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Original Article

Clinical and Cardiovascular Characteristics of Patients with Obstructive Sleep Apnoeas without Excessive Daytime Sleepiness

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ABSTRACT

Objectives: To investigate whether patients with obstructive sleep apnoea (OSA) without excessive daytime sleepiness (EDS) have cardiovascular problems and different clinical characteristics to OSA with EDS.
Methods: Two groups of patients were compared retrospectively, one without EDS (Epworth<11) and another control group with EDS (Epworth>10), adjusted for sex, age, body mass index (BMI) and apnoea-hypopnoea index (AHI). The diurnal and nocturnal symptoms of OSA were analysed along with polysomnography variables, prevalence of hypertension, diabetes mellitus, hyperlipaemia, and history of previous cardiovascular events. After adjusting for multiple confounding factors, a logistic regression was performed to identify the variables associated with OSA without EDS.
Results: A total of 166 patients without EDS were studied (Epworth 7.2 [2.4]) and 295 with EDS (Epworth 14.5 [2.5]). In the adjusted multivariate logistic regression, OSA without EDS is independently associated with a feeling of restful sleep (95%CI 1.70-3.93), less intellectual deterioration (95%CI, 0.30-0.95) and less effective sleep (95%CI, 0.96-0.99). No differences were found as regards prevalence of cardiovascular comorbidity, previous cardiovascular events, sleep structure, or nocturnal clinical symptoms of OSA. When the patients, who were in the extreme quartiles of the Epworth scale, were analysed, the results obtained were equivalent to those of the whole series, with only intellectual deterioration disappearing from the final model.
Conclusions: After adjusting for confounding variables, OSA without EDS has a similar prevalence of cardiovascular comorbidity and less diurnal symptoms than OSA with EDS.

Características cardiovasculares y clínicas de los pacientes con apneas obstructivas del sueño sin somnolencia diurna excesiva

Palabras clave:
Apneas obstructivas del sueño
Enfermedad cardiovascular
Somnolencia diurna excesiva

RESUMEN

Objetivos: Investigar si los pacientes con apneas obstructivas del sueño (AOS) sin somnolencia diurna excesiva (SDE) presentan problemas cardiovasculares y características clínicas diferentes de los AOS con SDE.
Métodos: Se compararon retrospectivamente dos grupos de pacientes con AOS, uno de ellos sin SDE (Epworth < 11) y otro control con SDE (Epworth > 10), ajustados por sexo, edad, índice de masa corporal (IMC) e índice de apneas-hipopneas (IAH). Se analizaron síntomas diurnos y nocturnos de AOS, variables polisomnográficas, prevalencia de hipertensión arterial, diabetes mellitus, hiperlipemia y antecedentes de eventos cardiovasculares previos. Se realizó una regresión logística ajustada por múltiples factores de confusión para identificar variables asociadas al AOS sin SDE.

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Resultados: Se estudiaron 166 pacientes sin SDE (Epworth 7,2 ± 2,4) y 295 con SDE (Epworth 14,5 ± 2,5). En la regresión logística multiajustada, el AOS sin SDE se asoció de forma independiente con sensación de sueño reparador (IC95% 1,70 a 3,93), menor deterioro intelectual (IC95% 0,30 a 0,95) y menor eficacia del sueño (IC95% 0,96 a 0,99). No se encontraron diferencias en cuanto a prevalencia de comorbilidades cardiovasculares, eventos cardiovasculares previos, estructura de sueño o clínica nocturna de AOS. Cuando se analizaron los pacientes que se encontraban en los cuartiles extremos del Epworth, los resultados obtenidos fueron superponibles a los del total de la serie, desapareciendo únicamente el deterioro intelectual del modelo final.

Conclusiones: Tras ajustar por variables de confusión, el AOS sin SDE tiene una prevalencia similar de comorbilidades cardiovasculares y menor sintomatología diurna que el AOS con SDE.

Introduction

The definition of sleep apnoea-hypopnoea syndrome is based on the presence of recurrent episodes of obstruction of the upper airway which disrupt sleep, leading to excessive daytime sleepiness (EDS) and cardiovascular complications.[1] In fact, EDS is not only one of the main symptoms that define this disease but is one of the pillars underpinning the move towards continuous positive airway pressure therapy (CPAP).[2] However, EDS does not occur in the same way in all patients and, in fact, only 40% of moderate-severe cases in the Sleep Heart Health Cohort Study[3] and less than 30% of cases in a large Spanish cohort study had EDS.[4] Although several clinical and epidemiological studies[5,6] have shown a correlation between the severity of sleep apnoea and the presence of EDS, other studies have found no such association.[7,8] Furthermore, EDS appears to be more closely related to depression or metabolic disorders than sleep-disordered breathing[9]; and a recent study showed that, apart from these latter factors, body mass index (BMI), consumption of alcohol, and comorbidity, such as a stroke, may also explain differences in the degree of sleepiness in patients with this sleep disorder.[10]

Most of the studies published on patients without EDS have focused on identifying the mechanisms by which this sleep disorder causes sleepiness in some cases and not in others. They propose the degree of nocturnal hypoxaemia and sleep fragmentation as the underlying mechanisms explaining these differences.[11,12] However, several recent reviews[13,14] have shown an worrying lack of information regarding both the manifestation and cardiovascular consequences of sleep apnoea without EDS. The few studies available have focused on analysing the effectiveness of CPAP treatment in reducing high blood pressure (HBP), in patients with and without associated EDS, but with contradictory results.[15,16]

The purpose of this study is to analyse cardiovascular comorbidity and clinical characteristics in a group of patients with obstructive sleep apnoea (OSA) without EDS, and to compare it with a series of OSA patients with EDS, adjusted for various confounding variables.

Methods

Design and Patients

A case-control retrospective study was performed. All the data was obtained from the patients' medical records. Those patients diagnosed with OSA (apnoea-hypopnoea index [AHI] ≥10/h, <50% central apnoea) by polysomnography between January 2004 and December 2006 were included. All of the cases were from the sleep-disordered breathing consultation of our unit. They were referred to our unit under clinical suspicion of OSA when at least two of the following symptoms were present: snoring, observed pauses, episodes of nocturnal asphyxia or EDS. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and a patient was diagnosed with EDS when the score was >10.[17,18] The study group consisted of all OSA patients without EDS detected consecutively during the inclusion period. iSubsequently, a control group was formed of OSA patients with EDS, adjusted for sex, age (±5 years), BMI (±1 kg/m^2) and AHI (±5/hr).

The cases excluded were those where the sleep study was not analysed manually, the total sleep time was <3hr, EDS was not established by ESS and there was no sleep observer. The study was approved by the hospital ethics committee.

Clinical Evaluation

All patients initially underwent a structured clinical examination by protocol, with a physical examination and systematic blood tests.

The signs and symptoms of OSA were assessed using a modified version of two validated questionnaires; the Berlin questionnaire[19] and the Ballester et al. questionnaire.[20] It asked about the following: habitual snoring (≥3 times/week), regular pauses observed (≥3 times/week), number of nocturnal awakenings per night, episodes of nocturnal asphyxia in the previous month (yes/no), nocturia (≥2 times/night), headaches in the morning (≥1 time/week), restless sleep (≥3 times/week), difficulties in concentrating due to tiredness or sleepiness (yes/no) and recent memory loss (yes/no). Patients were considered to have intellectual impairment if they answered yes to at least one of these last two questions.

To determine the patients' history of previous cardiovascular events and the prevalence of cardiovascular comorbidity, a thorough investigation was carried out based on the clinical interview and on data obtained from the patients' medical history. Patients were classified as hypertensive (HTN), diabetic (DM) or hyperlipidaemic (HLP) if they had been previously diagnosed with any of these conditions, were receiving specific treatment for any of them, or had a systolic/diastolic blood pressure (BP) >140/90 in 2 or more ambulatory measurements, had fasting glucose levels >110mg/dl in 2 or more measurements, or fasting cholesterol and/or triglyceride levels >200mg/dl. Patients were considered to have suffered a prior cardiovascular event if they had a history of at least one of the following: stroke, heart failure, arrhythmia, or ischaemic heart disease. They were also questioned about their habitual consumption of potentially sedative drugs (antihistamines, benzodiazepines, non-benzodiazepine sedatives, antipsychotics, and barbiturates), ethanol intake (g/d) and smoking.

Sleep Study

The diagnosis of OSA was established in all cases by a full polysomnography (Compumedics PS®, Melbourne, Australia)

performed overnight in a sleep laboratory. The electroencephalogram, electrooculogram, electromyogram, oronasal flow and pressure, chest and abdominal effort, electrocardiogram, and arterial oxygen saturation (SaO_2) were recorded. All studies were analysed manually by medical experts, according to standard criteria.[21] Air flow was measured with an oronasal thermistor and respiratory movements with bands. Apnoea was defined as the absence of oronasal flow >10 seconds, classified as obstructive or central according to the presence or absence of breathing movements. Hypopnoea was defined as a reduction of 30%-90% in oronasal flow >10 seconds, associated with ≥3% desaturation or an arousal. We used the minimum SaO_2 (SaO_2 min) and the percentage of time with SaO_2 <90% (CT90) as markers of nocturnal hypoxia.

Statistical Analysis

The SPSS 16.0 software package (SPSS Inc. Chicago, IL, USA) was used for data processing and statistical analysis. Continuous variables were expressed as mean (SD) and qualitative variables were expressed as percentages. Normality in the distribution of the data was established using the Kolmogorov test. The means were compared using the unpaired Student t-test, while the Chi-square test with Yates' correction was used for qualitative variables.

Both groups were initially compared by carrying out a bivariate analysis. Subsequently, a forward logistic regression analysis was performed, including the variables with p<.15 in the bivariate analysis, to identify which variables were independently associated with AOS without EDS. To correct for potential confounding factors, the following variables were also included in the logistic regression: sex, age, BMI, AHI, CT90, consumption of drugs with a sedative effect, alcohol intake and smoking. A value of p≤.05 was considered significant. Finally, to investigate whether patients with extreme ESS values showed any differences that would not be seen if only a single cut-off point was used, the series was divided into ESS quartiles (ESS<9, 104 cases; ESS 9-12, 144 cases; ESS 13-15, 109 cases; and ESS>15, 99 cases). An additional analysis was performed comparing the extreme quartiles (ESS<9 v ESS>15) using bivariate analysis and logistic regression, as had been performed previously for the entire series.

To calculate a sample size, it was assumed that 35% of patients would have experienced a prior cardiovascular event and 50% would be hypertensive.[22] The sample size was calculated to detect a 10% difference in the prevalence of hypertension or previous cardiovascular events between both groups. According to this calculation, at least 136 patients were needed in each group, taking into consideriation an error of α=.05 and a power of 0.8.

Results

During the study period, 181 cases of OSA without EDS and 318 OSA cases with EDS were included, after adjusting for sex, age, BMI and AHI. 10 patients were excluded because the sleep study was not analysed manually , 5 where the total sleep time was <3hr. 5 where EDS was not established by ESS, and 18 due to the absence of a sleep observer. As a result, 166 cases of OSA without EDS and 295 with EDS were analysed. The clinical, polysomnographic and cardiovascular features of both groups are shown in table 1, 2 and figure 1.

Both groups were comparable in terms of sex, age, BMI, and severity of OSA (measured by AHI, SaO_2 min and CT90). In the bivariate analysis, less apnoea was observed in cases without EDS than for the group with EDS (73.4% vs 81.6%, p=.05), morning headache (25.3% vs 39.3%, p=.003), intellectual impairment (11.5% vs 23.6%, p=.002), total sleep time (301.9 [69.6] vs 316.8 [65.6 min], p=.02) sleep efficiency (71.5% [15.1] vs 75.7% [13.4], p=.002), and more reparative sleep (45.7% vs 23.3%, p<.0005), (table 1 and 2). There were no differences in the prevalence of HTN, DM, HLP or in the history of previous cardiovascular events between the groups (fig. 1).

The results of the logistic regression analysis adjusted for multiple confounding factors are shown in table 3. After adjusting for sex, age, BMI, AHI, CT90, smoking, alcohol intake, and use of sedative drugs, the variables independently associated with OSA without EDS were

Table 2
Polysomnographic features of OSA patients with and without EDS

Polysomnographic variables	OSA without EDS	OSA with EDS	p
Total sleep time (min)	301.9 (69.6)	316.8±65.6	0.02
Efficiency (%)	71.5±15.1	75.7±13.4	0.002
Phase I (%)	41.0 (17.5)	40.9 (18.6)	0.97
Phase II (%)	36.3 (12.7)	35.0 (12.8)	0.27
Phase III-IV (%)	11.4 (9.5)	11.8 (9.2)	0.71
REM phase (%)	10.4 (5.8)	11.2 (6.1)	0.15
AHI mean	37.5 (21.9)	38.0 (25.0)	0.81
AHI >30, No. (%)	84 (50.6%)	143 (48.4%)	0.73
SaO_2 minimum (%)	75.8 (10.8)	76.0 (11.8)	0.81
CT90 (%)	9.6 (16.3)	11.7 (19.8)	0.24

All variables are expressed as mean (SD), unless otherwise indicated. OSA: obstructive sleep apnoea-hypopnoea; CT90: time with arterial oxygen saturation below 90%; AHI: apnoea-hypopnoea index; EDS: excessive daytime sleepiness; SaO_2 min: minimum arterial oxygen saturation.

Table 1
Clinical features of patients with OSA, with and without EDS

Clinical variables	AOS without SDE	AOS with SDE	p
Males, No. (%)	113 (68.0)	198 (67.1)	0.91
Age, mean (SD)	55.2 (11.2)	53.2 (11.7)	0.07
BMI (kg/m^2), mean (SD)	34.1 (5.6)	34.0 (6.3)	0.89
Epworth scale, mean (SD)	7.2 (2.4)	14.5 (2.5)	<0.0005
Active smokers, No. (%)	87 (52.4%)	158 (53.5%)	0.88
Alcohol intake (g/d), mean (SD)	14.8 (26.3)	14.2 (24.3)	0.80
Sedatives, No., (%)	39 (23.4%)	54 (18.3%)	0.20
Habitual snoring, No. (%)	163 (98.1%)	289 (97.9%)	0.85
Pauses observed, No. (%)	122 (73.4%)	241 (81.6%)	0.05
No. of awakenings per night, mean (SD)	2.3 (1.7)	2.5 (1.8)	0.19
Night asphyxial crises, No. (%)	55 (33.1%)	110 (37.2%)	0.38
Morning headache, No. (%)	42 (25.3%)	116 (39.3%)	0.003
Nocturia, No. (%)	60 (36.1%)	120 (40.6%)	0.75
Reparative sleep, No. (%)	76 (45.7%)	69 (23.3%)	<0.0005
Intellectual impairment, No. (%)	19 (11.5%)	69 (23.6%)	0.002

OSA: obstructive sleep apnoea-hypopnoea sleep; BMI: body mass index; EDS: excessive daytime sleepiness.

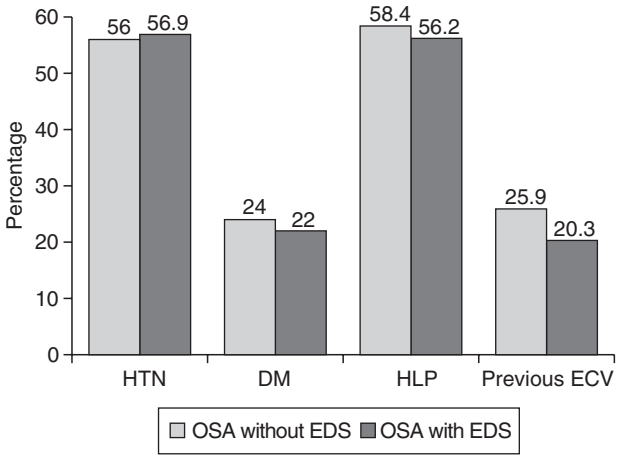

Figure 1. Prevalence of cardiovascular disease in OSA patients with and without EDS.

Table 3
Predictors of OSA without EDS. Results of logistic regression analysis adjusted for sex, age, BMI, AHI, CT90, smoking, consumption of alcohol and of sedative drugs

Variables	Multi-adjusted (OR, 95% CI)	p
TST	1.01 (0.99-1.01)	.95
Sleep efficiency	0.98 (0.97-0.99)	.003
Snoring	1.33 (0.89-1.05)	.75
Pauses observed	1.21 (0.49-2.94)	.67
No. of awakenings	1.01 (0.89-1.15)	.78
Morning headaches	0.66 (0.40-1.08)	.10
Reparative sleep	2.64 (1.73-4.02)	<.0005
Intellectual impairment	0.54 (0.31-0.96)	.035
Hypertension	0.76 (0.49-1.19)	.24
Diabetes mellitus	1.01 (0.62-1.65)	.94
Hyperlipidaemia	1.08 (0.73-1.60)	.69
Cardiovascular events	1.28 (0.78-2.12)	.31

Table 4
Variables associated with the OSA group with ESS<9. Results of the logistic regression analysis adjusted for sex, age, BMI, AHI, CT90, smoking, consumption of alcohol and of sedative drugs

Variables	Multi adjusted (OR, 95% CI)	p
Sleep efficiency	0.97 (0.95-0.99)	.02
Snoring	1.32 (0.87-1.08)	.70
Pauses observed	1.07 (0.33-3.46)	.90
No. of awakenings	1.05 (0.85-1.29)	.61
Morning headaches	0.70 (0.32-1.52)	.36
Reparative sleep	6.42 (3.20-12.89)	<.0005
Intellectual impairment	0.44 (0.17-1.13)	.08
Hypertension	0.82 (0.39-1.74)	.61
Diabetes mellitus	1.16 (0.46-2.89)	.75
Hyperlipidaemia	0.79 (0.40-1.53)	.48
Cardiovascular events	0.71 (0.29-1.72)	.45

lower sleep efficiency (OR 0.98, 95 % CI, 0.97-0.99), less intellectual impairment (OR 0.54, 95% CI, 0.31-0.96) and more restful sleep (OR 2.64, 95% CI, 1.73-4.02). No significant association was found with any of the cardiovascular variables analysed.

Comparing ESS Extreme Quartiles

After splitting the series into ESS quartiles, the lower quartiles (ESS<9, 104 patients) were compared with the upper quartiles (ESS>15, 99 patients). In the bivariate analysis, the patients with OSA and ESS<9 showed fewer morning headaches (24.0% vs 39.3%, p=.02), less intellectual impairment (8.7% vs 24.2%, p=.005), lower sleep efficiency (72.2% (5.2) vs 76.4% (12.4), p=.03) and more sleep (50% vs 14.1%, p<.0005) compared with the group with OSA and ESS>15. The logistic regression analysis results are shown in table 4. After adjusting for multiple confounding factors, the variables independently associated with the lowest ESS quartile were lower sleep efficiency (OR 0.97, 95% CI, 0.95-0.99) and more reparative sleep (OR 6.42, 95% CI, 3.20-12.89). No significant association was found with any of the cardiovascular variables analysed.

Discussion

The results of this study show that, when adjusted for confounding variables, patients with OSA with and without EDS have a similar prevalence of cardiovascular comorbidity at diagnosis. Cases without EDS showed less daytime symptoms resulting from their sleep apnoea compared with the EDS group, despite having similar nocturnal symptoms. These results remained virtually unchanged when patients with extreme degrees of ESS were compared.

This study attempted to analyse whether OSA patients without EDS had different characteristics compared to a typical patient with EDS, especially if the absence of hypersomnia was associated with a lower prevalence of cardiovascular comorbidity, as has been suggested by some authors.15,16 To investigate this, two groups of patients similar in age, sex, BMI and AHI were compared, with subsequent adjustment for these and other variables that could influence the clinical and cardiovascular parameters analysed. In the end, no differences were found regarding the prevalence of HTN, DM, HLP or history of previous cardiovascular events, irrespective of the presence or absence of EDS. The results were unchanged when patients in the extreme quartiles of the ESS were compared. These data suggest that the absence of EDS in OSA does not provide a special protection against major cardiovascular comorbidity nor does it alter the risk of suffering a cardiovascular event, even in those patients with very low ESS values.

Although only a few studies have directly compared the cardiovascular complications in OSA with and without associated EDS, our results are supported by studies which have shown that EDS is not a factor in the development of cardiovascular disease in these patients. The Wisconsin prospective cohort study[23] found that cardiovascular mortality was 5 times higher in severe OSA compared to the control group, independent of the presence of hypersomnia. Kohler et al[24] compared 64 patients with mild OSA without EDS with 15 healthy controls in a trial, which showed endothelial dysfunction and increased arterial stiffness in the OSA group. This suggested that there is an increased cardiovascular risk, even in mild cases and without associated EDS. Kaneko et al[25] showed that treatment with CPAP in OSA patients without daytime sleepiness and heart failure improved the ejection fraction of the left ventricle.

By contrast, two authors obtained inconclusive results when analysing the effect of CPAP on BP in OSA patients without EDS. Barbe et al15 studied 55 patients with severe OSA without EDS for 6 weeks in a multicentre, placebo-controlled study, and found that CPAP did not reduce BP compared to sham-CPAP. Robinson et al16 found similar results in a study of 35 patients with OSA without hypersomnia and mild hypertension. This author suggests that sleep fragmentation could be the main mechanism involved in the pathophysiology of HTN in these patients, as EDS is a marker for it. However, this theory could not be tested, as the patients were not diagnosed by conventional polysomnography in this study. In contrast to these authors, several meta-analyses did not find the degree of daytime sleepiness in patients with OSA and hypertension to be a predictor of lower BP.[26,27] Moreover, a recent multicentre

study of 359 hypertensive patients with severe OSA without EDS (ESS<11) showed that 1 year of treatment with CPAP significantly reduced BP, despite the lack of EDS. A dose-response effect was also detected, with greater BP reductions in patients with a higher treatment completion rate (>5.6hr/d).[28]

The clinical characterisation of these patients is another interesting but little studied aspect. In the absence of EDS, it would be interesting to have other daytime symptoms that would act as disease markers and would help us to determine which patients should undergo a sleep study or need treatment with CPAP. We found that OSA patients without EDS, generally, have less daytime symptoms derived from their sleep apnoea than the EDS group. These patients complain of less intellectual impairment and of more restful sleep, despite having an equivalent OSA severity level and similar nocturnal symptoms, in terms of snoring, nocturia, number of nighttime awakenings or episodes of nocturnal asphyxia. When comparing the extreme quartiles of ESS, the patients with the lowest EDS still felt that they had had more reparative sleep than the group with greater EDS in the series. These results indicate that this group of patients not only have less daytime sleepiness, but also in general have less subjective symptoms arising from their sleep disorder. Although the aim and design of the study was not intended to analyse the reasons for the differences in the perception of EDS or other daytime symptoms between the two groups, they would not, according to our results, appear to be attributable to differences in sleep macrostructure or severity of OSA.

Finally, we found that patients without EDS have significantly lower sleep efficiency than those with EDS. This has been reported on before.[29,30] It has been suggested that patients without EDS suffer greater sleepiness throughout the whole circadian rhythm, and that, therefore, sleep disturbance caused by apnoea was not the primary cause of EDS, at least in ~~all~~ ~~the~~ patients with this pathology.

Our study has two main limitations; the first being its retrospective nature. However, clinical and cardiovascular variables were investigated during the initial visit, before the diagnosis of OSA, and were based on a structured interview and data from the clinical history, fasting blood tests and BP. These data were not subsequently modified. Moreover, as this is a case series study to diagnose or exclude OSA, even if there were errors in the data collection, we do not believe that they would present a bias, as they would be unlikely to affect one group more than another. The second limitation relates to possible selection bias. One could argue that the cases without EDS would have arisen preferentially from cardiovascular comorbidity, while typical cases would have arisen due to EDS. Obviously, this bias is inherent in any clinical series where patients are sent with varying degrees of clinical suspicion of OSA, and a population cohort would be needed to completely avoid this bias. In any case, this study required patients to have at least two of the most common symptoms of OSA, such as snoring, observed pauses, nocturnal or EDS episodes of asphyxia, before being included in this study, so as to avoid this problem as far as possible. Finally, including a control group as well as the study group ~~, this~~ might have led to oversampling. However, we do not consider that this has influenced the final results, as is shown by the results obtained when comparing the ESS extreme quartiles, where the size of both groups was similar.

In conclusion, the results of this study indicate that, when adjusted for multiple confounding variables, the prevalence of cardiovascular comorbidity in OSA patients with and without associated EDS is similar. Furthermore, the latter had less daytime symptoms resulting from their sleep disorder. Prospective studies are needed to confirm that patients without EDS have a similar risk of cardiovascular complications to those with EDS.

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Conflict of Interest

The authors affirm they have no conflict of interest.

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