

Effect of Sleep-Disordered Breathing on Appropriate Implantable Cardioverter-Defibrillator Therapy in Patients With Heart Failure A Systematic Review and Meta-Analysis

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Background—Patients with heart failure and reduced ejection fraction are at increased risk of malignant ventricular arrhythmias. Implantable cardioverter-defibrillator (ICD) is recommended to prevent sudden cardiac death in some of these patients. Sleep-disordered breathing (SDB) is highly prevalent in this population and may impact arrhythmogenicity. We performed a systematic review and meta-analysis of prospective studies that assessed the impact of SDB on ICD therapy.

Methods and Results—Relevant prospective studies were identified in the Ovid MEDLINE, EMBASE, and Google Scholar databases. Weighted risk ratios of the association between SDB and appropriate ICD therapies were estimated using random effects meta-analysis. Nine prospective cohort studies (n=1274) were included in this analysis. SDB was present in 52% of the participants. SDB was associated with a 55% higher risk of appropriate ICD therapies (45% versus 28%; risk ratio, 1.55; 95% confidence interval, 1.32–1.83). In a subgroup analysis based on the subtypes of SDB, the risk was higher in both central (risk ratio, 1.50; 95% confidence interval, 1.11–2.02) and obstructive (risk ratio, 1.43; 95% confidence interval, 1.01–2.03) sleep apnea.

Conclusions—SDB is associated with an increased risk of appropriate ICD therapy in patients with heart failure and reduced ejection fraction. (*Circ Arrhythm Electrophysiol.* 2017;10:e004609. DOI: 10.1161/CIRCEP.116.004609.)

Key Words: death, sudden, cardiac ■ defibrillators, implantable ■ heart failure ■ meta-analysis ■ sleep apnea syndrome

Heart failure (HF) imposes a major public health burden in the United States with a prevalence of 5.1 million and accounts for >30 billion dollars in total costs each year.^{1,2} Sudden arrhythmic death constitutes an important cause of mortality in patients with HF. In randomized controlled trials, implantable cardioverter-defibrillator (ICD) therapy was associated with a reduction in all-cause mortality in patients with a previous cardiac arrest and in some patients with HF and reduced ejection fraction ($\leq 35\%$) who never had cardiac arrest.^{3–7}

Sleep-disordered breathing (SDB), presenting as either obstructive sleep apnea (OSA) or central sleep apnea syndrome (CSA with Cheyne–Stokes breathing) is highly prevalent in patients with HF and is associated with increased cardiovascular mortality.^{8,9} The pathophysiological consequences of SDB, including intermittent hypoxia, autonomic dysfunction, and repetitive intrathoracic pressure changes in the case of OSA, may play a role in adverse outcomes in this population.¹⁰

Several investigations have examined the impact of SDB on the incidence of malignant ventricular arrhythmias in

higher risk HF patients, using data from their ICD.^{11–19} These studies, derived from single-center experiences, had various study designs and yielded mixed results. Therefore, we sought to perform a systematic review and meta-analysis of the published data to evaluate the association of underlying untreated SDB with the incidence of appropriate ICD therapy in patients with HF.

Methods

The present review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).²⁰

Search Strategy

Two independent reviewers (Y.K. and R.K.) in collaboration with a biomedical librarian searched Ovid MEDLINE, EMBASE, and Google Scholar from January 1990 through December 2015. We included broad search terms by using sleep apnea, ventricular arrhythmia and implantable cardioverter defibrillator, sleep disordered breathing, malignant arrhythmia, and implantable devices.

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WHAT IS KNOWN

- Sleep-disordered breathing (SDB) is common in patients with heart failure (HF).
- SDB is associated with increased cardiovascular mortality in patients with HF, of which malignant ventricular arrhythmias may play an important role.

WHAT THE STUDY ADDS

- This meta-analysis of prospective studies (n=9) found an increased risk of appropriate implantable cardioverter-defibrillator therapy in HF patients with SDB compared to those without SDB.
- These findings infer that SDB may be associated with an increased risk of potentially life-threatening arrhythmias in patients with HF.

Study Selection

We retrieved and read the abstracts from those with a relevant title. If necessary, we read the full text when the abstract was inconclusive. Results from this step were compared, and any discrepancies were resolved through consensus. Finally, we reviewed the reference lists from the included studies to find any other eligible studies.

To be eligible, studies had to fulfill the following criteria: (1) randomized controlled trial or prospective cohort study; (2) all study subjects had objective assessment of SDB; (3) all study subjects had an ICD; and (4) reported information on appropriate ICD therapies (shock or antitachycardia pacing) based on the presence or absence of SDB. Studies reporting different measures of risk ratio (RR), such as the hazard ratio or odds ratio, were included in this meta-analysis.

Data Extraction

Data were extracted from each of the identified studies and included year of publication, study design, subject characteristics, type of SDB (OSA or CSA), incidence of appropriate ICD therapies, and sufficient data to allow calculation of the RR and 95% confidence interval (CI). One study primarily focused on the treatment effect of SDB on ICD therapy.¹¹ In that study, we included the patient group without SDB and a group with SDB but refused treatment of SDB. Finally, we also extracted findings on circadian variation of ICD therapy when available. Any disagreements were resolved by discussion and consensus.

Risk of Bias Assessment

Assessment of risk of bias was conducted as described by Downs and Black²¹ by 2 independent reviewers (Y.K. and R.K.). We categorized each study as high, medium, or low risk of bias in reporting, external validity, internal validity bias, internal validity confounding, and power.²²

Statistical Analysis

Because the incidence of ICD therapy is a clinically more relevant outcome than the time to first ICD therapy, in this analysis, we chose RR rather than hazard ratio to show the difference in risk of ICD therapy between patients with versus without SDB. Moreover, results based on the time-to-event analysis were not available in all the included studies. Unadjusted RRs from individual studies were pooled to derive an overall RR and 95% CI using random effects models. The primary analysis included all studies involving subjects with SDB, including studies with undifferentiated SDB, studies that differentiated OSA and CSA, and studies with either OSA or CSA. For studies that differentiated OSA and CSA, we combined the 2 subtypes to derive combined SDB cases for the main analysis. We performed a

secondary analysis separating studies into those with either OSA or CSA. For those studies reporting only crude data, we calculated the RR and CI. Any number of appropriate ICD therapies occurring within a patient was counted as one event. Heterogeneity across studies was assessed using I^2 statistics, with a value $>50\%$ considered significant heterogeneity. A formal test for publication bias was not performed because of the limited number of eligible studies. All analyses were performed with Stata 13.1 (StataCorp. 2013; Stata Statistical Software: Release 13; StataCorp LP, College Station, TX).

Results**Study Selection**

We identified 1025 nonduplicate publications, of which 1014 were excluded by title/abstract screening (Figure 1). After reviewing the remaining 11 manuscripts, 2 were excluded (one focused only on inappropriate ICD therapy²³ and the other study did not allow us to derive a RR²⁴). The final meta-analysis was conducted from 9 prospective cohort studies published between 1999 and 2013, with a total of 1274 patients. Four studies reported SDB without differentiating subtypes.^{13,17-19} Three studies reported OSA and CSA separately.^{12,14,16} Two studies included patients with only CSA.^{11,15} As a result, the number of eligible studies was 9 for our main analysis, which included any SDB and 3 and 5 for the separate analysis of OSA and CSA, respectively (Table 1). The recent SERVE-HF trial (The Treatment of SDB With Predominant CSA by Adaptive Servo Ventilation in Patients With HF), in which patients with HF and CSA were randomized to adaptive servo ventilation (ASV, a form of continuous positive airway pressure therapy) or no ASV to treat for CSA included appropriate ICD therapy as one of the components of the primary composite outcome. However, this study was not included in our analysis because it only included patients with SDB, having an intervention group (SDB with ASV) versus a control group (SDB without ASV) but not those without SDB. Moreover, only a portion of the participants had ICDs, and the ICD data were considered incomplete because of early termination of the study.²⁵

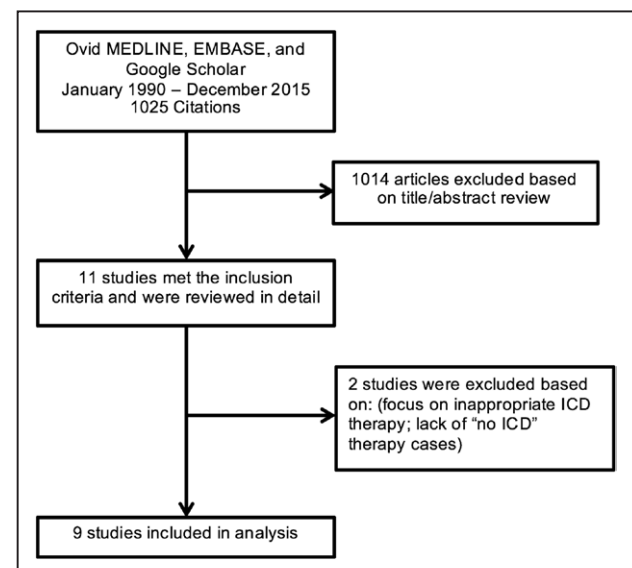


Figure 1. Study flow diagram. ICD indicates implantable cardioverter-defibrillator.

Table 1. Summary of Prospective Cohort Studies of SDB and ICD Therapy

Author, Year Published	N	Country	ICD Indication (1° or 2° Prevention)	Patients With CRT-D Included	Programming for Appropriate ICD Therapy Equally Balanced Between the Groups	Average Detection Rate for VT/VF for SDB (–) vs SDB (+), [Beats per min]	Definition of SDB	Method of SDB Diagnosis	Subtype of SDB Reported	Follow-Up Duration, mo
Fries et al, ¹⁴ 1999	40	Germany	2°	No	NR	NR	AHI >10	Attended PSG	CSA and OSA separately	24
Staniforth et al, ¹⁵ 2005	101	United Kingdom	Both	Yes	NR	NR	Sinusoidal pattern of O ₂ saturation and 4% desaturation rate of >15 dips/h	Overnight pulse oximetry	CSA only	6
Serizawa et al, ¹⁷ 2008	71	Japan	Both	No	NR	NR	AHI ≥10	Unattended cardiorespiratory polygraphy	Combined	6
Tomaello et al, ¹³ 2010	22	Italy	1°	No	Yes	VT: 150±14 vs 151±16 VF: 191±15 vs 190±14	AHI ≥10	Unattended cardiorespiratory polygraphy	Combined	19±14
Bitter et al, ¹² 2011	255	Germany	1°	Yes	NR	NR	AHI ≥5 or AHI ≥15*	Unattended cardiorespiratory polygraphy	CSA and OSA separately	48
Zeidan-Shwiri et al, ¹⁸ 2011	45	Israel	Both	Yes	Yes	VT: 152±4 vs 149±7 VF: 212±18 vs 210±17	AHI ≥10	Attended PSG	Combined	12
Bitter et al, ¹¹ 2013	403	Germany	Both	Yes	Yes	VT: 171 (170, 171) vs 171 (170, 171) VF: 200 (200, 200) vs 200 (200, 200)	AHI ≥15	Unattended cardiorespiratory polygraphy	CSA only	21±25
Grimm et al, ¹⁶ 2013	204	Germany	Both	Yes	Yes	VT: 181 vs 181 (OSA) vs 179 (CSA)	AHI ≥5	Attended PSG or unattended cardiorespiratory polygraphy	CSA and OSA separately	38±26
Kreuz et al, ¹⁹ 2013	133	Germany	1°	Yes	Yes	VT: 162±18 vs 160±27 VF: 245±6 vs 250±4	AHI ≥10	Unattended cardiorespiratory polygraphy	Combined	24±8

For column Average detection rate for VT/VF, values are given as mean±SD unless specified as median (25th–75th percentile). AHI indicates apnea–hypopnea index; ASV, adaptive servo ventilation; CRT-D, cardiac resynchronization therapy-defibrillator; CSA, central sleep apnea; CSR, Cheyne–Stokes respiration; ICD, implantable cardioverter-defibrillator; NR, not reported; OSA, obstructive sleep apnea; PSG, polysomnography; SDB, sleep-disordered breathing; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*AHI ≥15 events/h was used for this analysis.

Risk of Bias

Risk of bias analysis suggested low risk of reporting bias in all studies except for the study by Fries et al¹⁴, which had high risk; medium risk of external validity bias in all studies; low risk of internal validity bias in all studies except for the study by Fries et al,¹⁴ Kreuz et al,¹⁹ and Tomaello et al,¹³ which had high risk; medium risk of internal validity confounding bias in all studies except for the study by Fries et al,¹⁴ Kreuz et al,¹⁹ and Staniforth et al,¹⁵ which had high risk; and high risk of bias because of lack of power in all studies (Figure 2).

Summary of all Eligible Studies

Of the 9 included studies, 5 were conducted in Germany and 1 each in the United Kingdom, Italy, Japan, and Israel (Table 1). All studies except 2 were published within the past 10 years. All of the included studies used a prospective cohort study design. Sample size of the studies varied widely, ranging from 22 to 255 patients. Mean observation time varied significantly, ranging from 6 months to 4 years (median observation time: 22 months). Four studies only included patients who received an ICD for either primary (n=410) or secondary (n=40) prevention of sudden cardiac death (SCD),

whereas the other studies included patients with both indications. For SDB diagnoses, the most commonly used method was unattended respiratory polygraphy (n=5) followed by full-standard polysomnography (n=3). The remaining study by Staniforth et al¹⁵ used overnight oximetry, which was internally validated in a subgroup of participants against the standard polysomnography. The definition of SDB differed between studies using apnea/hypopnea index cut points of 5, 10, or 15 events per hour. The study by Staniforth et al used >15/h of any event with oxygen desaturation $\geq 4\%$ as a cut point to define CSA in the presence of a sinusoidal pattern of nocturnal oxygen desaturation. In all studies, ICDs were programmed at the discretion of clinicians. Although 5 studies reported average ventricular tachycardia and ventricular fibrillation detection thresholds, with similar settings between the 2 groups with and without SDB,^{11,13,16,18,19} the rest of the studies did not specify such information. Patient characteristics in the included studies are described in Table 2. The proportion of patients with moderate-to-severe symptomatic HF (New York Heart Association class III–IV) markedly varied from 25%¹⁴ to 75%.¹⁹ Study participants were on average overweight, with mean body mass index between 25

and 30 kg/m², except 1 study, in which mean body mass index was within the normal range at 23.3 kg/m².

Baseline demographic characteristics, left ventricular ejection fraction, HF symptom class, and proportion of antiarrhythmic agents and β -blocker for patients with and without SDB were well balanced, whereas body mass index was higher in those with SDB versus without those SDB in most studies (Table 1).^{16,17,19} The majority of patients were receiving β -blocker and angiotensin-converting enzyme inhibitor therapy in the most recent 7 studies (range, 81%–100%) but not in the 2 earliest studies (range: 25%–59%). Use of antiarrhythmic therapy was balanced between the 2 groups in all the studies. Incidence of appropriate ICD therapy varied widely among studies, $\approx 25\%$ (during 6-month follow-up) to as high as 47% and 73% (during 12-month follow-up) for those without and with SDB, respectively (Figure 3).

Meta-Analysis of Appropriate ICD Therapy

Combined studies included 658 patients with SDB and 616 without SDB. The pooled analysis using all studies found that SDB was associated with a 55% higher risk of appropriate ICD therapies (45% versus 28%; RR, 1.55; 95% CI, 1.32–1.83). Heterogeneity across the studies was negligible with an I^2 of 5.6% (Figure 4). The risk was higher in both subtypes of SDB: CSA (RR, 1.50; 95% CI, 1.11–2.02; $I^2=47.2\%$; Figure 5) and OSA (RR, 1.43; 95% CI, 1.01–2.03; $I^2=0\%$; Figure 6).

Circadian Variation of Appropriate ICD Therapy

Four studies attempted to determine circadian variation of ICD therapy. The individual study data are summarized in Table 3. The 2 earliest studies that reported no difference in ICD therapy in patients with versus those without SDB also failed to show any circadian variation, whereas the 2 other studies with significant findings in the primary analysis showed evidence of nocturnal peaking of ICD therapy in the SDB group. In these 2 studies, incidence of ICD therapy between 12:00 and 6:00 AM was higher in those with SDB versus those without SDB.

Discussion

The purpose of this systematic review and meta-analysis was to review a growing number of studies assessing the clinical impact of SDB on the incidence of appropriate ICD therapy, a surrogate for malignant ventricular arrhythmia. Our meta-analysis showed that in patients with HF and reduced ejection fraction, the risk of appropriate ICD therapy is higher among patients with SDB compared with those without. Separate pooled analyses limited to studies with either subtype of SDB (ie, OSA or CSA) showed consistent results. The results of this study support the emerging body of evidence about the adverse impact of SDB on HF outcomes and highlights arrhythmogenicity as one of the potentially important mediating mechanisms.²⁶

Patients with SDB are at higher risk of ventricular ectopy and arrhythmias.²⁷ SDB has also been suggested as a risk factor for SCD in the general population. A study by Gami et al²⁸ found that nocturnal hypoxemia, a surrogate marker for OSA, was an independent predictor of SCD

	Reporting	External Validity	Internal Validity-Bias	Internal Validity-Confounding	Power
Fries	Red	Yellow	Red	Red	Red
Staniforth	Green	Yellow	Green	Red	Red
Serizawa	Green	Yellow	Green	Yellow	Red
Tomaello	Green	Yellow	Red	Yellow	Red
Bitter (2011)	Green	Yellow	Green	Yellow	Red
Zeidan-Shwiri	Green	Yellow	Green	Yellow	Red
Bitter (2013)	Green	Yellow	Green	Yellow	Red
Grimm	Green	Yellow	Green	Yellow	Red
Kreuz	Green	Yellow	Red	Red	Red

Figure 2. Risk of bias assessment. Green indicates low risk of bias, yellow indicates medium risk of bias, and red indicates high risk of bias.

Table 2. Baseline Characteristics of Patients With and Without Sleep Disordered Breathing

Variable	Fries et al ¹⁴		Staniforth et al ¹⁵		Serizawa et al ¹⁷		Tomaeillo et al ¹³		Bitter et al ¹²		Zeidan-Shwiri et al ¹⁸		Bitter et al ¹¹		Grimm et al ¹⁶		Kreuz et al ¹⁹	
	SDB (N=16, 40%)	No SDB (N=24)	SDB (N=42, 42%)	No SDB (N=59)	SDB (N=47, 66%)	No SDB (N=24)	SDB (N=17, 77%)	No SDB (N=5)	SDB (N=112, 44%)	No SDB (N=143)	SDB (N=26, 58%)	No SDB (N=19)	SDB (N=134, 66%)	No SDB (N=70)	SDB (N=82, 62%)	No SDB (N=51)		
Age, y	65±8	65±8	68.1	65.6	62±11	54±16	65±8	60±12	68.6	66.1	60±10	56±10	61.4	57±15	63±11	61±12		
Men, %	100	96	NR	NR	89	71	100	100	86	69	54	37	91	71	NR	NR		
BMI, kg/m ²	28±4	25±4	28	26	24±4	22±4	28±3	27±2	27	26	29±6	27±5	27	26±4	29±1	25±2		
Ischemic heart disease/previous MI, %	81	71	86	76	11	17	60	80	47	40	62	60	53	31	68	76		
Nonischemic cardiomyopathy, %	19	17	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	44	59	32	24		
NYHA class II, %	75	63	40	36	51	33	NR	NR	49	43	NR	NR	37	41	26	24		
NYHA class III-IV, %	25	25	50	34	9	0	NR	NR	51	57	NR	NR	57	52	74	76		
Mean AHI, events/hr	32	NR	NR	NR	23±11	4±3	25±12	NR	25	4	29±15	6±3	28	2±1	23±8	5±2		
Atrial fibrillation, %	NR	NR	19	8	NR	NR	0	0	12	12	59	62	17	13	30	27		
Hypertension, %	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	53	47	NR	NR	71	53		
Diabetes mellitus, %	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29	32	NR	NR	33	21		
Creatinine, mg/dL	NR	NR	NR	NR	NR	NR	NR	NR	1.4	1.2	1.0±0.4	0.9±0.3	1.4	1.1	1.3±0.4	1.2±0.3		
β-Blocker therapy, %	13	33	64	56	96	88	100	100	92	90	91	92	86	71	98	98		
ACE/AT1 inhibitors, %	NR	NR	98	83	70	92	100	100	97	99	79	82	89	81	98	96		
Aldosterone blockers, %	NR	NR	38	27	NR	NR	NR	NR	71	70	NR	NR	52	53	NR	NR		
Antiarrhythmic therapy, %	75	58	24	22	43	63	NR	NR	36	31	88	89	18	11	NR	NR		
Digitalis, %	NR	NR	NR	NR	NR	NR	NR	NR	60	56	100	96	38	46	NR	NR		
Diuretics, %	NR	NR	90	64	70	75	NR	NR	98	97	NR	NR	81	79	NR	NR		
LVEF by Echo, %	35	37±14	29	37	31±12	34±11	29±5	26±6	27	30	NR	NR	29	30±10	26±5	28±6		
LVEF ≤35%	NR	NR	NR	NR	100	100	NR	NR	100	100	62	42	NR	NR	NR	NR		
LVEDd, mm	NR	NR	NR	NR	NR	NR	NR	NR	70	68	NR	NR	65	64±9	NR	NR		
ICD primary prevention, %	0	0	29	24	36	42	100	100	100	100	42	47	58	60	100	100		
ICD secondary prevention, %	100	100	71	76	64	58	0	0	0	0	58	53	42	40	0	0		

ACE indicates angiotensin-converting enzyme; AHI, apnea-hypopnea index; AT1, angiotensin II receptor type 1; BMI, body mass index; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic diameter; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association; and SDB, sleep-disordered breathing.

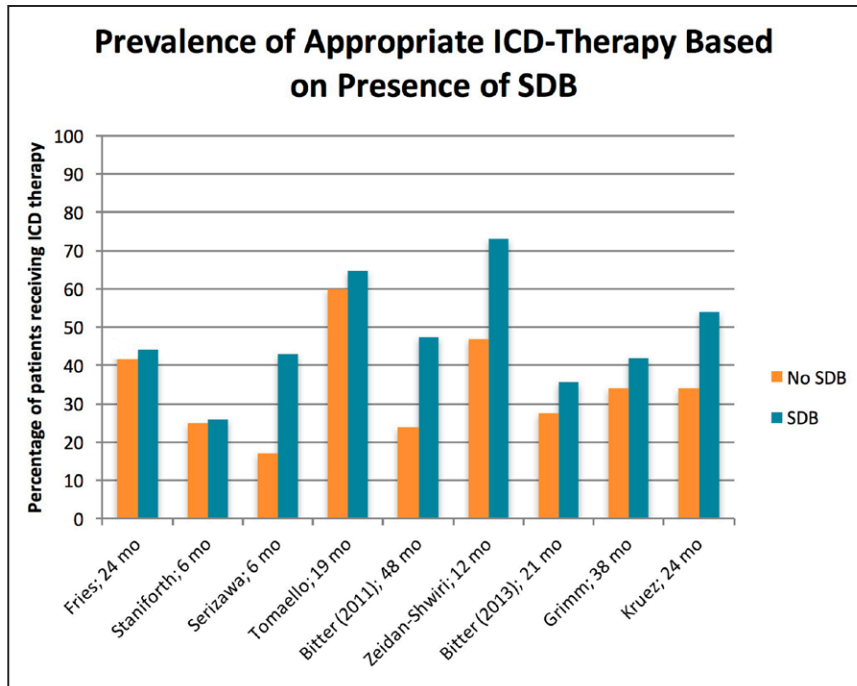


Figure 3. Prevalence of appropriate implantable cardioverter-defibrillator (ICD) therapy based on presence or absence of sleep-disordered breathing (SDB). Reported as prevalence of ICD therapies through mean number of months of observation.

among a sleep clinic cohort. Patients with SDB also carry a higher risk of nonsustained ventricular tachycardia and complex ventricular ectopy during sleep.²⁹ Several electrocardiography-based studies have showed that patients with SDB exhibit abnormal ventricular repolarization, including prolongation of the QTc interval, prolongation of the interval between the peak and end of the T wave (Tp-e), the Tp-e/QT ratio, and the Tp-e/QTc ratio, which have all been implicated as risk factors for ventricular arrhythmogenesis.^{30,31}

SDB is common in patients with HF with a reported prevalence of 50% to 70%.^{32,33} Given such a disproportionately high prevalence of SDB and its association with SCD and electrocardiographic markers of ventricular arrhythmogenesis, whether or not SDB increases the risk of malignant

ventricular arrhythmia in patients with HF, the highest risk group for SCD, is a clinically important question.

We observed a wide range of event rates across the selected studies, which could, in part, be attributed to differences in follow-up, patient characteristics, and ICD settings for delivering therapy. In spite of this, the studies revealed a higher incidence of appropriate ICD therapy among those with SDB versus those without. In contrast to the 7 most recently conducted studies, the 2 earliest studies did not reveal an association between SDB and the incidence of ICD therapy.

The secondary analysis also showed an increased risk of appropriate ICD therapy across both subtypes of SDB. CSA is a well-established risk factor for high mortality in HF. Our finding of increased risk of ICD therapy in patients with CSA suggests that malignant arrhythmia may be one of the

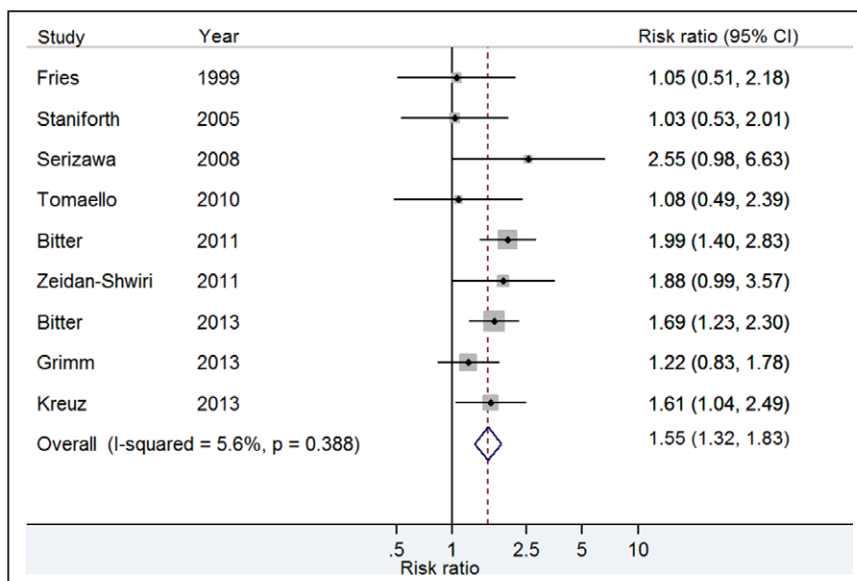


Figure 4. Risk of appropriate implantable cardioverter-defibrillator therapy in patients with sleep-disordered breathing (SDB) vs those without SDB. CI indicates confidence interval.

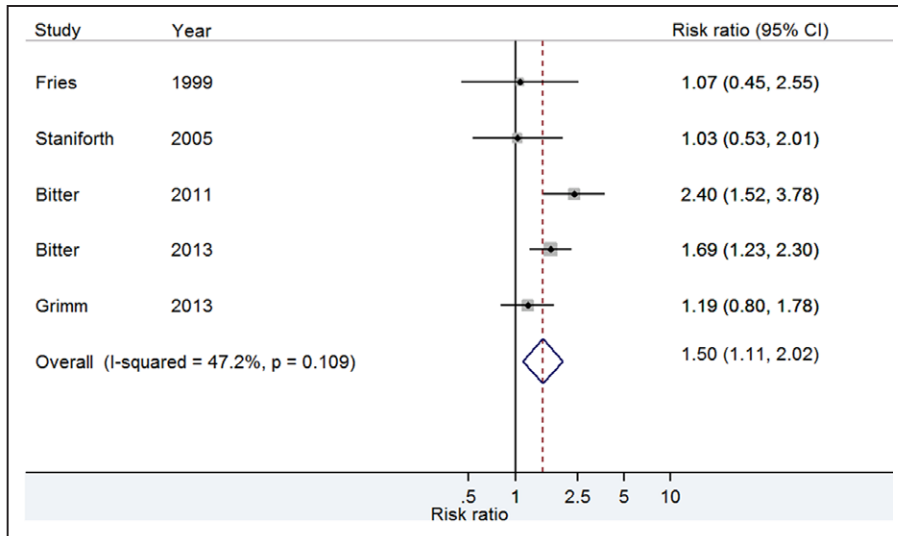


Figure 5. Risk of appropriate implantable cardioverter-defibrillator therapy in patients with central sleep apnea (CSA) vs those without CSA. CI indicates confidence interval.

mechanisms of mortality in HF patients with CSA. However, unlike CSA, the association between OSA and ICD therapy needs to be carefully interpreted given the small number of studies included in the analysis. Although both subtypes are common in HF, as reaffirmed in this analysis, CSA is primarily only found in HF, which may be why the majority of these studies defined patients by the presence or absence of CSA or simply by SDB, while often disregarding OSA. It is, therefore, highly plausible that OSA is under-represented in our study.

Although the pathophysiologies of OSA and CSA respiratory events are unique, both types frequently coexist in patients with HF in a given night.³⁴ Thus, the classification of SDB can be somewhat arbitrary. In addition, both respiratory events can lead to a common pathway of intermittent hypoxemia, arousal, and ultimately heightened sympathetic activity,^{35,36} which may account for the arrhythmogenic effect of both subtypes.³⁷ In addition, the large hemodynamic shift in OSA is thought to be arrhythmogenic via mechanical stretching of the heart and subsequent mechanoelectric feedback.³⁸ Taken together, although the association between SDB as a group and the incidence of appropriate ICD therapy seems to be present, how such an association truly differs by subtypes of SDB warrant further investigation.

Although it was not addressed in this study, patients with SDB and underlying HF may also be subject to serious

bradyarrhythmias in sleep.³⁹ Nocturnal bradyarrhythmias, including prolonged sinus pauses occurring during apneic episodes, are much more prevalent in patients with SDB than those without.⁴⁰⁻⁴² Excessive parasympathetic response to apneic respiratory events is thought to be an underlying mechanism for bradyarrhythmias. Such a response can be exaggerated by impaired baroreflexes, which is frequently encountered in HF.⁴³ Although severe bradyarrhythmias such as sinus pauses or high-grade atrioventricular block occurring in sleep have been generally considered benign, the prevalence and its potentially deleterious impact on the outcome of patients with HF in association with SDB may merit future studies.⁴⁴ Using ICD or other implantable recording data would likewise provide insightful answers to these questions.

Several studies included in our review also investigated circadian pattern of ICD therapy in patients with SDB, taking advantage of the unique ability of ICDs to record the timing of therapies. In a community-based study, Gami et al⁴⁵ showed distinctively different circadian peaking of SCD events in people with OSA. One would speculate such a pattern could be found in the HF setting as well. Our review showed mixed results in this regard. One report showed a predilection toward a nocturnal distribution of ICD therapy in HF patient with OSA but not with CSA.²⁴ The earliest 2 studies, one including

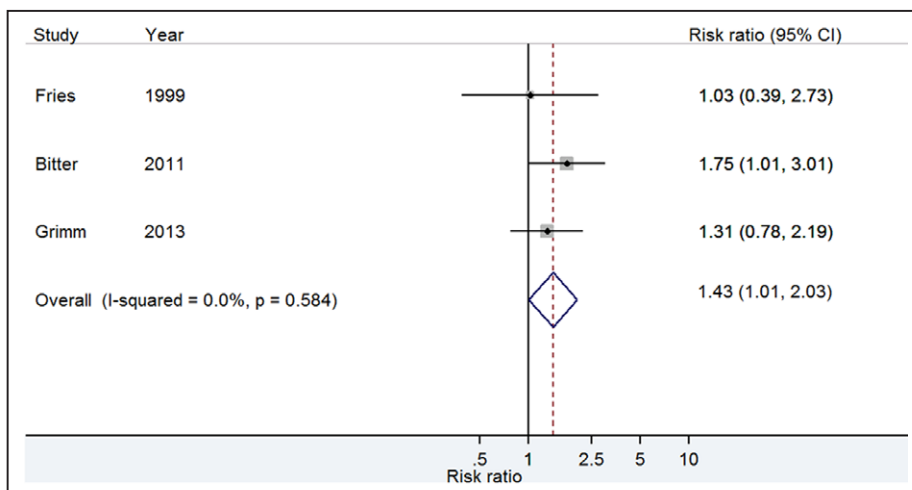


Figure 6. Risk of appropriate implantable cardioverter-defibrillator therapy in patients with obstructive sleep apnea (OSA) vs those without OSA. CI indicates confidence interval.

Table 3. Circadian Timing of Appropriate ICD Therapy Based on SDB

Fries et al ¹⁴ (N=40)	Staniforth et al ¹⁵ (N=101)	Serizawa et al ¹⁷ (N=71)	Zeidan-Shwiri et al ¹⁸ (N=45)
Frequency distribution of ICD therapy for the three 8-h intervals between CSA+ vs OSA+ vs SDB–	Frequency distribution of ICD therapy for the four 6-h intervals between CSA+ and CSA–	Frequency distribution of ICD therapy for the four 6-h intervals between SDB+ and SDB–	Frequency distribution of ICD therapy for the sleep and nonsleep hours between SDB+ and SDB–
10:00 PM to 6:00 AM: 19% vs 10% vs 8%	12:00 AM to 6:00 AM: 9.7% vs 1.4%	12:00 AM to 6:00 AM: 34% vs 13%; <i>P</i> =0.046	12:00 AM to 6:00 AM (sleep hours) 69% vs 32%; <i>P</i> =0.01
6:00 AM to 2:00 PM: 63% vs 47% vs 52%	6:00 AM to 12:00 PM: 35.6% vs 61.6%	6:00 AM to 12:00 PM: 29% vs 38%; <i>P</i> =NS	6:00 AM to 12:00 PM (nonsleep hours) 27% vs 16%; <i>P</i> =0.38
2:00 PM to 10:00 PM 18% vs 43% vs 40%	12:00 PM to 6:00 PM: 31.9% vs 25.9%	12:00 PM to 6:00 PM: 21% vs 17%; <i>P</i> =NS	
	6:00 PM to 12:00 AM: 22.7% vs 11.1%	6:00 PM to 12:00 AM: 16% vs 33%; <i>P</i> =NS	
Any evidence of differential diurnal pattern of ICD therapy between the two groups?	Any evidence of differential diurnal pattern of ICD therapy between the two groups?	Any evidence of differential diurnal pattern of ICD therapy between the two groups?	Any evidence of differential diurnal pattern of ICD therapy between the two groups?
No	No	Yes	Yes

CSA indicates central sleep apnea; ICD, implantable cardioverter-defibrillator; NS, not significant; OSA, obstructive sleep apnea; and SDB, sleep-disordered breathing.

OSA and CSA separately and the other including CSA only, did not demonstrate different diurnal patterns of ICD therapy based on SDB.^{14,15} Two other studies that showed nocturnal peaking of ICD therapy in the SDB group did not classify SDB by subtype.^{17,18} Thus, it is impossible to attribute the discrepant findings to difference in subtypes of SDB between the studies. Although inconclusive from our review, circadian pattern of ICD therapy deserves further investigation because such information can offer important insights into the pathophysiology of how SDB might lead to nocturnal SCD events.

Limitations

Several important limitations need to be acknowledged. Our study is limited by inherent bias related to the observational nature of included studies. There was a minor difference in the definition of SDB based on apnea/hypopnea index across the studies, although this should not have influenced the results as they were consistent for each study. Given differing rates of appropriate ICD therapy between primary prevention versus secondary prevention ICD indications,⁴⁶ a separate analysis would have been ideal, but this was not possible as most studies that included both indications did not differentiate them. However, it is important to note that even in these studies, the proportion of each indication was similar between the 2 groups (SDB versus no SDB). Each of the study results used for the meta-analysis was unadjusted. However, because the patient characteristics were generally well balanced between the 2 groups (SDB versus no SDB), this is unlikely to have made a substantial effect on the results. A wide range of observation periods across the studies could have impacted the meta-analysis of RR. However, there was no significant influence of length of follow-up on the results based on post hoc meta-regression analysis.

Future Directions

Our findings highlight the importance of recognizing SDB as a risk for increased appropriate ICD therapy in patients with HF. This, in conjunction with the high prevalence of SDB, may

justify screening for SDB in patients with HF undergoing ICD implantation. However, we recognize that at this time there is insufficient evidence as to whether treatment of SDB can effectively decrease the incidence of appropriate ICD therapy in patients with HF or not. There is conflicting evidence about whether treatment of SDB with continuous positive airway pressure therapy improves electrocardiographic markers of ventricular depolarization/repolarization and prevents malignant ventricular arrhythmias in non-HF population.²⁷ In the HF population, one observational study included in our analysis compared the event-free survival from appropriate ICD therapies between patients with and without treatment of CSA with Cheyne–Stokes breathing using ASV.¹¹ This study demonstrated a reduction of the events by ASV. Moreover, the recent SERVE-HF randomized controlled trial showed a trend toward lower appropriate ICD therapy in patients treated with ASV versus no ASV. However, there was an unexpected finding of increased all-cause and cardiovascular mortality with ASV.²⁵ Some have speculated the possibility of an adaptive, protective effect of CSA in HF, and therefore, treatment of it may have prevented this potential compensatory mechanism, thus causing a direct harmful effect.⁴⁷ With regard to the treatment effect of OSA, a recent randomized controlled study (SAVE trial [Sleep Apnea Cardiovascular Endpoints]) failed to show reduction in cardiovascular events by adding continuous positive airway pressure to usual care in patients with moderate-to-severe OSA and established cardiovascular disease.⁴⁸ However, this study included only a small proportion of patients with HF (1.8%) without any information about ICD therapy.

In this regard, future studies should investigate the therapeutic implications of SDB in HF patients in the prevention of appropriate ICD therapy and in the context of overall outcome.

Conclusions

In conclusion, this meta-analysis shows that SDB is associated with an increased incidence of appropriate ICD therapy in patients with HF and reduced ejection fraction.

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Disclosures

None.

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Effect of Sleep-Disordered Breathing on Appropriate Implantable Cardioverter-Defibrillator Therapy in Patients With Heart Failure: A Systematic Review and Meta-Analysis

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