Obstructive sleep apnoea in acute coronary syndrome

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ABSTRACT Obstructive sleep apnoea (OSA) syndrome affects about 13% of the male and 7–9% of the female population. Hypoxia, oxidative stress and systemic inflammation link OSA and cardiovascular and metabolic consequences, including coronary artery disease. Current research has identified several clinical phenotypes, and the combination of breathing disturbances during sleep, systemic effects and end-organ damage might help to develop personalised therapeutic approaches. It is unclear whether OSA is a risk factor for acute coronary syndrome (ACS) and might affect its outcome. On the one hand, OSA in patients with ACS may worsen prognosis; on the other hand, OSA-related hypoxaemia could favour the development of coronary collaterals, thereby exerting a protective effect. It is unknown whether positive airway pressure treatment may influence adverse events and consequences of ACS. In non-sleepy patients with OSA and stable coronary artery disease, randomised controlled trials failed to show that continuous positive airway pressure (CPAP) treatment protected against cardiovascular events. Conversely, uncontrolled studies suggested positive effects of CPAP treatment in such patients. Fewer data are available in subjects with ACS and OSA, and results of randomised controlled studies on the effects of CPAP are expected shortly. Meanwhile, the search for reliable markers of risk continues. Recent studies suggest that daytime sleepiness may indicate a more severe OSA phenotype with regard to cardiovascular risk. Finally, some studies suggest sex-related differences. The picture is still incomplete, and the potential role of OSA in patients with ACS awaits confirmation, as well as clear definition of subgroups with different degrees of risk.

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Coronary artery disease and the pathogenesis of acute coronary syndrome

Coronary artery disease (CAD) is the major cause of death and disability in Western countries [1]. Although the mortality has declined over the past decades, 20% of all deaths in Europe are still attributed to CAD and especially to acute coronary syndrome (ACS) [2]. The clinical spectrum of ACS includes unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) [3].

The pathogenesis of CAD is usually based on the atherosclerosis of the coronary arteries, forming plaques and progressive coronary stenosis. Major risk factors for atherosclerosis comprise smoking, obesity, age, sex, lack of physical activity, high blood cholesterol levels, arterial hypertension and diabetes mellitus [4]. However, many individuals with CAD present with only one or two traditional risk factors, indicating that other factors also play an important role in the pathogenesis of atherosclerosis [5, 6].

Atherosclerosis of the coronary arteries involves the interaction between the coronary endothelium, disturbed blood flow and the blood elements. Within the past decades, there has been growth in the evidence for the underlying mechanisms of endothelial dysfunction, including physical and biochemical injuries as well as immune-mediated damage [7]. Impaired homeostatic properties of the endothelium promote smooth muscle cell proliferation and migration, thrombotic dysfunction, vasomotor tone alterations and leukocyte adhesion and migration [8]. In particular, oxidative stress seems to play a major role, as the accompanying overproduction of reactive oxygen species (ROS) exceeds the anti-oxidant defence system and consequently maintains pathogenic mechanisms [9, 10].

Over time, vulnerable plaques emerge, which typically consist of a thin fibrous cap, a large lipid pool inside the plaque, macrophage infiltration and apoptosis, inducing a growing necrotic core [11]. *Post mortem* studies in the 1980s suggested inflammatory mechanisms to weaken the collagen structure of the fibrous cap, inducing atherothrombosis and the clinical presentation of ACS [12–14]. Two clinical studies support the concept of inflammation being responsible for plaque rupture but also highlight that inflammation may not be the only trigger [15, 16]. Cristell *et al.* [15] found increased C-reactive protein levels in only 59% of ACS patients. In addition, Scalone *et al.* [16] recently investigated prevalence of inflammatory cell infiltration by optical coherence tomography, showing that one-third of ACS patients had no evidence for inflammation.

Today, various mechanisms causing ACS are discussed, including plaque rupture with or without inflammation, superficial plaque erosion and microvascular spasms due to an imbalance of vasoconstrictor and vasodilator agents. Beside the well-known major risk factors for atherosclerosis, affected anti-thrombotic, anti-proliferative and anti-inflammatory properties of the coronary endothelium play a decisive role in the pathogenesis and course of ACS and most likely represent the linking element to obstructive sleep apnoea (OSA).

Epidemiology, symptoms and consequences of OSA

Repetitive reductions or cessations of the airflow through mouth and nose, due to narrowing or closure of the upper airways, characterise OSA. Respiratory drive generated by the brain stem, consequent activation of respiratory muscles, and breathing effort are not reduced in OSA, while they are diminished in central apnoea. Data from population-based epidemiological studies showed that up to 25% of women and 50% of men present with $\geqslant$15 breathing disturbances per hour of sleep [17, 18]. However, the combination with clinical symptoms, known as the obstructive sleep apnoea syndrome (OSAS), is less frequent and affects about 13% of the male and 7–9% of the female population [17, 19]. The obstructive events are associated with frequent shifts between hypoxia and re-oxygenation, arousals from sleep, increased work of breathing and sympathetic activation (systemic effects).

Besides excessive daytime sleepiness (EDS), OSA patients often present with fatigue, insomnia or non-restorative sleep, neurocognitive deficits, depression, or increased frequency of accidents while driving or at work. The consequences on a cellular and subcellular level may lead to a variety of clinical sequelae such as diabetes, metabolic syndrome, hypertension and other cardiovascular disorders [17, 20, 21]. The results of cluster analyses of huge databases have stimulated discussions on phenotyping and personalised treatment of OSA. These phenotypes may differ according to symptoms (sleepiness, insomnia, depression), anthropometric factors (sex, body constitution) or consequences (comorbidities) [22].

The link between the number of apnoeas and hypopnoeas per hour (apnoea–hypopnoea index (AHI)) and clinical manifestations of OSAS has proved elusive. Patients with a high AHI may be low on symptom scales, and *vice versa*. Differences in the individual susceptibility to the systemic effects of OSAS may explain this diversity. Substances from molecular pathways that are triggered by these mechanisms may serve as biomarkers reflecting the end-organ strain or damage inflicted by OSAS [23–26].

The clinical findings are in line with data from basic studies on the effects of hypoxia. Avezov *et al.* [27] investigated the role of endothelial cell-colony forming units (EC-CFUs), which might contribute to repair

vascular damage or limit the effects of tissue ischaemia. They evaluated the effect of intermittent and sustained hypoxia on the development of EC-CFUs in blood samples taken from healthy volunteers. They measured the extent of EC-CFUs and the production of ROS. The investigators found increases in the number of EC-CFUs depending on intermittent hypoxia, with large inter-individual variability. Also, markers of ROS production and oxidative stress were increased, while these effects could be diminished with anti-oxidants. The authors concluded that the variable responses to intermittent hypoxia might represent an individual trait of potential clinical significance [27]. Bauça *et al.* [28] tried to elucidate the molecular mechanisms of the relationship between OSA and CAD. They analysed biomarkers that are released during cell death to the blood stream, including nucleosomes and double-stranded DNA (dsDNA). Of the 549 patients included, 145 suffered from ACS, 290 from ACS plus OSA, 62 from OSA alone and 52 served as controls. Nucleosomes and dsDNA were significantly increased in OSA patients. In addition, ACS increased the biomarkers independently of OSA [28].

OSA and ACS: associations, sex differences and phenotyping

The consequences of breathing disturbances during sleep (sleep disordered breathing (SDB)), including hypoxia/re-oxygenation, oxidative stress, systemic inflammation, arousals and increased work of breathing, suggest a correlation between OSA and ACS. Huang *et al.* [29] performed a meta-analysis to evaluate the prevalence of SDB in ACS. They analysed 32 studies including 3360 patients. 69% of patients (95% CI 61–77%) presented with an AHI $\geqslant$5 events·h^{-1}, 43% (36–49%) with AHI $\geqslant$15 events·h^{-1} and 25% (17–33%) with AHI $\geqslant$30 events·h^{-1}. Studies using portable devices with limited numbers of parameters (cardiorespiratory polygraphy) showed a pooled prevalence of 77%, while polysomnography studies demonstrated a mean prevalence of 60%. The authors did not find substantial differences between studies performed in different ethnic groups [29]. These data on OSA in ACS patients clearly exceed the figures of SDB in the general population. However, evidence suggests that severity and prevalence of OSA in ACS may decrease over time. Buchner *et al.* [30] investigated the natural course of SDB in interventionally treated acute myocardial infarction (AMI) patients and showed a decrease of OSA severity and prevalence within 12 weeks. This improvement was associated with a recovery of left ventricular ejection fraction (LVEF). The authors discussed whether the reduction of fluid retention and less significant chronic hyperventilation were responsible for the improvement of OSA [30].

Epidemiological studies suggest age and sex differences in the association between OSA and cardiovascular outcome. Analyses of the Sleep Heart Health Study found the coexistence of CAD and OSA to be more pronounced in men within an age range of 40–70 years. The authors of these analyses discussed potential explanations for this phenomenon, including a healthy survivor effect and biological differences in OSA pathophysiology between older and younger individuals [31–33]. Mokhlesi *et al.* [34] showed a higher prevalence of ischaemic heart disease in men with OSA as compared to women. Sánchez-de-la-Torre *et al.* [35] asked if sex influences the severity of ACS in patients with OSA. The severity of ACS was evaluated based on LVEF, Killip class, number of diseased vessels and stents implanted, and plasma peak troponin level. The authors included 693 men and 133 women with a mean AHI of 37±18 and 35±18 events·h^{-1}, respectively, and found substantial differences in anthropometric parameters and life style habits. Men were younger (59±11 *versus* 66±11 years), had a higher neck circumference, and a higher prevalence of smokers or alcohol users as compared to women. Body mass index (BMI) and number of hypertensive or diabetic patients did not differ between the sexes. Regarding CAD, men presented with more diseased vessels and stents and lower LVEF.

As mentioned, epidemiological studies have pointed out the heterogeneity of OSA in terms of symptomatology, comorbidities and outcome. Zinchuk *et al.* [36] performed cross-sectional and longitudinal analyses of 1247 patients to discriminate associations between polysomnographic phenotypes and cardiovascular outcomes. Patients were clustered based on sleep architecture, autonomic dysregulation, breathing disturbances, and hypoxia in the polysomnography. The authors identified seven clusters: "mild sleep apnoea", "periodic limb movements during sleep", "NREM (non-rapid eye movement) and arousal", "REM (rapid eye movement) and hypoxia", "hypopnoea and hypoxia", "arousal and poor sleep", and "combined severe sleep apnoea". As compared to "mild sleep apnoea", the risk of impaired outcome was increased in "periodic limb movement", "hypopnoea and hypoxia" and "combined severe". In contrast, the categorisation based on the AHI did not show a difference in risk assessment [36]. Clinicians should not only focus on the simple number of breathing disturbances but integrate symptoms and sleep disturbances.

Prognostic relevance of OSA in ACS/AMI

The prevalence of breathing disturbances during sleep in patients with AMI has been shown to be up to 60% [37]. While some studies have described impaired outcome of AMI in patients with OSA, others have discussed that intermittent hypoxaemia may have protective effects on the heart because of ischaemic preconditioning and development of collateral vessels.

Chronic hypoxaemia due to significant coronary artery stenosis has been shown to lead to the development and recruitment of collateral vessels. Mechanisms responsible for the underlying angiogenesis and arteriogenesis include the release of growth factors and inflammatory mediators, and monocyte activation, as well as upregulation of growth factor receptors [38–40]. It is under debate whether these mechanisms are in full effect in intermittent hypoxaemia as seen in OSA. Only few studies have found indirect evidence that OSA might have protective effects based on ischaemic preconditioning. Ben Ahmed *et al.* [41] examined the extent of coronary collaterals in 71 patients with inaugural myocardial infarction and found that OSA patients showed better collateral development as compared to patients without OSA. Shah *et al.* [42] performed an observational cohort study in 136 patients with AMI. 35% of the sample presented with OSA with an AHI >5 events·h^{-1}. After adjustment for age, sex, race, smoking and other cardiovascular risk factors or comorbidities, AHI was inversely associated with troponin-T levels. The odds ratio (OR) suggested a protective effect of SDB on higher troponin-T levels [42]. In addition, Sánchez-de-la-Torre *et al.* [43] measured peak cardiac troponin-I levels in 89 patients with and 38 without OSA (mean AHI 32 *versus* 4.8 events·h^{-1}) who were admitted for ACS. Blood samples were taken every 6 h until the peak of troponin-I was exceeded. Patients with OSA showed significantly lower troponin-I level as compared to patients without OSA. Multivariate linear regression analysis showed that OSA patients had 54% lower troponin-I levels. This suggests that OSA might have a protective effect in myocardial infarction, leading to less severe myocardial injury [43].

Conversely, Porto *et al.* [44] performed a systematic review of the available literature on the association between OSA and AMI. They found three prospective studies in 142 selected articles. The studies included 5067 OSA patients, predominantly males. The studies showed associations between OSA and fatal and non-fatal cardiovascular outcomes. 12.7% showed AMI, stroke or revascularisation procedures. 29.5% of the adverse events were myocardial infarctions. 25.6% of all events were fatal. In addition, Buchner *et al.* [45] and Nakashima *et al.* [46] investigated the association of SDB and infarct size after AMI based on cardiovascular magnetic resonance and left ventricular angiography, respectively. They found less myocardial salvage, smaller reduction in infarct size and less recovery of left ventricular function in patients with AHI $\geqslant$15 events·h^{-1} after 3 months and after 21 days, respectively. These findings reinforce that SDB contributes to impaired outcome after AMI.

Bearing these controversial data in mind, several studies have been performed to further elucidate the clinical relevance of OSA on the outcome of ACS patients. The findings of Mohananey *et al.* [47] seem to support the theory of preconditioning of vessels in intermittent hypoxia. They identified a group of OSA patients with primary discharge diagnosis of STEMI from a nationwide sample. The cohort included 1 850 625 patients with STEMI, of whom 24 623 patients (1.3%) had documented OSA. The prevalence of male sex, smoking, chronic pulmonary disease, depression, hypertension, known history of CAD, dyslipidaemia, obesity and renal failure was higher in OSA patients. Interestingly, OSA patients had significantly lower in-hospital mortality, but longer hospital stays.

In contrast, other studies have emphasised a negative prognostic impact of OSA on ACS. Barbé *et al.* [48] asked if OSA influences the severity and short-term outcome of patients admitted for ACS. They included 213 OSA patients (AHI >15 events·h^{-1}) and compared them with 218 controls. Patients with OSA showed higher prevalence of arterial hypertension, higher BMI and lower percentage of smokers. After adjusting for these confounders, OSA was associated with higher peak troponin levels in plasma and longer stay in the coronary care unit. The authors found an association of breathing disturbances with the severity of CAD. The higher the figure of the AHI was, the higher was the number of diseased vessels [48].

Jia *et al.* [49] studied 529 patients with ACS in a prospective cohort study. The patients were hospitalised for coronary angiography or percutaneous coronary intervention (PCI) and underwent polysomnography. They were divided into two groups, according to whether their AHI was below or above 15 events·h^{-1}. The mean AHI was 29±19 events·h^{-1} and 70.5% of patients presented with moderate to severe OSA (AHI >15 events·h^{-1}). Compared to controls, OSA patients showed higher prevalence of hypertension and elevated BMI. They were sleepier according to the Epworth Sleepiness Scale (ESS), had longer hospitalisation periods and more major adverse cardiac events (MACEs) over a period of 32 months. Moderate to severe OSA was an independent risk factor of long-term MACEs (hazard ratio (HR) 1.618, 95% CI 1.069–3.869; p=0.047) [49].

Zhu *et al.* [50] investigated the prevalence of OSA in 86 patients with first admission for AMI undergoing emergency PCI, and determined the impact of OSA on cardiac damage. 65 (75.6%) out of 86 patients fulfilled the OSA criteria. There were no differences in the day–night pattern of the incidence of AMI. OSA patients were older and had higher incidence of smoking, diabetes and arrhythmias. While there was no difference in collateral vessels, the sensitive serum troponin-T, creatine kinase isoenzyme MB and LVEF, the level of pro-brain natriuretic peptide and the Gensini score were higher in sleep apnoea patients. The Gensini score quantifies arteriosclerosis based on angiography, with higher values indicating higher severity [50, 51].

Correia *et al.* [52] asked if the prevalence of OSA influences the outcome of patients with non-ST-elevation ACS in hospital. They included 168 consecutive patients with unstable angina pectoris or NSTEMI. The Berlin questionnaire was used to evaluate the probability of OSA. The median duration of the hospital stay was 8 days, the incidence of death, non-fatal myocardial infarction and refractory angina was 13% in the total group. Patients with a high OSA probability had an 80% incidence of these major cardiac events, compared to no events in those with low probability. OSA remained an independent predictor of cardiac events even after logistical regression adjustment for the Global Registry of Acute Coronary Events (GRACE) risk score, anatomic severity of CAD and hospital treatment [52].

OSA is characterised by breathing disturbances, as measured by the AHI or a parameter of oxygen saturation, by impairment of sleep measured with polysomnography, by symptoms such as sleepiness and impairment of quality of life, and by comorbidities. Most of the previously mentioned studies and current guidelines focus mainly on the AHI as a marker of the disease severity. However, it is unclear which component of the syndrome is critical for the outcome in ACS. To elucidate this question, Xie *et al.* [53] included 112 patients without prior diagnosis of OSA in a prospective cohort study. The patients underwent polysomnography within a median of 7 days after AMI and were followed for a total of 48 months. 14 patients were excluded because of central apnoea or usage of positive airway pressure (PAP). 41% of the patients showed an obstructive AHI $\geqslant$15 events·h^{-1}. OSA patients had a higher rate of MACEs compared to those patients without OSA (47.5% *versus* 24.1%). After adjusting for anthropometric parameters and comorbidities, minimal oxygen saturation during sleep $\leqslant$85% (but not the AHI) proved to be an independent risk factor for MACEs (HR 6.05) [53]. More recently, this group published additional data on the effect of EDS on cardiovascular outcome after AMI. EDS was defined by an ESS $\geqslant$11. Patients with EDS presented with significantly higher rates of major cardiovascular events (48.4% *versus* 27.4%) and re-infarction (29.0% *versus* 5.5%) compared to those patients without sleepiness. After adjusting for age, diabetes, depression, LVEF, AHI and nocturnal nadir oxygen saturation, EDS was also a significant risk factor in moderate to severe OSA [54].

Patients with STEMI are at risk for malignant ventricular arrhythmia. Disturbed cardiac repolarisation is a predictor of these arrhythmias. Fisser *et al.* [55] investigated whether OSA is associated with disturbed cardiac repolarisation in patients with STEMI. They included 33 STEMI patients before PCI. The heart rate corrected interval from peak to end of the T-wave (TpTec) and the QTc interval served as measures of disturbed cardiac repolarisation. OSA patients presented with significantly prolonged TpTec and a trend to longer QTc intervals before PCI. There was a trend to reduction of these parameters after PCI. The authors found significant associations of AHI with prolonged TpTec intervals, with prolonged QTc intervals and with higher TpTec/QT ratio.

Qu *et al.* [56] performed a meta-analysis to evaluate the outcome of OSA patients after PCI. They included cohort studies measuring overnight sleep patterns within 1 month after PCI and investigating cardiac death, non-fatal myocardial infarction and coronary revascularisation as primary outcome parameters. The authors identified seven studies including 2465 patients. OSA significantly increased the risk for MACEs (OR 1.52, 95% CI 1.2–1.93), including non-fatal myocardial infarction and coronary revascularisation. The OR for cardiac death was doubled (2.05, 95% CI 1.15–3.65), while there was no significantly increased risk for re-admission for heart failure or stroke.

These data consistently support the idea that the outcome of ACS is impaired in OSA patients. Li *et al.* [57] added interesting findings to the understanding of this association by investigating whether OSA is associated with high risk of early stent thrombosis after PCI. They performed a case–control study including 23 patients with and 92 without early stent thrombosis during a 2-year follow-up period. The Berlin questionnaire was used to estimate the probability of OSA but patients did not undergo sleep studies. The OR for stent thrombosis was 4.17 (95% CI 1.6–0.84; p=0.003) in patients with positive Berlin questionnaire, *i.e.* at high risk for OSA. Such risk remained significant after adjusting for other risk factors for stent thrombosis. The authors also found a significant association between OSA and early stent thrombosis in patients with $\leqslant$1 conventional cardiovascular disease risk factor [57]. These data are in line with findings from the Sleep and Stent Study, a prospective, multinational register study on patients successfully treated with PCI [58]. Lee *et al.* [58] analysed the data of 1311 patients who completed a sleep study within 7 days of PCI. Those patients with an AHI $\geqslant$15 events·h^{-1} showed a significantly higher figure of major adverse cardiac and cerebrovascular events (MACCEs) compared to those without OSA. The adjusted HR of 1.57 (95% CI 1.1–2.24) was independent of anthropometric parameters and comorbidities.

The effect of OSA might be intensified if associated with other risk factors. Koo *et al.* [59] presented data of a *post hoc* analysis of the Sleep and Stent Study, asking if the coexistence of OSA and diabetes mellitus would further increase the risk of major cardiovascular events. 20.7% of the patients suffered from both OSA and diabetes mellitus, 24.6% from OSA without diabetes mellitus, 21.7% from diabetes mellitus

without OSA and 33% showed neither OSA nor diabetes mellitus. The incidence of MACCEs and of cardiovascular mortality was highest in the comorbid OSA and diabetes mellitus group, while it was similar in the other three groups. In patients with diabetes mellitus, OSA was associated with a two-fold risk increase of MACCEs and cardiovascular mortality after adjustment for age, sex, ethnicity, BMI and hypertension. However, there was no difference in risk among patients without diabetes mellitus. The authors stated that this *post hoc* analysis was limited by incomplete information on diabetes mellitus and objective parameters of the disease. The study included only a small number of female patients and was mainly performed in an Asian population [59]. Based on these findings, Quan *et al.* [60] re-analysed the Sleep Apnea Cardiovascular Endpoints (SAVE) data in a *post hoc* analysis. They identified four clinical OSA phenotypes: CAD without diabetes mellitus (39%), CAD with diabetes mellitus (15%), cerebrovascular disease without diabetes mellitus (37%), and cerebrovascular disease with diabetes mellitus (9%). The risk for the composite cardiovascular end-point was highest in the "CAD plus diabetes mellitus" comorbid group and for stroke in the "cerebrovascular plus diabetes mellitus" group (HR 2.08 and 6.84, respectively). Moreover, regular continuous positive airway pressure (CPAP) use $\geqslant$4 h·night^{-1} was associated with the lowest risk of cardiovascular outcome in the "cerebrovascular disease plus diabetes mellitus" phenotype [60].

Structural changes of the myocardium may influence the long-term outcome of patients with OSA and CAD. Alonderis *et al.* [61] investigated the impact of SDB on left ventricular hypertrophy in stable CAD patients. They performed a cross-sectional study in 772 patients with CAD and untreated OSA. Patients filled in the ESS and underwent echocardiography and polysomnography. 39% of the patients presented with an AHI $\geqslant$5 events·h^{-1}, many without daytime sleepiness. OSA patients showed higher age, BMI and prevalence of hypertension. Parameters of left ventricular hypertrophy, including left ventricular mass/height relationship, wall thickness criteria and concentric left ventricular hypertrophy, were all higher in OSA. Even mild OSA independently predicted left ventricular hypertrophy after multiple logistic regression [61].

Putting all these aspects together, OSA seems to increase the risk of poor outcome of ACS patients with OSA. Although the repetitive change between hypoxia and re-oxygenation may promote vascular preconditioning in CAD, evidence suggests higher mortality, predisposition to malignant arrhythmias, and remodelling of the myocardium. Most studies are based on observational cohorts, which substantially limits any conclusions. Thus, there is an urgent need for well-designed prospective studies.

As a consequence of the epidemiological and pathophysiological findings, the 2015 European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommended considering OSAS in the differential diagnosis of bradyarrhythmias (recommendation class IIa, level of evidence B) [62]. Moreover, the guidelines stated that the presence of sleep apnoea and reduced oxygen saturation may be considered as a risk factor for sudden cardiac death (recommendation class IIb, level of evidence C). The 2016 European guidelines on cardiovascular disease prevention in clinical practice stated that there is evidence of a positive relationship between OSA and hypertension, CAD, atrial fibrillation, stroke and heart failure [63].

Diagnosis of sleep disturbances, risk factors, predictors and biomarkers for poor ACS outcome

Interestingly, OSAS might not be the only sleep disorder influencing the outcome of ACS. The participants of the SOLID-TIMI-52 study (the stabilisation of plaques using darapladib-thrombolysis in myocardial infarction) filled in the Berlin questionnaire and a study-specific sleep questionnaire [64]. These standardised questionnaires included questions on snoring, breathing disturbances during sleep, daytime sleepiness, shift work and average sleeping hours. SOLID-TIMI-52 randomised 13 026 patients to receive darapladib *versus* placebo in a double-blind controlled design. Patients were included within 30 days after hospitalisation for ACS and at least one additional cardiovascular risk factor. After 2.5 years of follow-up, the primary outcome parameter of major coronary events was evaluated. The authors found an adjusted HR of 1.29 for those with <6 h of sleep (a possible marker of insomnia) as compared to those with longer sleep. A screening risk for OSA was associated with a HR of 1.12 (95% CI 1.0–1.24; p=0.04) and overnight shift work showed a HR of 1.15 (95% CI 1.03–1.29; p=0.01). Individuals with all three sleep-related risk factors had a two-fold higher risk of MACEs [64].

The question arises as to whether the presence of OSA can be predicted in ACS patients based on clinical or laboratory parameters. de Batlle *et al.* [65] studied 978 patients with ACS and analysed their sociodemographic, anthropometric, lifestyle, pharmacological and clinical parameters. OSA was defined by an AHI $\geqslant$15 events·h^{-1} on respiratory polygraphy. 298 patients showed an AHI <15 events·h^{-1}; 680 had $\geqslant$15 events·h^{-1}. Age, BMI, ESS, peak level of troponin and use of calcium antagonists were all associated with OSA, but no statistical model allowed prediction of OSA [65]. This confirms data from Reuter *et al.* [66] in stable patients with chronic cardiovascular diseases. They found that the STOP-BANG and Berlin

questionnaires did not reliably detect or exclude SDB in patients with cardiovascular diseases. Both studies support the idea that only a systematic screening based on measures of respiration-related parameters (*i.e.* respiratory flow, blood oxygen saturation, *etc.*) is able to reliably detect or exclude SDB in these patients.

There is growing interest in the identification of biomarkers, which may indicate the presence, severity or prognostic impact of the OSA–ACS comorbidity. Placental growth factor (PIGF), a biomarker of ACS, is increased in damaged hearts, including AMI patients [67], and has been shown to be a marker of short-term outcome in ACS [68]. PIGF also correlates with the improvement in left ventricular function in chronic ACS [69]. As hypoxia induces PIGF, it might be hypothesised that the presence and severity of OSA influence its plasma level. Barcelo *et al.* [70] included 538 patients admitted for ACS; 312 were defined as OSA patients (AHI >15 events·h^{-1}), while 226 served as controls. The two groups differed in age, BMI and prevalence of hypertension; all these parameters had higher values in the OSA group. After adjusting for these parameters, PIGF levels were significantly higher in OSA patients compared to controls and the AHI correlated with PIGF. In addition, patients with high PIGF levels showed more diseased vessels [70]. Matsumura *et al.* [71] hypothesised that circulating autoantibodies against neuroblastoma suppressor of tumorigenicity 1 (NBL1-Ab) are associated with the prevalence of CAD in patients with OSA. They enrolled 82 patients with OSA, 96 with ACS and 64 healthy volunteers and found a significant elevation of the NBL1-Ab level in patients with OSA and ACS compared to healthy controls and OSA patients without CAD. The marker was significantly elevated in patients with severe OSA and patients with a history of CAD but correlated only weakly with AHI, age, oxygen saturation and the arousal index [71]. While the connection between ACS and OSA suggests a potential benefit of OSA treatment, these data do not yet allow for practical recommendations. However, they may guide directions for further research, especially focussing on the differentiation of pathophysiological, clinical and prognostic phenotypes. Based on current knowledge, well-established life-saving interventions (myocardial revascularisation) and medication therapy during the immediate onset of ACS are of primary significance. The value of OSA treatment in the setting of coexisting ACS finds its potential value in limiting the development of heart failure and preventing the re-occurrence of ACS.

Treatment effect

The application of PAP by a flow generator device *via* a tube and a facial or orofacial mask has proven effective to overcome upper airway obstruction in OSA. It improves daytime symptoms and normalises traffic and work-place accidents [72]. Constant, automatically adjusting, and fixed but different inspiratory and expiratory (bilevel) PAP algorithms have proven to be equally effective in suppressing obstructive events [73–75]. The influence of OSA therapies on cardiovascular comorbidities is of major interest. Available data overwhelmingly focus on the effect of PAP therapies, while studies on mandibular advancement devices or other options are very limited.

In general, PAP improves arterial hypertension only mildly. However, several studies have included non-hypertensive or pharmaceutically well-treated patients. CPAP has been shown to improve blood pressure in patients with treatment-refractory hypertension and in CPAP-adherent patients [76–78]. CPAP may improve oxygenation, cardiac function and survival in patients with reduced LVEF [79–90]. A systematic review on the efficacy of CPAP on atrial fibrillation demonstrated a significant risk reduction of atrial fibrillation in sufficiently treated OSA patients, especially in younger, obese and male patients ($p<0.05$). Moreover, CPAP therapy and atrial fibrillation recurrence were correlated inversely [91].

The prognostic impact of PAP in patients with OSA and CAD is under debate [92]. Data from observational studies [93, 94] have shown significantly more life-threatening cardiovascular events in untreated patients with severe OSAS (AHI $\geqslant$30 events·h^{-1}) compared with untreated patients with lesser degrees of the disease, simple snorers, healthy controls, and patients treated effectively with CPAP. Most recently, McEvoy *et al.* [92] investigated the influence of CPAP in addition to usual care, compared with usual care alone, in moderate to severe OSA and a history of cardiovascular diseases. The study failed to show a difference in the primary composite cardiovascular end-point (death from cardiovascular causes, myocardial infarction, stroke, and hospitalisation for unstable angina, heart failure, or transient ischaemic attack). However, CPAP significantly improved quality of life, daytime sleepiness, anxiety, depression, the numbers of accidents causing injury and the days off from work. Secondary outcome parameters showed improvement in the number of strokes and combined cerebral events in CPAP-adherent patients. Many questions remained open in this trial. Most importantly, patients used CPAP for only 3.3 h·day^{-1}, although a minimum daily usage of >4 h is recommended. This may be due to a low level of sleepiness, which is a well-known factor of poor compliance [95]. In addition, the trial included patients under optimal conventional cardiac treatment so that there was limited room for improvement with any additional therapy [92–96].

Milleron *et al.* [97] compared 25 OSA patients, treated with CPAP (n=21) or upper airway surgery (n=4), with 29 patients who refused treatment in a non-randomised cohort study. Inclusion criteria included an

oxygen desaturation index (ODI) ⩾15 events·h^{-1} and coronary artery stenosis ⩾70%. The groups did not differ substantially in anthropometric parameters, risk factors or comorbidities at baseline. After a median follow-up of 86.5±39 months, 24% of the treatment group compared to 58% of the untreated group reached the composite end-point of cardiovascular death, ACS, hospitalisation for heart failure or need for coronary revascularisation. The HR for treated patients was 0.24 (95% CI 0.09–0.62; p<0.01) [97].

Lewis *et al.* [98] studied the influence of three different treatment options on parameters of quality of life in OSA patients (AHI ⩾15 events·h^{-1}) with pre-diagnosed CAD or at least three major risk factors in a randomised controlled trial. 318 patients were randomised to receive CPAP, nocturnal supplemental oxygen or healthy lifestyle education and evaluated using validated self-assessment questionnaires (36-item Short-Form Health Survey (SF-36) and Patient Health Questionnaire-9 (PHQ-9)). After 12 weeks of treatment, CPAP improved the mental health status significantly more than oxygen. Moreover, CPAP was superior to healthy lifestyle education in terms of vitality, social function and depressive symptoms. However, oxygen was superior in physical components and equally effective in terms of depressive symptoms [98].

Lin *et al.* [99] performed a longitudinal study in 207 patients with AMI and OSA. The group included 110 patients with pre-diagnosed and 69 patients with newly diagnosed OSA. Patients were identified out of 9453 patients with incident AMI from a national database. Non-OSA patients with AMI from this database served as propensity score matched controls. After a median follow-up of 4.2 years, all-cause mortality and MACCEs were analysed. The risk of MACCEs was significantly increased in OSA patients diagnosed after AMI (HR 1.412, 95% CI 1.037–1.923; p=0.029). The HR was highest in patients diagnosed with OSA within 1 year after AMI (HR 2.029, 95% CI 1.265–3.254), but not increased in patients treated with CPAP [99]. The authors concluded that early diagnosis and treatment might improve the outcome of AMI patients with OSA.

Peker *et al.* [100] published in 2016 the results of the RICCADSA trial (randomised intervention with CPAP in CAD and OSA), a single-centre, prospective, randomised, controlled, open-label, blinded evaluation trial. The authors included 244 consecutive non-sleepy OSA patients with newly revascularised CAD who were randomised to receive CPAP or no PAP therapy. The primary end-point (first event of repeat revascularisation, myocardial infarction, stroke, cardiovascular mortality) did not differ after a median follow-up of 57 months between those treated with or without CPAP. However, the authors found a significant risk reduction in those who used their devices for ⩾4 h·day^{-1}. They concluded that a routine prescription of CPAP to non-sleepy OSA patients with CAD does not result in significant improvement of cardiovascular outcome, but that it is beneficial for those with good CPAP adherence [100]. In addition, Peker *et al.* [101] compared CAD patients without OSA with treated sleepy OSA patients (ESS ⩾10) who also had CAD, in a parallel observational arm of the RICCADSA trial. For ethical reasons, the study did not randomise sleepy OSA patients for treatment or no treatment of OSA. There was no significant difference in the incidence of MACCEs between treated OSA patients and patients without sleep apnoea (23.2% *versus* 16.1%; adjusted HR 0.96, 95%, CI 0.4–2.31; p=0.923). However, the treated sleepy OSA patients showed far more comorbidities in comparison to patients without OSA, indicating a potential protective effect of OSA treatment [101].

Thunström *et al.* [102] analysed the RICCADSA data regarding levels of high-sensitivity C-reactive protein, interleukin (IL)-6, IL-8 and tumour necrosis factor-α. The biomarkers were measured at baseline and after 1 year of follow-up in 220 patients randomised to CPAP or no CPAP. The IL-6 level differed at baseline but it was significantly reduced after 1 year of follow-up, with no difference between the groups. The other biomarkers did not show significant changes over time in either group. In addition, Stradling *et al.* [103] focussed on the question of whether CPAP treatment influences oxidative stress in moderate-to-severe OSA (mean ODI 46 events·h^{-1}). They randomised 59 patients to withdraw or stay on CPAP for 2 weeks, but failed to find any significant change in markers of oxidative stress (malondialdehyde, lipid hydroperoxides, total anti-oxidant capacity, superoxide generation from mononuclear cells and urinary F2-isoprostane).

Wang *et al.* [104] performed a systematic review and meta-analysis to evaluate the effect of CPAP treatment on long-term cardiovascular outcome in patients with OSA and CAD. They focussed on the primary outcome parameter of MACE. They found two randomised controlled trials and seven observational studies, including 1430 patients. The median follow-up period was 36–86.5 months. While six out of seven observational studies showed a significant risk reduction of MACE, all-cause death and cardiovascular death under CPAP, the randomised controlled trials failed to reach statistical significance.

The main findings from the most relevant studies of CPAP treatment effects in OSA on cardiovascular outcome are summarised in table 1.

TABLE 1 Overview of main findings from studies investigating effects on cardiovascular outcome of continuous positive airway pressure (CPAP) treatment in obstructive sleep apnoea (OSA) patients

First author [ref.]	Population characteristics	Definition and measurement of OSA	Design/total size for primary analysis	Groups/interventions	(Primary) outcome	Main result
Mil [97]	CAD ⩾70% stenosis of a major carotid artery OSA (exclusion of predominant CSA/CSR not reported)	AHI ⩾15 events·h^{-1} In-lab PSG Symptoms consistent with OSA	Prospective, long-term observational cohort study, n=54	Treated OSA, n=25 (nasal CPAP n=21, surgery n=4); median follow-up 86 months Untreated OSA, n=29; median follow-up 90 months	MACCE (cardiovascular mortality, ACS, HF-related hospitalisation, repeat revascularisation)	HR 0.24 (0.09–0.62), treated *versus* untreated
Stradling [103]	OSA >1 year on CPAP Average compliance >4 h·night^{-1} AHI <10 events·h^{-1} on CPAP CSR excluded	ODI >20 events·h^{-1} (4%) Oximetry during 4 nights off CPAP Previous OSA diagnosis with ODI >20 events·h^{-1}	Prospective, short-term, RCT, n=59	CPAP continuation, n=30 Sham CPAP, n=29 Duration 2 weeks	Blood markers of oxidative stress (MDA, lipid hydroperoxides, total anti-oxidant capacity, superoxide generation from mononuclear cells) Urinary F2-isoprostane Superoxide dismutase as a marker of hypoxic preconditioning	No significant change of blood markers of oxidative stress Urinary F2-isoprostane fell significantly by ~30% Superoxide dismutase increased similarly
Thunström [102]	CAD OSA Non-sleepy (ESS <10) Predominantly central apnoeas with CSR excluded	AHI >15 events·h^{-1} Home-based PG	Prospective, long-term RCT RCT arm of RICCADSA trial, n=220	CPAP, n=115 No CPAP, n=105 Follow-up 1 year	Change in circulating levels of inflammatory biomarkers from baseline to 1 year	Inflammatory biomarkers did not change significantly over time, except for IL-6 levels, which reduced to the same extent in the CPAP and no-CPAP groups
Peker [101]	CAD OSA/no OSA Sleepy (ESS ⩾10) Predominantly central apnoeas with CSR excluded	AHI >15 events·h^{-1} (no OSA: AHI <5 events·h^{-1}) In-lab PSG	Prospective, long-term observational cohort study Observational arm of RICCADSA trial, n=267	OSA with CPAP, n=155 No OSA, n=112 Median follow-up 57 months	MACCE (repeat revascularisation, MI, stroke and cardiovascular mortality)	Adjusted HR 0.96 (0.40–2.31), OSA with CPAP *versus* no OSA
Peker [100]	CAD OSA Non-sleepy (ESS <10) Predominantly central apnoeas with CSR excluded	AHI >15 events·h^{-1} Home-based PG	Prospective, long-term RCT RCT arm of RICCADSA trial, n=244	CPAP, n=122 No CPAP, n=122 Median follow-up 57 months	MACCE (repeat revascularisation, MI, stroke and cardiovascular mortality)	Adjusted HR 0.62 (0.34–1.13), CPAP *versus* no CPAP

Continued

TABLE 1 Continued

First author [ref.]	Population characteristics	Definition and measurement of OSA	Design/total size for primary analysis	Groups/interventions	(Primary) outcome	Main result
Lin [99]	MI OSA Including unspecified sleep apnoea	Sleep apnoea as defined by ICD-9-CM 780.51, 780.53, 780.57, 327.23 Partly validated against PSG	Prospective, long-term observational cohort study, n=207	Sleep apnoea diagnosis before MI: with CPAP, n=26; without CPAP, n=74 Sleep apnoea diagnosis after MI: with CPAP, n=33; without CPAP, n=60 Median follow-up 4.2 years	MACCE (repeat MI, repeat revascularisation, hospitalisation for IHD, or stroke)	Sleep apnoea diagnosis before MI: adjusted HR 0.79 (0.55–1.12), no CPAP *versus* CPAP Sleep apnoea diagnosis after MI: adjusted HR 1.48 (1.01–2.19), no CPAP *versus* CPAP
Lewis [98]	CAD or ⩾3 CAD risk factors OSA ESS ⩽15 Predominant CSA excluded HF excluded	AHI ⩾15 events·h^{-1} (max. 50 events·h^{-1}) Home-based sleep study	Prospective, short-term, RCT, n=318	CPAP, n=106 Nocturnal supplemental oxygen, n=106 Healthy lifestyle education, n=106 Duration 12 weeks	HRQoL (SF-36) Depression (PHQ-9)	CPAP improved vitality and mental status (SF-36) with greater improvement with higher levels of sleepiness (ESS ⩾12) CPAP gave greater improvement in PHQ-9 scores compared with healthy lifestyle education
McEvoy [92]	CAD (51%) or cerebrovascular disease (49%) OSA ESS ⩽15 NYHA III–IV HF excluded CSR excluded	ODI (4%) ⩾12 events·h^{-1} Home-based oximetry and nasal pressure	Prospective, long-term RCT, n=2687	CPAP plus standard of care, n=1346 Standard of care, n=1341 Mean follow-up 3.7 years	MACCE (death from cardiovascular causes, MI, stroke, or hospitalisation for unstable angina, HF, or transient ischaemic attack)	HR 1.10 (0.91–1.32) In CPAP-adherent subgroup, HR 0.80 (0.60–1.07), n=561 CPAP significantly reduced snoring and daytime sleepiness and improved HRQoL and mood
Buchner [93]	OSA 23.6% of patients with CAD Predominant CSA, CSR, hypoventilation syndromes or PLM excluded	AHI ⩾5 events·h^{-1} In-lab PSG	Prospective, long-term observational cohort study, n=449	Treated OSA, n=364 (CPAP n=296, BiPAP n=48, MAD n=20) Untreated OSA, n=85 Median follow-up 72 months	MACCE (death from MI or stroke, MI, stroke, and acute coronary syndrome requiring revascularisation procedures)	Adjusted HR 0.36 (0.21–0.62)

Continued

TABLE 1 Continued

First author [ref.]	Population characteristics	Definition and measurement of OSA	Design/total size for primary analysis	Groups/interventions	(Primary) outcome	Main result
Weaver [95]	OSA Age max. 60 years HF excluded "Other sleep disorders" excluded	AHI ⩾15 events·h^{-1} In-lab PSG	Prospective, short-term, observational, "quasi-experimental" study, n=149	ESS, MSLT, FOSQ normalised on therapy (n=70/106, 30/85, 68/120) ESS, MSLT, FOSQ not normalised on therapy (n=36/106, 55/85, 52/120)	ESS MSLT FOSQ	Those who normalised on therapy used CPAP on average 1.1 (0.2–2.0), 1.1 (0.2–2.1), and 1.0 (0.2–1.8) h·night^{-1} more than those who did not, for the ESS, MSLT and FOSQ, respectively
Marin [94]	OSA Men only	AHI of different severity levels In-lab PSG	Prospective, long-term, observational cohort study, n=1651	Healthy controls, n=264 Simple snorers, n=377 Untreated mild-to-moderate OSA, n=403 Untreated severe OSA, n=235 OSA plus CPAP, n=372 Mean follow-up 10 years	MACCE, fatal (MI, stroke) MACCE, non-fatal (MI, stroke, CABG, PTCA)	Incidence per 100 person-years of fatal and non-fatal MACCE, respectively: Higher in untreated severe OSA: 1.06 and 2.13 Untreated mild-to-moderate OSA: 0.55, p=0.02, and 0.89, p<0.0001 Simple snorers: 0.34, p=0.0006, and 0.58, p<0.0001 OSA plus CPAP: 0.35, p=0.0008, and 0.64, p<0.0001 Healthy controls: 0.3, p=0.0012, and 0.45, p<0.0001 Adjusted HR for untreated severe OSA: fatal MACCE 2.87 (1.17–7.51) and non-fatal MACCE 3.17 (1.12–7.51) *versus* healthy controls

CAD: coronary artery disease; CSA: central sleep apnoea; CSR: Cheyne–Stokes respiration; AHI: apnoea–hypopnoea index; PSG: polysomnography; MACCE: major adverse cardiac and cerebrovascular event; ACS: acute coronary syndrome; HF: heart failure; ODI: oxygen desaturation index; RCT: randomised controlled trial; MDA: malondialdehyde; ESS: Epworth Sleepiness Scale; PG: polygraphy; IL: interleukin; MI: myocardial infarction; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; IHD: ischaemic heart disease; HRQoL: health-related quality of life; SF-36: 36-item Short-Form Health Survey; PHQ-9: Patient Health Questionnaire-9; NYHA: New York Heart Association; PLM: periodic limb movements; BiPAP: bilevel positive airway pressure; MAD: mandibular advancement device; MSLT: multiple sleep latency test; FOSQ: Functional Outcomes of Sleep Questionnaire; CABG: coronary artery bypass graft surgery; PTCA: percutaneous transluminal coronary angioplasty.

Adherence

The SAVE and RICCADSA data underline the importance of PAP adherence in cardiovascular patients. EDS, the typical symptom of OSA, is often missing in patients with CAD. However, the daily use of CPAP treatment depends mainly on the awareness of the improvement of parameters of quality of life. Therefore, Baniak *et al.* [105] investigated sleep-related functional impairment in patients with CAD, and the influence of CPAP. 105 CAD patients without and 105 with moderate-to-severe OSA were matched based on disease severity and were included in a sub-study of the RICCADSA trial. 80 OSA patients were allocated to receive CPAP. After cardiac revascularisation, patients reported sleep-related functional impairment but there was no difference between those with or without OSA. The baseline score of the Functional Outcomes of Sleep Questionnaire (FOSQ) was not related to moderate-to-severe OSA, while EDS was four- to five-fold higher in OSA patients (OR 4.82, 95% CI 2.12–11; p=0.001). Interestingly, CPAP use significantly improved the FOSQ scores after 1 year in patients with EDS, despite sub-optimal adherence.

Florés *et al.* [106] performed an ancillary study of the ISAACC trial, a multicentre prospective, open-label randomised controlled trial in patients with ACS. The investigators randomised non-sleepy patients with moderate to severe OSA to receive CPAP or optimal cardiac care. 35.3% of the patients showed a mean CPAP use $\geqslant 4$ h·day^{-1} after 12 months. Adherence was associated with AHI, smoking pack-years, long intensive care stay and higher age in multivariable logistic regression analysis.

Luyster *et al.* [107] investigated long-term use and predictors of adherence in OSA patients with CAD from the RICCADSA trial over a mean period of 4.8 years (minimum 2 years). 122 non-sleepy patients were randomised to receive CPAP, and the treatment was offered to 155 sleepy OSA patients. 60% of the non-sleepy patients and 77% of the sleepy patients used their CPAP devices for at least 2 years. In non-sleepy patients, age and CPAP use after 1 month were independently associated with long-term CPAP use. CPAP use after 1 month was also a predictor in sleepy patients, with BMI and AMI at baseline as additional parameters [107]. These data underline the importance of close supervision and support of the patients during the first weeks and days of the therapy.

Marotta *et al.* [108] followed a cohort of 103 obese OSA patients treated with CPAP or noninvasive ventilation for 5.6 years. The mean±SD treatment use was 6.3±2.4 h·day^{-1} and 31 patients stopped treatment. Three patients on noninvasive ventilation died, and 27 non-fatal cardiovascular events occurred in 19 patients. Patients with cardiovascular events were older, and had a higher number of comorbidities and triglyceride levels, compared to those without events. Cardiovascular events were significantly lower in those patients treated with CPAP or noninvasive ventilation. The event rate was high in non-adherent patients and increased with the number of comorbidities. There was a significant interaction between treatment and comorbidities.

Conclusions

OSA and ACS co-exist to a large extent, which remains the case even after adjustment for common risk factors such as obesity and male sex. There is an ongoing controversy about protecting or damaging effects of intermittent hypoxia in CAD. It focusses on the question of whether hypoxia may stimulate the development of collateral vessels or whether it is a risk factor for poor outcome. The synergistic effect of hypoxia in co-existing OSA and ACS is supported by cluster analyses, biomarkers and the pathophysiological components of OSA (hypoxia/re-oxygenation, oxidative stress and systemic inflammation). At present, the majority of clinical studies show a substantial elevation of MACEs and poor outcome in ACS patients with OSA. However, the current lack of results from randomised controlled trials limits the possibility to draw conclusions. Current literature suggests that reliable detection of OSA in cardiovascular patients can only be achieved by a systematic screening based on measures of respiration-related parameters, as existing questionnaires have been shown to be unreliable for detecting SDB in these patients. Furthermore, severity of OSA might decrease during the course of ACS treatment and recovery of ejection fraction. This should be kept in mind when deciding upon long-term therapy strategies. The ISAACC trial will soon provide new data on the role of CPAP treatment in non-sleepy OSA patients followed for 3 years after ACS. Current evidence is based on cohorts and longitudinal and cross-sectional studies. From an ethical point of view, it is hardly possible to perform placebo-controlled trials in patients with severe OSA suffering from daytime sleepiness. However, non-sleepy patients often show limited treatment adherence, which affects statements on treatment effects. Adherence is a major challenge in the treatment of OSA patients. It depends on the patients' awareness of symptoms and their relief. Unfortunately, minimal symptomatology is a characteristic of cardiac patients with OSA, leading to high risk of non-adherence. As a consequence, physicians should closely supervise adherence of those patients with severe OSA and ACS, to reduce their probability of poor outcome.

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