Summary and Conclusions

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Cardiovascular complications, diabetes mellitus and death

- ❑ Obstructive sleep apnoea syndrome covaries with cardiovascular disease, including stroke and early death in men (Evidence Grade 2). There is insufficient evidence for women. There is insufficient scientific evidence of a relationship between obstructive sleep apnoea syndrome and arterial hypertension or diabetes mellitus.

Traffic accidents

- ❑ Obstructive sleep apnoea covaries with traffic accidents independent of daytime sleepiness and driving exposure among men (Evidence Grade 3).

Diagnostic procedures

- ❑ The apnoea-hypopnoea index (AHI) shows good agreement between two nights of polysomnographic recordings (Evidence Grade 2).

- ❑ Manually scored portable devices including airflow, respiratory movements and pulse oximetry during one night of sleep have high sensitivity and specificity to identify a pathologic apnoea-hypopnoea index compared with polysomnography (Evidence Grade 1). Automatic scoring of the results of portable devices has high sensitivity and identifies most patients with a pathologic apnoea-hypopnoea index, but specificity is low (Evidence Grade 1). Automatic scoring programs cannot score sleep time and it is unclear whether these programs can differentiate obstructive from central apnoeas.

- ❑ Pulse oximetry with results from the oxygen desaturation index is insufficient to identify a pathologic apnoea-hypopnoea index and there is a high risk that patients with sleep apnoea syndrome will be incorrectly classified as normal (Evidence Grade 1).

- ❑ A global impression from a case history and a physical examination alone are insufficient to identify or to rule out obstructive sleep apnoea syndrome (Evidence Grade 1).

Treatments

Continuous positive airway pressure therapy (CPAP)

- ❑ There is strong evidence that CPAP reduces daytime sleepiness regardless of the severity of the sleep apnoea syndrome (Evidence Grade 1). CPAP is highly effective in reducing obstructive sleep apnoeas (Evidence Grade 1). There is contradictory scientific evidence concerning the effect of CPAP on quality of life (measured as functional outcomes and vitality) or arterial blood pressure.

- ❑ Tolerance and compliance with CPAP is good, and about 70% of patients still use it after 1–4 years for a mean of 5.3 (range 4.4–6.2) hours per night (Evidence Grade 2) – provided that patients and their CPAP equipment are seen by physicians shortly after treatment starts and subsequently at individual intervals, but always at least once a year.

- ❑ Mild to moderate discomfort from the CPAP mask – pain at the bridge of the nose, skin problems, air leaks and disturbing noise from the CPAP machine – are common adverse effects of CPAP (Evidence Grade 2). Mild nasal adverse effects, such as rhinitis, are common (Evidence Grade 3). Auto-CPAP utilises a lower mean pressure than fixed CPAP, but the effects on daytime sleepiness, apnoea reduction and compliance are the same (Evidence Grade 1).

Mandibular repositioning appliances (MRAs)

- ❑ Custom-made mandibular repositioning appliances reduce daytime sleepiness in patients with mild to moderate sleep apnoea syndrome (Evidence Grade 3). They reduce apnoea frequency but to a lesser extent than CPAP (Evidence Grade 3). There is insufficient evidence concerning the effect of MRAs on quality of life (measured as functional outcomes and vitality) or arterial blood pressure.

- ❑ MRAs are still used by 76% of patients after one year and 56% after five years (Evidence Grade 3). A majority of patients experience mild adverse effects – including discomfort in the teeth, hypersalivation and minor reductions in overjet and overbite – during the first few months (Evidence Grade 3).

Surgery

- ❑ There is insufficient scientific evidence for the effect of any surgical modality on daytime sleepiness or quality of life. There is contradictory scientific evidence for the effect of laser-assisted uvulopalatoplasty (LAUP) in reducing apnoea frequency. There is insufficient scientific evidence for other surgical interventions in reducing apnoea frequency.

- ❑ The adverse effects of uvulopalatopharyngoplasty (UPPP) due to snoring or obstructive sleep apnoea include serious perioperative and postoperative complications, including death, bleeding and respiratory compromise (Evidence Grade 2). Persistent adverse effects are frequent, and difficulty in swallowing occurs in about 28% of patients (Evidence Grade 2). Voice changes are also common (Evidence Grade 3).

- ❑ The adverse effects of uvulopalatoplasty (UPP) and laser-assisted uvulopalatoplasty (LAUP) due to snoring or obstructive sleep apnoea include serious postoperative complications (Evidence Grade 3). Persistent adverse effects occur in 50–60% of patients and difficulty swallowing in about 26% (Evidence Grade 2). Globus sensation in the throat and voice changes are common (Evidence Grade 3).

Other treatments and lifestyle modifications

- ❑ No studies that meet the present inclusion criteria show that weight reduction programmes, bariatric surgery, drugs, pacemakers, devices for sleep in lateral position, didgeridoo-playing or any other suggested treatment or lifestyle modification for obstructive sleep apnoea syndrome have any effect.

Fact Box 1 Study Quality and Relevance, Evidence Grade.

Study quality and relevance refers to the scientific quality of a particular study and its ability to reliably address a specific question.

Evidence Grade refers to the total scientific evidence for a conclusion, ie, how many high-quality studies support the conclusion.

Evidence Grade 1 – Strong Scientific Evidence
A conclusion assigned Evidence Grade 1 is supported by at least two studies with high study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the evidence grade may be lower.

Evidence Grade 2 – Moderately Strong Scientific Evidence
A conclusion assigned Evidence Grade 2 is supported by at least one study with high study quality and relevance as well as two studies with medium study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 3 – Limited Scientific Evidence
A conclusion assigned Evidence Grade 3 is supported by at least two studies with medium study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Insufficient Scientific Evidence
If no studies meet the study quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

Contradictory Scientific Evidence
If different studies are characterized by equal study quality and relevance but generate conflicting results, the scientific evidence is rated as contradictory and no conclusions can be drawn.

Summary

Background

An estimated 4% of men and 2% of women have obstructive sleep apnoea syndrome (OSAS), ie, daytime sleepiness and obstructive apnoeas during sleep. The apnoea-hypopnoea index (AHI) is the mean number of apnoeas and hypopnoeas per hour of sleep, and an AHI greater than 5 is considered pathological. Overnight polysomnography – including respiratory monitoring, pulse oximetry, electrocardiogram (ECG) and sleep staging with electroencephalogram (EEG) – is the reference diagnostic procedure.

Daytime sleepiness and snoring are the most common symptoms. OSAS is considered a risk for traffic accidents due to sleepiness. It has also been suggested that sleep apnoea is a risk factor for cardiovascular disease, diabetes mellitus and early death. The most common treatments are continuous positive airway pressure (CPAP), mandibular repositioning appliances and various surgical modalities. A number of other treatments and lifestyle modifications have been suggested. A diversity of portable simplified diagnostic equipment has been introduced due to the high cost of overnight polysomnograms.

This report contains the results of a systematic review regarding diagnosis and treatment of OSAS in adults. The aim of the review was to investigate:

- Consequences of OSAS on cardiovascular morbidity, diabetes mellitus, death and traffic accidents.
- How to diagnose OSAS.
- The effects of various treatment modalities, including compliance and adverse effects.

Methodology

The inclusion criteria and quality assessments were predefined. Systematic literature searches were performed in Medline, Embase and Cochrane Library. Randomised controlled trials, including a minimum of 20

subjects with a follow-up of at least 4 weeks, were included with daytime sleepiness as the primary outcome. Any trial design was considered for adverse effects, and a minimum of 100 patients and follow-up of at least one year were considered for compliance. Portable devices measuring airflow, oxygen saturation, respiratory movements, pulsoximetry alone and global impression were compared with polysomnography during the same night, with pooled sensitivity and specificity for the AHI or oxygen desaturation index as the outcome measure. The search also included night-to-night variability of polysomnography. Meta-analyses were performed for the effect of different treatment modalities and for different diagnostic methods compared to polysomnography. Prospective trials were considered when investigating the relationship of obstructive sleep apnoea to cardiovascular disease, death and diabetes mellitus.

Because the assessed surgical modalities are used for treating both snoring and OSAS, all adverse effects of these procedures were included in this report, regardless of diagnosis.

Titles and abstracts of all identified trials were screened by two independent investigators, and full reports were requested for all possible relevant articles. Data were independently extracted by two reviewers. The authors were contacted if any questions arose.

Cardiovascular diseases, diabetes mellitus and death

A covariation between OSAS and cardiovascular disease or early death in men was shown in 4 studies of medium or high quality comprising a total of 2 979 patients. Only 307 were women. Five prospective studies, 4 in the general population, investigated the association of obstructive sleep apnoea (ie an AHI over a critical level) with the above conditions. A dose-dependent association between apnoea-hypopnoea frequency and hypertension was found in one population study. Reduced survival was not found in a population study of seniors. The AHI was related to neither diabetes in a third population study nor stroke in a fourth. One prospective study on patients with coronary artery disease reported an independent covariation between an AHI greater than 10 and the incidence of stroke.

Traffic accidents

Four studies of medium quality investigated the effect of obstructive sleep apnoea on traffic accidents. All 4 reported an increased frequency of accidents in obstructive sleep apnoea subjects independent of driving exposure. One study reported an adjusted odds ratio of 2.6 (95% CI 1.1–64) for accidents when the AHI was above 20, regardless of whether they had daytime sleepiness. Another study reported an odds ratio of 11 (95% CI 4.0–30) at an AHI greater than 5 regardless of daytime sleepiness. A third study reported that patients with OSAS had more traffic accidents. Only the fourth study included a sufficient number of women. Obstructive sleep apnoea in men, but not in women, covaried with traffic accidents in this study.

Diagnostics

Night-to-night variability in polysomnographic recordings was investigated in 5 studies of medium quality that included patients seeking medical attention for sleep apnoea and 5 studies of medium quality in the general population. Between 81% and 90% of patients in 3 studies did not cross a certain AHI level when two recordings were compared. One study reported an interclass correlation of 0.92 (95% CI 0.90–0.95) during 4 nights. Between 64% and 87% in 4 studies of subjects in the general population did not cross a certain level of the AHI when two recordings were compared. One study reported an interclass correlation of 0.80 (95% CI 0.71–0.86) and another study of 0.80 (95% CI 0.69–0.87).

Manual scoring of portable simplified sleep apnoea investigations (n = 6) compared with in-lab polysomnography during the same night had a pooled LR+ of 9.95 (95% CI 4.01–24.6), LR– of 0.09 (95% CI 0.05–0.16), sensitivity of 0.93 (95% CI 0.89–0.97) and pooled specificity of 0.92 (95% CI 0.87–0.96), suggesting that about 7% will be false negative and 8% false positive. The scoring was performed by professionals trained in polysomnographic scoring. Automatic scoring of portable simplified devices (n = 3) compared with polysomnography had a pooled LR+ of 6.6 (95% CI 1.3–34.0) with heterogeneity, LR– of 0.11 (95% CI 0.05–0.16) with heterogeneity, sensitivity of 0.92 (95% CI 0.83–0.97) with

heterogeneity and pooled specificity of 0.85 (95% CI 0.73–0.93) with heterogeneity, suggesting that about 8% will be false negative and 15% false positive. Whether the automatic scoring systems can differentiate obstructive from central sleep apnoeas has not been tested.

Using pulse oximetry with ODI (oxygen desaturation index) 4% as a measure of sleep apnoea, the pooled LR+ was 10.4 (95% CI 5.0–21.4) with heterogeneity, LR– was 0.32 (95% CI 0.21–0.52), specificity was 0.93 (95% CI 0.91–0.95) and sensitivity was 0.69 (95% CI 0.66–0.72) with heterogeneity, suggesting that about 31% of patients with sleep apnoea will be classified as normal and 7% will obtain false positive results. Desaturations defined at 2% had better sensitivity of 0.87 (95% CI 0.83–0.90) with heterogeneity but lower specificity of 0.64 (95% CI 0.59–0.69) with heterogeneity.

A global impression from a case history and physical examination had a pooled LR+ of 1.7 (95% CI 1.5–2.0), LR– of 0.68 (95% CI 0.59–0.77), sensitivity of 0.54 (95% CI 0.49–0.58) with heterogeneity and specificity of 0.69 (95% CI 0.65–0.72) with heterogeneity, suggesting that about 46% will be false negative and 31% false positive.

Treatment

Continuous positive airway pressure (CPAP)

Continuous positive airway pressure treatment (CPAP) significantly reduced subjective sleepiness measured with the Epworth sleepiness scale by –2.7 (95% CI –3.2 to –2.2) and objective measurements of sleep latency as a proxy for daytime sleepiness according to the multiple sleep latency test and maintenance of wakefulness test. The frequency of apnoeas and hypopnoeas was significantly reduced by CPAP by –13.0 (95% CI –17.7 to –8.25) to a mean apnoea-hypopnoea index of 5.4 ± 4.8. There were conflicting results regarding quality of life measured as the short form-36 subscale vitality and functional outcome of sleep questionnaire. There were also conflicting results regarding the effect on blood pressure in patients with OSAS.

About 70% of patients still used CPAP after 4 years for a mean of 5.3 (range 4.4–6.2) hours per night, provided that patients and their equipment were seen by physicians after about 1 month and subsequently every 6–12 months with additional phone support. Mild to moderate discomfort from the CPAP mask – pain at the bridge of the nose, skin problems, air leaks and disturbing noise from the CPAP machine – were common adverse effects of CPAP. Mild nasal adverse effects, such as rhinitis, were also common.

The utilised pressure was lower using auto-CPAP than fixed CPAP –2.2 (–1.9 to 2.5) cm – but the effect on daytime sleepiness, apnoea reduction and compliance was the same according to 4 systematic reviews of medium and high quality. Most participants preferred auto-CPAP to fixed CPAP when their preference was measured. Auto-CPAP has not been tested for subjects with central apnoea.

Mandibular repositioning appliances (MRAs)

A number of different oral appliances have been suggested for the treatment of snoring and OSAS. Custom-made oral appliances for mandibular advancement significantly reduce subjective sleepiness measured as the Epworth sleepiness scale and objective measurements according to the multiple sleep latency test and maintenance of wakefulness test. The AHI was significantly less when using MRAs than a placebo device, but the difference was smaller compared to CPAP. Only single studies measured the functional outcome of sleep questionnaire and short form 36 subscale vitality. Thus, no conclusions regarding these variables can be drawn. Pooled data from 2 studies did not demonstrate any effect on blood pressure.

Two studies of medium quality that assessed compliance reported that 76% of patients used the appliance after 1 year and 56% after 5 years. Patients using MRAs reported temporary discomfort in the jaw or teeth in the mornings more often than those who used placebo devices or CPAP. Excessive salivation or dry mouth, pain, soreness or other discomfort in the teeth were also common during the first few months of

treatment. Small reductions (less than one millimetre) in overjet and overbite were reported. No increase in symptoms in the masticatory system could be seen during an observation period of 4 years.

Surgery

Only three randomised controlled studies comparing surgical treatment with sham surgery or conservative treatment were identified. Two studies investigated the effect after laser-assisted uvulopalatoplasty (LAUP) and one after temperature-controlled radio frequency tissue volume ablation (TCRAFTA). We did not find any studies fulfilling the inclusion criteria that reported treatment effects from uvulopalatopharyngoplasty (UPPP) or any other surgical modality. Regarding adverse effects from surgery, all studies were included regardless of indication for surgery, ie, obstructive sleep apnoea or snoring.

Uvulopalatopharyngoplasty

No randomised controlled trial fulfilling inclusion criteria investigated the treatment effects of uvulopalatopharyngoplasty (UPPP) for OSAS. But severe complications – including death, bleeding and loss of airway in up to 16% of patients – in the perioperative and postoperative period have been reported for this surgical modality when it comes to obstructive sleep apnoea or snoring. A total of 30 cases of death were reported in 6 studies. Respiratory compromise, bleeding, intubation difficulties, infections and cardiac arrest were the main causes of death. A recent study of high quality comprising 3 130 operations reported perioperative and postoperative death in 7 patients (0.2%). Persistent adverse effects occurred in 14–62%. Adverse effects included difficulty in swallowing in 13–36% and voice changes in 7–14%.

Uvulopalatoplasty

Two randomised controlled trials compared laser-assisted uvulopalatoplasty (LAUP) with sham surgery or conservative treatment for OSAS. One LAUP study reported a slight reduction in the AHI. But the other study found no difference. There were no effects on subjective sleepiness measured with the Epworth sleepiness scale. No effects were reported on sleep latency, wakefulness, quality of life or blood pressure. Uvulopalatoplasty performed with a scalpel (UPP) or laser-assisted uvulopa-

latoplasty (LAUP) for obstructive sleep apnoea or snoring was followed by perioperative and postoperative complications – including postoperative bleeding and infections with one report of death from septicaemia – in up to 5%. Persistent adverse effects were reported in 52–62%. Adverse effects included difficulty in swallowing in 19–29%, globus sensation in 17–36% and voice changes in 6–10%.

Radio frequency tissue volume ablation

One randomised controlled study compared temperature-controlled radio frequency tissue volume ablation (TCRAFTA) with sham surgery for OSAS. There was no effect on either the functional outcome of the sleep questionnaire or subjective sleepiness measured with the Epworth sleepiness scale. TCRAFTA used for obstructive sleep apnoea or snoring reported adverse effects that included palatal mucosal breakdown, mucosal ulcers, palatal fistula, uvula loss, haemorrhage and infections. Treatment of the tongue was associated with case reports of tongue base abscess, tongue swelling and mouth floor oedema. Long-term follow-up studies on adverse effects are lacking.

Other treatments and lifestyle modifications

No trials that fulfilled the inclusion criteria were found regarding the effects of weight reduction programmes, bariatric surgery, different drugs, pacemakers, devices to avoid sleep supine position or any other treatment for OSAS, except for one small study on didgeridoo playing. But there was no effect of didgeridoo playing vs no treatment at follow-up.

Future research

If surgery for OSAS or snoring is to be considered in the future, controlled trials for efficacy and long-term follow-up for adverse effects are necessary.

The covariation between cardiovascular disease and OSAS needs to be further elucidated. The effects of CPAP and/or MRAs on traffic accidents, morbidity and mortality are still unknown.

The effects of lifestyle changes are important issues, given that patients with OSAS often carry other risk factors for conditions such as obesity.

The Board of SBU is responsible for the conclusions of the report. The conclusions are not necessarily in accordance with the opinions of external experts.