Original Article

# High incidence of stroke in young women with sleep apnea syndrome

Chih-Cheng Chang [a,b], Hsiao-Chi Chuang [a,c], Cheng-Li Lin [d], Fung-Chang Sung [d,e], Yen-Jung Chang [d], Chung Y. Hsu [f,g,*], Ling-Ling Chiang [a,c,*]

[a] Division of Pulmonary Medicine, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[b] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[c] School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan
[d] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[e] Department of Public Health, China Medical University, Taichung, Taiwan
[f] Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
[g] Department of Neurology, China Medical University Hospital, Taichung, Taiwan

## ARTICLE INFO

## ABSTRACT

Objective: Patients with sleep apnea syndrome (SAS) carry a higher stroke risk. The differential stroke risk between sex and among different age groups has not yet been specifically addressed in previous studies.
Methods: Using a universal insurance claims database, we identified a large cohort of SAS patients from 1997 to 2010 and assessed the sex- and age-specific stroke risk compared with a control cohort matched for age, sex, and index date. Cox regression analyses were performed to assess the hazard ratio (HR) of stroke and the corresponding 95% confidence interval (CI). Stroke-free probabilities were computed using the Kaplan–Meier method and differences between both cohorts were examined using the log-rank test.
Results: We identified 29,961 patients with SAS and a control cohort of 119,844 subjects without SAS. The overall incidence of stroke in the SAS cohort was 37% higher compared to the non-SAS cohort (54.6 per 10,000 individual-years vs 39.8 per 10,000 individual-years). After controlling for sex and comorbidities, the SAS cohort exhibited a 19% higher risk for stroke compared to the control cohort (adjusted HR, 1.19 [95% CI, 1.09–1.30]). Women with SAS ages 35 years or younger had the highest stroke risk compared to older age groups of the same sex and their risk for stroke was relatively higher compared to their male counterparts.
Conclusion: Women aged 35 years or younger with SAS have a higher stroke risk.

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## 1. Introduction

A number of studies have reported on the epidemiology of sleep apnea syndrome (SAS). SAS is a common clinical disorder that consists of obstructive sleep apnea, central sleep apnea, and mixed sleep apnea. SAS is associated with impaired palate-pharyngeal collapse during sleep, including decreased muscle tone of the pharyngeal area and repetitive airway obstruction [1]. Repetitive nocturnal hypoxemia in patients with SAS has been increasingly associated with metabolic and inflammatory diseases [2]. Moreover, these mechanisms have been shown to be associated with the development of cardiovascular disease, suggesting that SAS may potentially contribute to the initiation and progression of cardiovascular disease.

Clinically, SAS is prevalent in patients with preexisting cardiovascular diseases. In the United States, obstructive sleep apnea affects an estimated 15 million adults and is found in a large proportion of patients with hypertension and patients with other cardiovascular disorders [3,4]. Increasing evidence indicates that SAS is a risk factor for stroke. For example, a previous study found that a sleep-clinic population with untreated SAS had a higher rate of fatal and nonfatal cardiovascular events such as ischemic heart disease and stroke compared to healthy subjects [5]. Stroke is the second or third leading cause of death and is the leading cause of adult disability worldwide.

Risk factors for stroke include hypertension, atrial fibrillation, diabetes mellitus, smoking, and obesity. Epidemiologic studies also have shown that SAS may be an independent risk factor for stroke. A cross-sectional study reported a strong association between

* Corresponding authors. Address: Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan. Tel.: +886 4 22052121x6033 (C.Y. Hsu). Address: School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan. Tel.: +886 2 27361661x3519; fax: +886 2 27391143 (L.-L. Chiang).
E-mail addresses: hsuc@mail.cmuh.org.tw (C.Y. Hsu), llchiang@tmu.edu.tw (L.-L. Chiang).

moderate to severe SAS and stroke prevalence [6]. Previous studies also have found that the development of SAS is associated with age and sex [7,8]; however, the association of age- and sex-specific differences between stroke and SAS patients remains unclear. In our study, we took advantage of a universal healthcare insurance system, the National Health Insurance in Taiwan, to study a large cohort of patients with SAS to assess the age- and sex-specific vulnerability of developing stroke. Our results showed that younger women aged 35 years or younger had the highest stroke risk compared to any other age group and the men.

## 2. Materials and methods

### 2.1. Data sources

The Taiwan National Health Insurance is a single-payer system that integrated 13 public insurance systems in 1995 to serve all Taiwanese residents. This insurance program covers approximately 99% of the 23.7 million residents [9]. The National Health Research Institute has been authorized by the Taiwan Department of Health to manage medical claims data and to establish databases for research use. For our study, we used population-based claims data on 1 million insured individuals from 1996 to 2010. Diagnoses were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification Codes* (ICD-9-CM).

### 2.2. Study sample

Patients aged 20 years and older with SAS (ICD-9-CM codes 780.51, 780.53, and 780.57) and who were newly diagnosed between 1997 and 2010 were identified from the inpatient claims database. For the diagnoses of sleep apnea, polysomnography was conducted according to the standard criteria [10]. Polysomnographic all-night recordings in the hospital-based sleep laboratory were performed. The average number of episodes of apnea and hypopnea per hour of sleep (apnea-hypopnea index [AHI]) was calculated. The minimum criterion for SAS was AHI ⩾ 5 events per hour. The inpatient diagnosis date of SAS was defined as the index date to determine the follow-up duration. Patients who had a history of stroke (ICD-9-CM codes 430–438) prior to the index date were excluded. For the diagnoses of stroke, computed tomography scans of brain were conducted. The non-SAS cohort consisted of randomly selected participants who were matched to the SAS cohort for age, sex, and index date. The SAS and non-SAS cohorts were selected at a 1–4 ratio to improve the statistical power. Subjects with a history of either stroke or SAS at baseline were excluded.

### 2.3. Outcome measurements

Both cohorts were followed from the index date until a new diagnosis of stroke was made or until the patients were censored due to a loss of follow-up, death, withdrawal from the insurance system, or the end of 2010—whichever came first. The comorbidities considered in our study included obesity (ICD-9-CM code 278.0), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), coronary artery disease (ICD-9-CM codes 410–413, 414.01–414.05, 414.8, and 414.9), congestive heart failure (ICD-9-CM codes 428, 398.91, and 402 × 1), and atrial fibrillation (ICD-9-CM code 427.31).

### 2.4. Statistical analysis

Distributions of the demographic characteristics and baseline comorbidities were compared between the SAS and non-SAS cohorts. Categorical variables were compared using the $\chi^2$ test and continuous variables were compared using $t$ tests. The stroke incidence rates were estimated and compared between the SAS and non-SAS cohorts. The SAS cohort to non-SAS cohort incidence rate ratio and the 95% confidence interval (CI) were estimated using Poisson regression analysis. The multivariable Cox proportional hazards regression model was used to assess the hazards ratio (HR) for stroke and the corresponding 95% CI. Stroke-free probabilities were computed using the Kaplan–Meier method and the differences between both cohorts were examined using the log-rank test. All analyses were performed using the SAS statistical software version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Two-sided $P$ values less than .05 were considered significant.

## 3. Results

We identified 29,961 patients with SAS who were matched with 119,844 participants without SAS based on age, sex, and index date (Table 1). No significant difference in sex, age, or follow-up years was found between both cohorts. Both SAS cohorts of men and women showed a significantly higher prevalence rate of selected comorbidities ($P < 0001$), including obesity, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, and congestive heart failure, compared to the non-SAS cohort.

The incidence and HR of stroke by age among men and women with and without SAS are shown in Table 2. Overall, the SAS cohort had a higher stroke incidence (52.4 per 10,000 individual-years for men and 61.7 per 10,000 individual-years for women) compared to the non-SAS cohort (40.7 per 10,000 individual-years for men and 37.3 per 10,000 individual-years for women), with adjusted HRs between men and women of 1.21 (95% CI, 1.01–1.24; $P < 05$) and 1.44 (95% CI, 1.20–1.72; $P < 05$), respectively. We further assessed the association between SAS and stroke risk stratified by age (Table 2). Among women, the effects of SAS on stroke risk decreased with age (adjusted HR, 4.90 [95% CI, 1.93–12.4] for subgroup aged 20–35 years; adjusted HR, 1.64 [95% CI, 1.01–2.65] for subgroup aged 36–50 years; adjusted HR, 1.38 [95% CI, 1.01–1.89] for subgroup aged 51–65 years). In men aged 36–50 years, we observed an association between SAS and an increased stroke risk (adjusted HR, 1.33 [95% CI, 1.10–1.62]). We further investigated the association of stroke and comorbidities among men and women with SAS (Table 3). No significant association between SAS and comorbidities was observed in men and women with SAS.

Kaplan–Meier analysis was used to estimate the cumulative probabilities of stroke between cohorts of men and women with and without SAS. The SAS cohort had a higher probability of stroke compare to the non-SAS cohort (log-rank test, $P < 001$), particularly among women aged 20 to 35 years as shown in Fig. 1.

## 4. Discussion

The main finding of our study was that SAS is a risk factor of stroke and exhibits sex- and age-specific differences. The results supporting our conclusion included the overall incidence rate of stroke, which was significantly higher in the SAS cohort compared to the non-SAS cohort. In particular, young women with SAS (ages 20–35 years) had the highest risk for stroke. These findings showed that young women with SAS were the most susceptible group for the development of stroke.

Clinically, sleep apnea in the form of obstructive apnea and central sleep apnea frequently occurs among stroke patients. Previous studies have found that sleep-disordered breathing (SDB) was frequently prevalent among stroke patients [11,12]. Post-stroke patients with moderate SDB had a higher risk for arterial stiffness

**Table 1**
Demographic characteristics and comorbidities in sleep apnea syndrome and non-sleep apnea syndrome cohorts.

| | Men SAS | | | | | Women SAS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No | | Yes | | P value | No | | Yes | | P value |
| | n = 90,296 | | n = 22,574 | | | n = 29,548 | | n = 7387 | | |
| | n | (%) | n | (%) | | n | (%) | n | (%) | |
| *Age (y)* | | | | | | | | | | |
| 20–35 | 30,016 | 33.2 | 7504 | 33.2 | .99 | 10,296 | 34.8 | 2574 | 34.8 | 0.99 |
| 36–50 | 36,100 | 40.0 | 9025 | 40.0 | | 8508 | 28.8 | 2127 | 28.8 | |
| 51–65 | 17,140 | 19.0 | 4285 | 19.0 | | 7116 | 24.1 | 1779 | 24.1 | |
| ⩾66 | 7040 | 7.80 | 1760 | 7.80 | | 3628 | 12.3 | 907 | 12.3 | |
| mean ± SD | 42.7 | 13.8 | 42.8 | 13.8 | | 44.4 | 16.1 | 44.4 | 16.1 | |
| Follow-up (y), mean ± SD | 4.73 | 3.35 | 4.75 | 3.39 | 0.36 | 4.72 | 3.35 | 4.65 | 3.38 | 0.10 |
| *Comorbidity* | | | | | | | | | | |
| Obesity | 33 | 0.04 | 426 | 1.89 | <.0001 | 18 | 0.06 | 283 | 3.83 | <.0001 |
| Diabetes mellitus | 1843 | 2.04 | 1433 | 6.35 | <.0001 | 722 | 2.44 | 702 | 9.50 | <.0001 |
| Hypertension | 2777 | 3.08 | 3862 | 17.1 | <.0001 | 1206 | 4.08 | 1411 | 19.1 | <.0001 |
| Hyperlipidemia | 1139 | 1.26 | 1220 | 5.40 | <.0001 | 305 | 1.03 | 414 | 5.60 | <.0001 |
| Coronary artery disease | 1533 | 1.70 | 1652 | 7.32 | <.0001 | 546 | 1.85 | 582 | 7.88 | <.0001 |
| Atrial fibrillation | 202 | 0.22 | 256 | 1.13 | <.0001 | 91 | 0.31 | 123 | 1.67 | <.0001 |
| Congestive heart failure | 400 | 0.44 | 714 | 3.16 | <.0001 | 197 | 0.67 | 451 | 6.11 | <.0001 |

*Abbreviations*: SAS, sleep apnea syndrome; y, years; SD, standard deviation.

**Table 2**
Incidence and hazard ratios of stroke according to sex, age, and comorbidity among patients with and without sleep apnea syndrome.

| Variables | Men SAS | | | | | Women SAS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No | | Yes | | Adjusted HR[c] (95% CI) | No | | Yes | | Adjusted HR[c] (95% CI) |
| | Event | Rate[a] | Event | Rate[a] | | Event | Rate[a] | Event | Rate[a] | |
| All strokes | 1738 | 40.7 | 562 | 52.4 | 1.21 (1.01–1.24)[*] | 520 | 37.3 | 212 | 61.7 | 1.44 (1.20–1.72)[***] |
| *Age (y)* | | | | | | | | | | |
| 20–35[b] | 63 | 4.45 | 30 | 8.14 | 1.03 (0.62–1.71) | 8 | 1.54 | 12 | 8.86 | 4.90 (1.93–12.4)[***] |
| 36–50 | 379 | 21.4 | 174 | 38.8 | 1.33 (1.10–1.62)[**] | 57 | 13.7 | 35 | 33.9 | 1.64 (1.01–2.65)[*] |
| 51–65 | 588 | 76.3 | 168 | 89.0 | 0.85 (0.71–1.03) | 154 | 47.9 | 70 | 91.3 | 1.38 (1.01–1.89)[*] |
| ⩾66 | 708 | 228.7 | 190 | 283.5 | 0.98 (0.83–1.17) | 301 | 214.8 | 95 | 336.4 | 1.02 (0.78–1.33) |

*Abbreviations*: SAS, sleep apnea syndrome; HR, hazards ratio; CI, confidence interval; y, years.
[a] Rate = incidence rate, per 10,000 individual-years.
[b] P value for interaction = .02.
[c] Adjusted HR: adjusted for age, diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, atrial fibrillation and congestive heart failure.
[*] P < 05.
[**] P < 01.
[***] P < 001.

[13]. It is important to identify the susceptible group for the development of stroke among SAS patients. Our population-based retrospective cohort study in Taiwan showed that SAS patients showed a higher risk for stroke incidence. SAS, a form of SDB, is associated with multiple major stroke risk factors; however, it also is an independent risk factor for stroke. On the basis of this evidence, we proposed that patients with SAS were susceptible to the development of stroke. However, few studies have identified which susceptible SAS groups had a greater stroke incidence rate for preventative medical purposes.

We observed that men with SAS aged 36–50 years and women SAS aged 20–65 years had a significantly higher HR of stroke, particularly women with SAS aged 20–35 years. The most vulnerable group (women aged 20–35 years) was identified in our study. Our results revealed that women with SAS had a higher risk for stroke incidence compared to men with SAS. The Wisconsin Sleep Cohort Study investigated the prevalence of SDB in the United States from 1988 to 1994 and 2007 to 2010 [14]. The prevalence of moderate to severe SDB was 10% among men aged 30–49 years,

17% among men aged 50–70 years, 3% among women aged 30–49 years, and 9% among women aged 50–70 years. Our results showed that SDB was predominant in men ages 50–70 years. Although men have a higher prevalence of SDB, we found that younger women with SAS were more susceptible to developing stroke compared to men. A follow-up study performed in 1042 incident cases of cardiovascular disease demonstrated that SDB was associated with an increased risk for cardiovascular disease in women [6]. In this study, the large SAS cohort and the age- and sex-matched control cohort provided adequate sample sizes for subgroup analyses to assess the differential stroke risk among different age groups and sex.

SAS is initiated at sleep onset. The wakeful state provides compensatory neuronal activation of the dilator muscles in an anatomically compromised collapsible pharynx. Accordingly, when this activation is lost at the onset of sleep, the airway narrows or collapses. There are some plausible reasons that may explain the sex differences observed in SAS patients, such as the upper airway caliber, metabolic rate, and chemoresponsiveness, which consequently

**Table 3**
Incidence and hazard ratios of stroke stratified by the presence of comorbidities among patients with and without sleep apnea syndrome.

| | Men SAS | | | | | Women SAS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No | | Yes | | Adjusted HR[b] (95% CI) | No | | Yes | | Adjusted HR[b] (95% CI) |
| | Event | Rate[a] | Event | Rate[a] | | Event | Rate[a] | Event | Rate[a] | |
| *Obesity* | | | | | | | | | | |
| No | 1738 | 40.7 | 549 | 51.9 | 1.12 (1.01–1.24)* | 520 | 37.3 | 191 | 57.1 | 1.40 (1.16–1.68)*** |
| Yes | 0 | 0 | 13 | 89.8 | | 0 | 0 | 21 | 231.3 | |
| *Diabetes mellitus* | | | | | | | | | | |
| No | 1579 | 37.5 | 465 | 45.3 | 1.16 (1.04–1.30)*** | 452 | 32.9 | 153 | 47.5 | 1.48 (1.21–1.82)*** |
| Yes | 159 | 258.7 | 97 | 206.3 | 0.79 (0.61–1.04) | 68 | 282.7 | 59 | 278 | 1.04 (0.70–1.53) |
| *Hypertension* | | | | | | | | | | |
| No | 1512 | 36.2 | 323 | 34.4 | 1.08 (0.95–1.22) | 424 | 31.2 | 113 | 38.1 | 1.52 (1.22–1.89)*** |
| Yes | 226 | 242 | 239 | 176.9 | 0.89 (0.74–1.08) | 96 | 247.5 | 99 | 210.8 | 1.04 (0.76–1.41) |
| *Hyperlipidemia* | | | | | | | | | | |
| No | 1676 | 39.6 | 502 | 48.7 | 1.13 (1.02–1.26)* | 497 | 35.9 | 175 | 53 | 1.37 (1.13–1.67)** |
| Yes | 62 | 145.1 | 60 | 141.6 | 0.89 (0.61–1.29) | 23 | 212.6 | 37 | 270.1 | 1.62 (0.92–2.85) |
| *Coronary artery disease* | | | | | | | | | | |
| No | 1621 | 38.5 | 440 | 43.3 | 1.09 (0.98–1.22) | 480 | 34.9 | 165 | 50.8 | 1.38 (1.14–1.69)** |
| Yes | 117 | 212.9 | 122 | 215.9 | 1.09 (0.84–1.42) | 40 | 210.6 | 47 | 249.1 | 1.30 (0.82–2.07) |
| *Atrial fibrillation* | | | | | | | | | | |
| No | 1712 | 40.1 | 540 | 50.7 | 1.13 (1.02–1.25)* | 509 | 36.5 | 195 | 57.3 | 1.47 (1.22–1.77)*** |
| Yes | 26 | 414.7 | 22 | 305.1 | 0.71 (0.39–1.31) | 11 | 488.9 | 17 | 521.5 | 0.83 (0.35–1.97) |
| *Congestive heart failure* | | | | | | | | | | |
| No | 1690 | 39.7 | 494 | 46.9 | 1.12 (1.01–1.24)* | 500 | 36 | 168 | 50.8 | 1.46 (1.21–1.76)*** |
| Yes | 48 | 409.6 | 69 | 341.6 | 0.99 (0.67–1.44) | 20 | 342.5 | 44 | 331.8 | 1.06 (0.60–1.88) |

*Abbreviations*: SAS, sleep apnea syndrome; HR, hazards ratio; CI, confidence interval. *$P < 05$, **$P < 05$, ***$P < 001$.
[a] Rate = incidence rate, per 10,000 individual-years.
[b] Adjusted HR: adjusted for age, sex, diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, atrial fibrillation, and congestive heart failure.
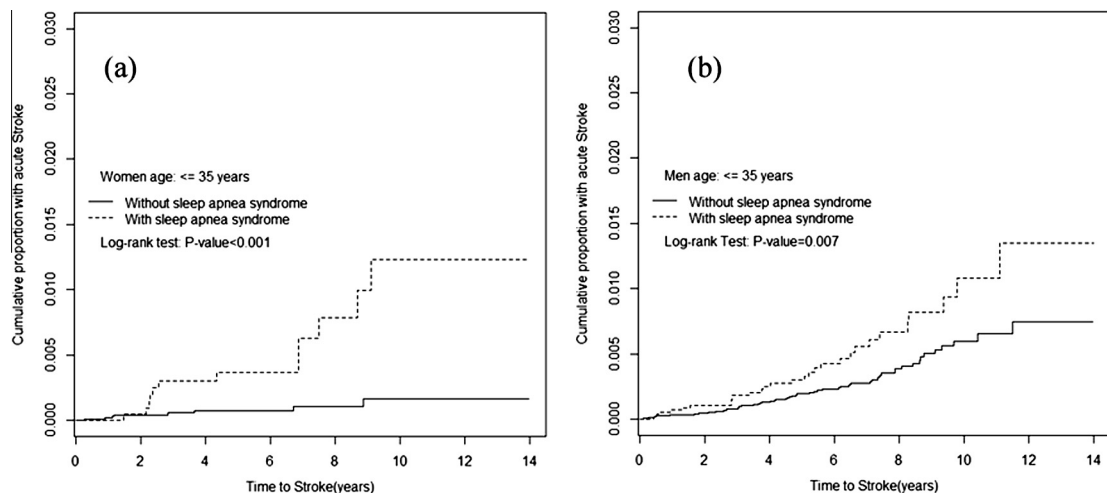


**Fig. 1.** Cumulative incidence of stroke in patients with and without sleep apnea syndrome.

result in a reduced ventilator motor output. For example, men have a larger upper airway compared to women when seated, and the upper airway caliber decreases in men and women with increased age [15]. Importantly, ethnicity is an important factor that can affect the SAS phenotype. One study reported that Asian SAS populations had features of craniofacial skeletal restriction, which were different from black individuals who demonstrated higher obesity and enlarged upper airway soft tissues or white individuals who showed evidence of bony and soft tissue abnormalities [16]. These observations indicated that the population observed in our study had physical–structural differences between men and women, which could have resulted in a higher SAS to stroke risk among women.

Moreover, hormonal differences also were considered as determinants for the sex differences observed in SAS prevalence [17]. Sex hormone levels change significantly with menarche, pregnancy, and menopause, resulting in a modification of SAS risk. Further investigations are required to elucidate these potential mechanisms.

The strengths of our study were its large sample size and the considerable period of follow-up. However, there also were specific limitations. The major limitations of our study were the surveillance bias and the inability to obtain more detailed personal information from the nationwide database such as lifestyle factors. Personal history details that were not recorded in this database included the body mass index and the smoking status of the patient.

Associations between SAS and stroke diagnosis according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification or ischemic–hemorrhagic classification need to be further investigated. However, despite these limitations, our study provides evidence that sex and age are significant factors for SAS and the development of stroke, though further studies are required to confirm this association.

## 5. Conclusion

Adult women with SAS are susceptible to developing stroke. However, the following main messages remain. SDB is common, affecting a significant proportion of the population. When untreated, SDB causes significantly increased social, cardiac, and cerebrovascular morbidity and mortality. However, a significant proportion of patients with SAS remain undiagnosed and untreated due to inadequate resources for case detection and investigation. Thus there is a need to identify optimal constructive and economic models to identify patients who are at risk for additional screening and management, particularly among the at-risk populations identified in our study.

## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.011.

## Acknowledgment

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