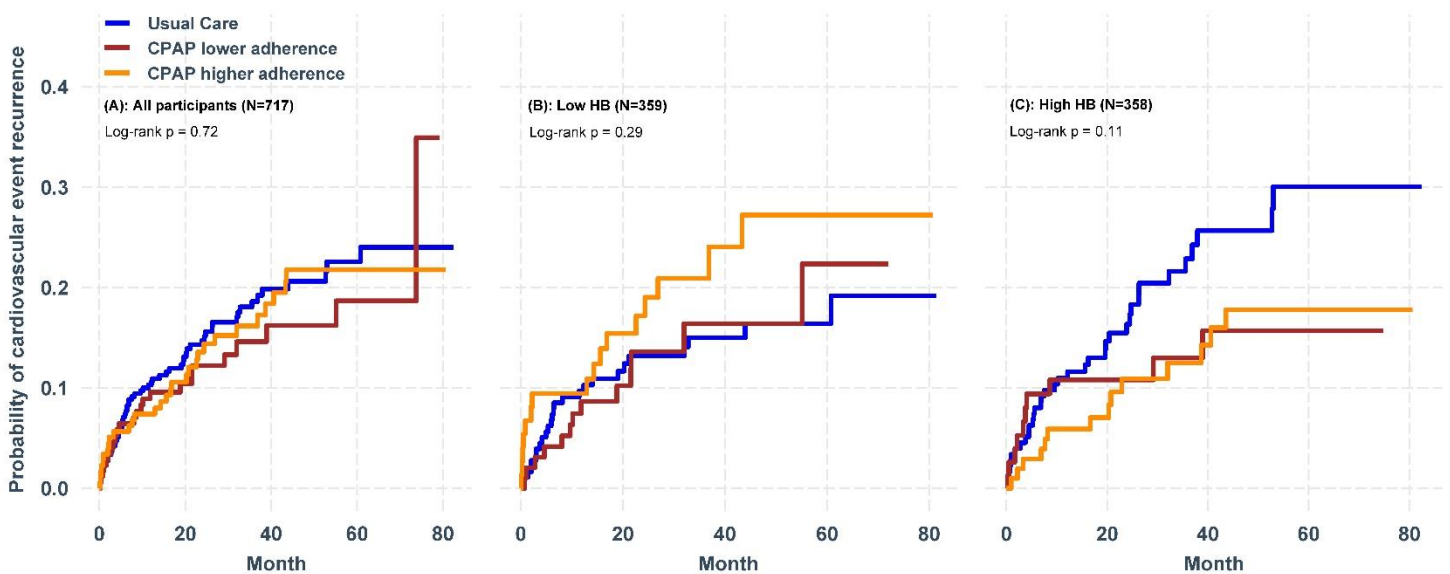
Figure S2. Cardiovascular response to CPAP treatment according to the conventional OSA severity metrics level. Unadjusted Kaplan–Meier curves showing the cumulative incidence of cardiovascular events in the CPAP *vs.* the Usual Care groups for **(A)** all participants, **(B)** participants with low OSA severity metric, and **(C)** participants with high OSA severity metric. The pre-intervention OSA severity measures were categorized as "low" and "high" when ≤ or > the median values, respectively. The median values were 30.8 events/h for AHI, 27.2 events/h for ODI and 3.3% for TSat90. Definitions of abbreviations: AHI = apnoea-hypopnoea index; CPAP = continuous positive airway pressure; ODI = oxygen desaturation index; TSat90 = percent of total sleep time spent with oxygen saturation <90%.

AHI

(A): All participants (N=727)
Log-rank p = 0.50

(B): Low AHI (N=365)
Log-rank p = 0.60

(C): High AHI (N=362)
Log-rank p = 0.69

ODI

(A): All participants (N=727)
Log-rank p = 0.50

(B): Low ODI (N=359)
Log-rank p = 0.61

(C): High ODI (N=358)
Log-rank p = 0.63

TSat90

(A): All participants (N=727)
Log-rank p = 0.50

(B): Low TSat90 (N=359)
Log-rank p = 0.87

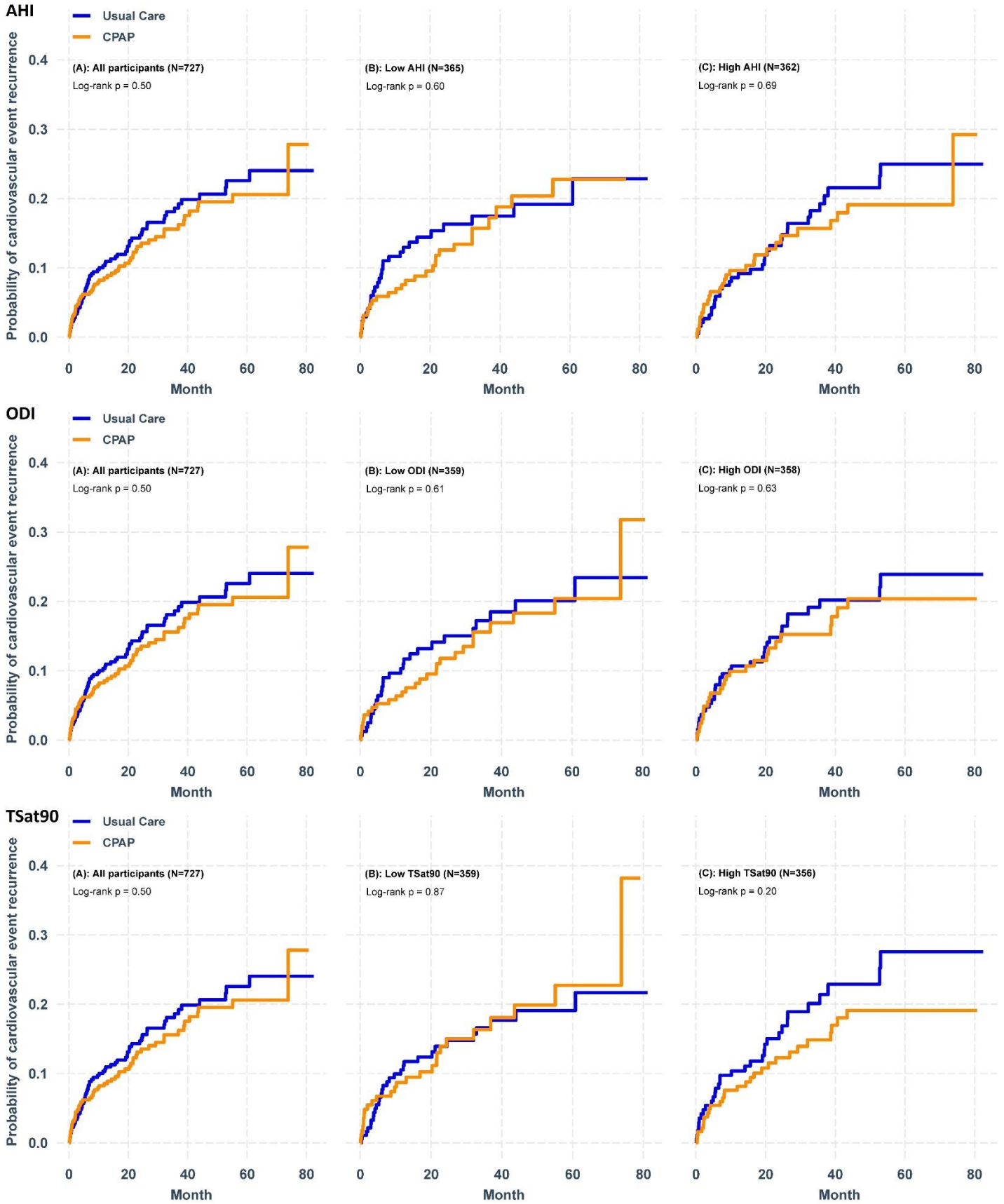(C): High TSat90 (N=356)
Log-rank p = 0.20

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Table S1. Characteristics of the included *vs.* excluded participants from the ISAACC cohort. Data are presented as the median [p25;p75] for quantitative variables and n (%) for qualitative variables. Definitions of abbreviations: ACE = angiotensin-converting enzyme; AHI = apnoea-hypopnoea index; BMI = body mass index; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; ESS = Epworth sleepiness scale; ODI = oxygen desaturation index; OSA = obstructive sleep apnoea; SaO_2 = oxygen saturation; TSat90 = time with SaO_2 <90%.

	INCLUDED	EXCLUDED
	n = 727	n = 528
Clinical data		
Demographic/anthropometric		
Age (years)	59.0 [52.5;67.0]	60.0 [54.0;68.0]
Sex		
Male	614 (84.5%)	444 (84.1%)
Female	113 (15.5%)	84 (15.9%)
BMI (kg/m^2)	29.0 [26.4;31.9]	29.0 [26.4;31.8]
Smoking status		
Never	173 (23.8%)	134 (25.4%)
Former	195 (26.8%)	158 (29.9%)
Current	359 (49.4%)	236 (44.7%)
Drinking status		
Never	536 (75.6%)	347 (67.5%)
Former	6 (0.85%)	7 (1.36%)
Current	167 (23.6%)	160 (31.1%)
Comorbidities		
Diabetes	194 (26.7%)	135 (25.6%)
Hypertension	408 (56.1%)	299 (56.6%)
Dyslipidaemia	424 (58.3%)	294 (55.7%)
Chronic pneumopathy	48 (6.60%)	26 (4.92%)
Previous CVD	141 (19.4%)	117 (22.2%)
Medication use		
Insulin	37 (5.09%)	43 (8.14%)
Oral antidiabetic drug	157 (21.6%)	104 (19.7%)
ACE inhibitors	166 (22.8%)	134 (25.4%)
Beta-blockers	142 (19.5%)	115 (21.8%)
Diuretic agents	137 (18.8%)	93 (17.6%)
Calcium-channel blockers	101 (13.9%)	78 (14.8%)
Angiotensin II receptor blockers	117 (16.1%)	90 (17.0%)
Lipid-lowering drugs	274 (37.7%)	198 (37.5%)
Antiplatelet drugs	164 (22.6%)	129 (24.4%)
Anticoagulants	32 (4.40%)	33 (6.25%)

Sleep data		
AHI (events/h)	30.8 [21.0;45.8]	32.0 [21.4;46.9]
ODI (events/h)	27.2 [17.0;43.1]	25.7 [14.4;40.8]
Mean SaO$_2$ (%)	93.0 [91.9;94.0]	92.8 [91.4;94.0]
Minimum SaO$_2$ (%)	84.0 [79.0;87.0]	83.0 [79.0;86.0]
TSat90 (%)	3.30 [0.50;12.0]	4.10 [0.95;16.0]
Somnolence (ESS)	5.00 [3.00;7.00]	6.00 [4.00;8.00]
Treatment allocation		
CPAP	362 (49.8%)	267 (50.6%)
Usual Care	365 (50.2%)	261 (49.4%)
Incidence of primary endpoint		
No	610 (83.9%)	439 (83.1%)
Yes	117 (16.1%)	89 (16.9%)

Table S2. Baseline characteristics of the study cohort by treatment allocation. Data are presented as the median [p25;p75] for quantitative variables and n (%) for qualitative variables. Definitions of abbreviations: ACE = angiotensin-converting enzyme; AHI = apnoea-hypopnoea index; BMI = body mass index; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; ESS = Epworth sleepiness scale; HB = hypoxic burden; ODI = oxygen desaturation index; OSA = obstructive sleep apnoea; SaO_2 = oxygen saturation; TSat90 = time with SaO_2 <90%.

	USUAL CARE n = 365	CPAP TREATMENT n = 362	p value	N
Clinical data				
Demographic/anthropometric				
Age (years)	59.0 [53.0;67.0]	59.0 [52.0;66.8]	0.314	727
Sex			0.508	727
Male	312 (85.5%)	302 (83.4%)		
Female	53 (14.5%)	60 (16.6%)		
BMI (kg/m^2)	29.1 [26.5;31.8]	28.7 [26.2;32.0]	0.429	716
Smoking status			0.687	727
Never	86 (23.6%)	87 (24.0%)		
Former	103 (28.2%)	92 (25.4%)		
Current	176 (48.2%)	183 (50.6%)		
Drinking status			0.367	709
Never	274 (77.4%)	262 (73.8%)		
Former	4 (1.13%)	2 (0.56%)		
Current	76 (21.5%)	91 (25.6%)		
Comorbidities				
Diabetes	88 (24.1%)	106 (29.3%)	0.136	727
Hypertension	206 (56.4%)	202 (55.8%)	0.922	727
Dyslipidaemia	205 (56.2%)	219 (60.5%)	0.267	727
Chronic pneumopathy	27 (7.40%)	21 (5.80%)	0.473	727
Previous CVD	71 (19.5%)	70 (19.3%)	1.000	727
Medication use				
Insulin	18 (4.93%)	19 (5.25%)	0.979	727
Oral antidiabetic drug	72 (19.7%)	85 (23.5%)	0.254	727
ACE inhibitors	88 (24.1%)	78 (21.5%)	0.463	727
Beta-blockers	74 (20.3%)	68 (18.8%)	0.680	727
Diuretic agents	68 (18.6%)	69 (19.1%)	0.957	727
Calcium-channel blockers	56 (15.3%)	45 (12.4%)	0.304	727
Angiotensin II receptor blockers	54 (14.8%)	63 (17.4%)	0.392	727
Lipid-lowering drugs	129 (35.3%)	145 (40.1%)	0.217	727
Antiplatelet drugs	82 (22.5%)	82 (22.7%)	1.000	727
Anticoagulants	17 (4.66%)	15 (4.14%)	0.875	727

Sleep data				
AHI (events/h)	32.7 [20.8;45.4]	29.8 [21.2;46.2]	0.835	727
ODI (events/h)	29.8 [17.5;44.5]	25.6 [16.8;42.2]	0.088	717
Mean SaO$_2$ (%)	93.0 [91.9;94.1]	93.0 [91.9;94.0]	0.591	723
Minimum SaO$_2$ (%)	84.0 [79.0;87.0]	83.0 [79.0;87.0]	0.316	719
TSat90 (%)	2.90 [0.40;12.0]	3.70 [0.70;11.9]	0.293	715
HB (%min/h)	70.9 [49.9;104]	74.5 [53.9;103]	0.270	727
Somnolence (ESS)	5.00 [3.00;7.00]	5.00 [3.00;7.00]	0.670	727

Table S3. Baseline characteristics of the study cohort by categories of baseline HB. Data are presented as the median [p25;p75] for quantitative variables and n (%) for qualitative variables. Significant p values (p <0.05) are presented in bold. Definitions of abbreviations: ACE = angiotensin-converting enzyme; AHI = apnoea-hypopnoea index; BMI = body mass index; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; ESS = Epworth sleepiness scale; HB = hypoxic burden; ODI = oxygen desaturation index; OSA = obstructive sleep apnoea; SaO_2 = oxygen saturation; TSat90 = time with SaO_2 <90%.

	Low HB (HB ≤73.1 %min/h)	High HB (HB >73.1 %min/h)	p value
	n = 364	n = 363	
Clinical data			
Demographic/anthropometric			
Age (years)	60.0 [53.0;67.0]	59.0 [52.0;67.0]	0.849
Sex			0.55
Male	60 (16.5%)	53 (14.6%)	
Female	304 (83.5%)	310 (85.4%)	
BMI (kg/m^2)	28.1 [25.5;30.8]	29.8 [27.3;32.9]	**<0.001**
Smoking status			0.904
Never	87 (23.9%)	86 (23.7%)	
Former	95 (26.1%)	100 (27.5%)	
Current	182 (50.0%)	177 (48.8%)	
Drinking status			0.934
Never	266 (75.1%)	270 (76.1%)	
Former	3 (0.85%)	3 (0.85%)	
Current	85 (24.0%)	82 (23.1%)	
Comorbidities			
Diabetes	90 (24.7%)	104 (28.7%)	0.266
Hypertension	192 (52.7%)	216 (59.5%)	0.078
Dyslipidemia	214 (58.8%)	210 (57.9%)	0.856
Chronic pneumopathy	24 (6.59%)	24 (6.61%)	1.000
Previous CVD	62 (17.0%)	79 (21.8%)	0.129
Medication use			
Insulin	13 (3.57%)	24 (6.61%)	0.090
Oral antidiabetic drug	67 (18.4%)	90 (24.8%)	**0.045**
ACE inhibitors	81 (22.3%)	85 (23.4%)	0.775
Beta-blockers	65 (17.9%)	77 (21.2%)	0.295
Diuretic agents	65 (17.9%)	72 (19.8%)	0.557
Calcium-channel blockers	43 (11.8%)	58 (16.0%)	0.129
Angiotensin II receptor blockers	52 (14.3%)	65 (17.9%)	0.220

Lipid-lowering drugs	127 (34.9%)	147 (40.5%)	0.138
Antiplatelet drugs	79 (21.7%)	85 (23.4%)	0.643
Anticoagulants	16 (4.40%)	16 (4.41%)	1
Sleep data			
AHI (events/h)	22.8 [17.7;31.2]	42.7 [30.6;57.5]	**<0.001**
ODI (events/h)	18.4 [13.6;25.6]	39.6 [29.3;52.8]	**<0.001**
Mean SaO$_2$ (%)	93.6 [92.2;94.6]	92.6 [91.1;93.6]	**<0.001**
Minimum SaO$_2$ (%)	86.0 [81.5;88.0]	82.0 [77.0;85.0]	**<0.001**
TSat90 (%)	0.90 [0.10;4.77]	7.20 [2.10;24.6]	**<0.001**
HB (%min/h)	51.8 [41.1;62.2]	104 [84.8;140]	**<0.001**
Somnolence (ESS)	4.00 [3.00;6.00]	5.00 [3.00;8.00]	**<0.001**