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Sleep apnoea: from numbers to the people

Obstructive sleep apnoea (OSA) is defined as the presence of more than five events of complete obstruction (apnoea) or partial obstruction (hypopnoea) of the pharynx [apnoea–hypopnoea index (AHI) >5] per hour of sleep. Amongst adults, more than 24% of men and 9% of women suffer from OSA each night [1]. When a patient with OSA presents daytime sleepiness that affects work or social activity, OSA syndrome is diagnosed. Almost all patients with OSA snore and experience unrefreshed sleep but tend not to consult their general practitioner (GP) regarding this symptomatology. In most cases, patients visit their doctor at the request of their partner who has observed cessation of breathing during sleep or inappropriate DS. Overall, OSA is underdiagnosed and therefore undertreated. Despite this, it is currently a very common cause of GP consultation. The high prevalence of OSA in the industrialized world is related to the increasing prevalence of its main risk factor: obesity. Excessive fat deposit in the pharynx reduces the diameter of the upper airway and favours its collapse during sleep, when the tone of the intrinsic muscles of the pharynx is reduced compared to wake time.

The immediate health consequences of undiagnosed and untreated OSA, that is occupational or traffic accidents and reduced neurocognitive performance, are due to sleep deprivation. During the night, patients with OSA suffer intermittent hypoxaemia and acute autonomic arterial and haemodynamic changes. In the long term, these changes induce a permanent state of oxidative stress, systemic inflammation, hypercoagulability and insulin resistance. Therefore it is not surprising that many epidemiological studies have shown a strong association between OSA and increased cardiovascular (CV) morbidity and mortality [2–5] and, more recently, increased risk of neoplasms [6].

In this issue of the Journal of Internal Medicine [7], Lamberts *et al.* used the nationwide database of the entire Danish population to evaluate the role of sleep apnoea and continuous positive airway pressure (CPAP) therapy on the incidence rate of stroke and the incidence rate of myocardial infarction (MI). Three main conclusions were presented by the authors: (i) a diagnosis of 'sleep apnoea' was associated with an increased risk of stroke and MI; (ii) this risk was especially significant for subjects under 50 years of age; and (iii) there was no reduction in the risk of stroke and MI, relative to the general population, in patients who had been prescribed CPAP. The Danish nationwide database has the advantage of including health data and follow-up of all citizens regardless of the type of medical care they receive. However, the information obtained depends only on diagnoses and treatments reported by the healthcare system. The authors acknowledge multiple limitations of such population studies to establish association between a specific disease and its health outcomes. In the case of sleep apnoea, there are other limitations that should be considered. According to Lamberts *et al.*, less than 1% of the Danish population is diagnosed with 'sleep apnoea' and, because results of sleep studies were not presented, the proportion of patients with central sleep apnoea or OSA, or the severity of these conditions, is unknown. The use of the undiagnosed sleep apnoea population as a reference for establishing the risk of CV events is problematic as most Danish individuals with sleep apnoea that are not diagnosed and are in fact included in the 'control group' therefore sets a selection bias that underestimates the risk of developing health outcomes amongst subjects diagnosed with sleep apnoea. Amongst patients treated with CPAP, the degree of adherence to therapy (e.g. number of hours of use per day) is unknown. On the other hand, assuming that the range of severity of OSA obtained by the authors in the validation cohort is the same as in the general population, more than 48% and 89% of patients with mild and moderate OSA, respectively, are treated with CPAP in Denmark. It is not surprising that more than 30% of patients discontinue treatment as it is well known that patients with less severe OSA are less compliant with CPAP therapy. In other health systems, the indication for CPAP therapy is confined to patients with severe (AHI >30) or moderate OSA (AHI >15) with DS [8, 9]. The health benefit of CPAP

treatment appears to be limited to patients with severe OSA and with good adherence (>4 h of daily use) [2, 10]. Finally, the authors compared the protective effect of CPAP therapy on CV morbidity in patients treated with CPAP and the general population, which includes subjects with undiagnosed sleep apnoea but mainly individuals without this disorder. Taken together, these limitations could have attenuated the differences in treatment effect on evaluated outcomes. In summary, the findings of Lamberts *et al.* support the common belief that OSA is an independent CV disease risk factor but do not exclude the possibility of a protective effect of CPAP therapy to eliminate this increased risk.

The causal relationship between OSA and cardiovascular morbidity may be established only by large randomized controlled trials (RCTs) conducted over a long period of time. Such studies are unlikely as CPAP therapy is so effective in patients with symptomatic OSA that for ethical reasons they cannot be denied this treatment. At present, there is strong evidence from RCTs of a causal relationship between OSA and markers of risk of CV events such as hypertension. In addition, in a recent RCT, it was found that in OSA without DS, patients with worse sleep apnoea and with CPAP adherence of <4 h/night showed a higher rate of incident hypertension or CV events compared to those who used CPAP for more than >4 h/night [10]. Large RCTs are not always feasible. In addition to ethical and safety issues with regard to treatment allocation for OSA patients, RCTs require a long period of time in which clinical equipoise may exist, are expensive and have limited generalizability. In the meantime, good clinical and community-based studies, such as this study by Lamberts *et al.*, can improve understanding about disease outcomes and therapy.

The work of Lamberts *et al.*, amongst other studies, confirms the importance of OSA as a global public health concern. It is unclear which patients with OSA are more likely to develop CV or metabolic disorders. It is possible that in addition to the severity of the disease, other factors such as sensitivity to intermittent hypoxia, systemic inflammation or epigenetic modifications in regulatory genes involved in accelerated atherosclerosis contribute to worsen the prognosis of patients with OSA [11]. Meanwhilst, in the absence of widely accepted and validated guidelines, management of patients with suspected OSA should be based on minimum criteria such degree of daytime sleepiness evaluated by appropriated questionnaires and adequate examination of the upper airway, accurate diagnosis using validated sleep studies and discussion with the patient of the best available therapies. CPAP therapy is still the primary treatment of OSA, and therapeutic pressure should be individualized by a second sleep study or at home autotitration of CPAP. This treatment should be reserved for patients with DS and for those with severe OSA with or without DS (Fig. 1). Treatment adherence should be assessed periodically and, as for any patient with OSA, must be accompanied by abstention from smoking, alcohol consumption and use of sleeping pills and by active measures to reduce obesity including surgery, if necessary.

Conflict of interest statement

No conflicts of interest to declare.

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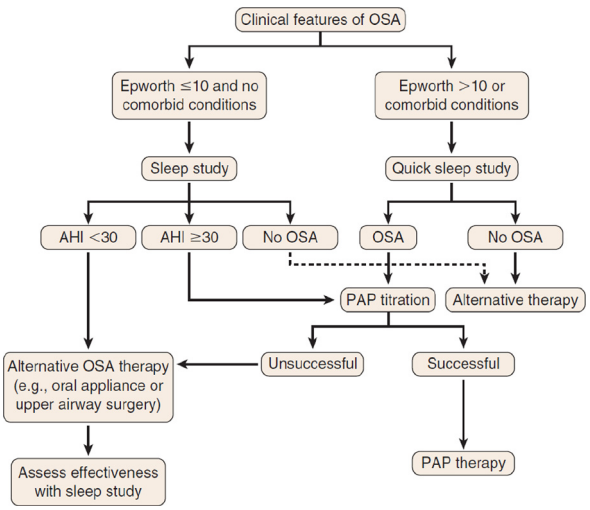

Fig. 1 *Treatment algorithm for obstructive sleep apnoea (OSA). Flow diagram showing a general approach to the management of patients with suspected OSA. Epworth, Epworth Sleepiness Scale; AHI, apnoea–hypopnoea index; PAP, positive airway pressure.*

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