Association of obstructive sleep apnoea with long-term cardiovascular events in patients with acute coronary syndrome with or without hypertension: insight from the OSA-ACS project

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ABSTRACT

Background A close relationship exists between obstructive sleep apnoea (OSA) and hypertension. However, the impact of hypertension on the prognostic significance of OSA in patients with acute coronary syndrome (ACS) remains unclear.

Methods This is a post hoc analysis of the OSA-ACS project, which consecutively included patients with ACS and receiving overnight sleep study from June 2015 to January 2020. OSA was defined as AHI ≥15 events/hour. The primary outcome was major adverse cardiovascular and cerebrovascular events (MACCE), including a composite of cardiovascular death, myocardial infarction, stroke, ischemia-driven revascularisation or hospitalisation for unstable angina or heart failure.

Results A total of 1927 patients with ACS were finally enrolled in this study. The mean patient age was 56.4±10.5 years. Among them, 1247 (64.7%) patients had hypertension, and 1014 (52.6%) patients had OSA. During 2.9 (1.5, 3.6) years of follow-up, OSA was associated with an increased risk of MACCE among patients with hypertension (HR=1.35, 95% CI 1.04 to 1.75, p=0.02), but not in patients without hypertension (HR=1.15, 95% CI 0.79 to 1.68, p=0.47). The interaction between OSA and hypertension for MACCE was not statistically significant (interaction p=0.29). For patients with pre-existing hypertension, OSA was associated with an increased risk of MACCE only among those with grade 3 hypertension (HR 1.54, 95% CI 1.12 to 2.13, p=0.008), but not those with grade 1 or 2 hypertension.

Conclusions OSA was associated with an increased risk of MACCE following ACS in patients with hypertension, especially in patients with pre-existing severe hypertension. These findings highlight the importance of identifying OSA in ACS patients with hypertension.

Trial registration number NCT03362385.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common chronic disease characterised by intermittent hypoxia, sleep fragmentation and sympathetic nerve activation during sleep. It is associated with an increased risk of cardiovascular comorbidities, including hypertension and acute coronary syndromes (ACS). Recent randomised controlled studies have found no benefit from continuous positive airway pressure (CPAP) therapy for secondary cardiovascular prevention. Current evidence suggested a bidirectional relationship between OSA and hypertension. However, it remains unclear how hypertension affects the prognostic implications of OSA in ACS patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior studies demonstrated that OSA is linked to a poor prognosis in ACS patients.
⇒ Recent randomised controlled studies have found no benefit from CPAP for secondary cardiovascular prevention.
⇒ Current evidence suggested a bidirectional relationship between OSA and hypertension. However, it remains unclear how hypertension affects the prognostic implications of OSA in ACS patients.

WHAT THIS STUDY ADDS

⇒ We found that OSA was associated with an increased risk of major adverse cardiovascular and cerebrovascular events following ACS in patients with hypertension, especially in patients with pre-existing severe hypertension.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlight the importance of identifying OSA in ACS patients with hypertension. Randomised trials examining the efficacy of OSA intervention in this high-risk subgroup are highly warranted.
METHODS

Study design and patients

The OSA-ACS project (Impact of Obstructive Sleep Apnea and Continuous Positive Airway Pressure Therapy on Outcomes in Patients with Acute Coronary Syndrome) is a prospective cohort study and the study design has been previously illustrated in the published literature.2 17 This is a post hoc analysis of the OSA-ACS project with the purpose to evaluate the impact of OSA on clinical outcomes following ACS in patients with or without hypertension. From June 2015 to January 2020, we consecutively recruited ACS patients aged 18 years to 85 years who were admitted to Beijing Anzhen Hospital, Capital Medical University. Patients were excluded if they had cardiogenic shock, cardiac arrest, malignancy, diagnosed secondary hypertension or if they had failed sleep studies (due to inadequate or unsatisfactory signal recordings during sleep). We also excluded patients with predominantly central sleep apnoea (at least 50% central events and a central apnoea hypopnea index (AHI) ≥10/hours) as well as those who received regular CPAP therapy (>4 hours/day and >21 days/month) after discharge. Patients who were lost to follow-up were also excluded from the analysis. This study was conducted in compliance with the Declaration of Helsinki, and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

The diagnosis and treatment of ACS were based on the guidelines.18 19 During the index ACS hospitalisation, all patients were provided with standard care in accordance with the established guidelines. If clinically necessary, patients underwent percutaneous coronary intervention (PCI) with stenting or coronary artery bypass grafting. On discharge, all patients were prescribed a daily dosage of aspirin (100 mg) along with either clopidogrel (75 mg) or ticagrelor (90 mg two times per day) for a minimum duration of 1 year, unless contraindications were present. Optimal drug therapy for secondary prevention was recommended according to guidelines. The patients’ medical records were used to identify hypertension. According to the Chinese guidelines for the management of hypertension,20 the diagnosis of hypertension is made if the systolic blood pressure in the office or clinic is ≥140 mm Hg and/or diastolic blood pressure is ≥90 mm Hg after repeated measurements. Based on the severity of elevated blood pressure, hypertension is classified as grade 1 (systolic 140–159 mm Hg and/or diastolic 90–99 mm Hg), grade 2 (systolic 160–179 mm Hg and/or diastolic 100–109 mm Hg) and grade 3 (systolic ≥180 mm Hg and/or diastolic ≥110 mm Hg) hypertension.20 Laboratory tests were conducted on blood collected from an elbow vein after fasting. The demographic and clinical characteristics of each group were reported based on their hypertension status.

Patient and public involvement statement

None.

Overnight sleep study

Following clinical stabilisation during hospitalisation, all patients underwent an overnight sleep study using a type III portable cardiorespiratory polygraphy (The ApneaLink Air, Resmed, Australia). During the study, nasal airflow, thoracoabdominal movements, snoring episodes, heart rate and arterial oxygen saturation (SaO2) were monitored. An apnoea was defined as a cessation of airflow lasting over 10s, which could be either obstructive with thoracoabdominal movement or central with no thoracoabdominal movement. A hypopnea was defined as a reduction in airflow lasting 30% lasting at least 10s, accompanied by a reduction in SaO2 of over 4%. The AHI was calculated as the number of apnoeas plus hypopneas per hour of sleep recording. Sleep studies lasting less than 3 hours of satisfactory signal recording were deemed invalid. Patients with AHI <15 events/hour were considered non-OSA, while those with AHI ≥15 events/hour were classified as OSA.21

Endpoints and follow-up

The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), which was defined as cardiovascular death, myocardial infarction, ischaemia-driven revascularisation, stroke or hospitalisation for unstable angina or heart failure. Secondary endpoints included the individual components of the primary outcome, all repeat revascularisation and other composites of cardiovascular events (including cardiovascular death, myocardial infarction, ischaemia-driven revascularisation, stroke or hospitalisation for heart failure). To define all endpoints, we used standard endpoint definitions from the Standardized Data Collection for Cardiovascular Trials Initiative.22 Follow-up data were collected through December 2020, and clinical events were tracked through clinic visit, medical records or telephone calls by research staff who were blinded to the patient’s sleep results.
**Statistical analyses**

To analyse the effects of OSA on MACCE and other events, we stratified patients according to their hypertension status and classification. Continuous variables were presented as mean±SD (if normally distributed) or median (IQR) and compared using Student’s t-test or Mann-Whitney U test, respectively. Categorical variables were shown as the number (percentage) and compared using χ² statistics or Fisher’s exact test, as appropriate. We compared the MACCE survival curves using log-rank tests between OSA and non-OSA groups by hypertension status and classification. For variables with a missing rate greater than 10%, we imputed missing values using the multiple imputation method implemented available in SPSS V.26. We also conducted multivariable Cox proportional hazard regression analyses to determine the association between OSA and outcomes by hypertension status, controlling for potential confounding factors such as age, sex, body mass index, diabetes mellitus, dyslipidaemia, prior stroke, smoking, prior myocardial infarction, left ventricular ejection fraction, creatinine, elective PCI and clinical presentation (ST-segment elevation myocardial infarction vs non-ST-segment elevation ACS). Multiplicative interaction terms were included in the fully adjusted models to evaluate whether hypertension modified the associations between OSA and risk of cardiovascular events. We reported unadjusted and adjusted HRs for different outcomes and corresponding 95% CIs. Sensitivity analyses of primary outcomes were conducted based on other parameters, including oxygen reduction index (ODI) (≥15 vs <15) and AHI (≥20 vs <10). A two-tailed p value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS V.26 (IBM SPSS, Armonk, New York).

**RESULTS**

**Baseline and procedures characteristics**

During the course of this study, a total of 2160 patients with ACS were initially recruited, of whom 2058 underwent a successful and effective sleep study. Patients without central sleep apnoea who received follow-up were also included (n=1969). Regular use of CPAP was noted in only 42 patients (4.1%), and the rate was similar in patients with and without hypertension (4.4% vs 2.1%, p=0.07). Ultimately, 1927 patients with ACS were included in the final analysis (online supplemental figure S1).

The mean age of the patients was 56.4±10.5 years, and 84.5% were men. Of the total cohort, 1247 (64.7%) patients had hypertension, and 1014 (52.6%) patients had OSA and 1339 (69.5%) patients underwent revascularisation. The mean follow-up time was 2.9 (1.5 to 3.6) years. Patients with hypertension were more likely to be men, elderly and obese and exhibited more risk factors such as diabetes mellitus, hyperlipidaemia, smoking and obesity (online supplemental table S1). The baseline and clinical characteristics of the patients are summarised in table 1 and table 2. Patients with OSA had higher body mass indexes, neck circumferences and waist-to-hip ratio and were more likely to have poor left ventricular function, regardless of hypertension status. Among the hypertension group, those with OSA were more likely to be men, current drinkers and current smokers and were diagnosed more frequently with ST-elevation myocardial infarction, with more severity of coronary lesions and a higher proportion of PCI procedures. Among the non-hypertension group, patients with OSA were more likely to receive an ACEI/ARB at discharge. Other baselines and clinical information were comparable between OSA and non-OSA patients in both groups.

**Primary and secondary outcomes**

Among patients with hypertension, those with OSA had a greater risk of developing MACCE than those without OSA (24.2% vs 18.9%; HR=1.41, 95% CI 1.11 to 1.81, p=0.006), primarily due to higher rates of myocardial infarction and ischaemia-driven revascularisation (table 3 and online supplemental table S2). This was demonstrated by the Kaplan-Meier curves, which depict the cumulative hazard of MACCE (figure 1). Conversely, in the non-hypertension group, there was no difference in the incidence of MACCE between patients with and without OSA (18.6% vs 16.0%; HR=1.15, 95% CI 0.80 to 1.65, p=0.45; table 3, figure 1). In multivariable Cox regression analysis, there was an increased risk of MACCE in OSA groups compared with non-OSA groups among patients with hypertension (HR=1.35, 95% CI 1.04 to 1.75, p=0.02), but not among those without hypertension (HR=1.15, 95% CI 0.79 to 1.68, p=0.47) (table 3). The interaction between OSA and hypertension for MACCE was not statistically significant (interaction p=0.29).

Patients with hypertension without OSA had a comparable rate of MACCE as all patients without hypertension (18.9% vs 17.2%, HR=0.923, 95% CI 0.71 to 1.20, p=0.55). Moreover, in both groups of patients without OSA, there was also no statistically significant in the incidence of MACCE (hypertension vs non-hypertension: 23.3% vs 19.0%; HR=1.17, 95% CI 0.85 to 1.61, p=0.35). In contrast, among patients with OSA, the incidence of MACCE was higher in patients with hypertension than in those without hypertension (31.9% vs 22.8%; HR=1.44, 95% CI 1.07 to 1.93, p=0.02) (online supplemental table S3). Other crude incidences of notable events are shown in online supplemental table S2.

Among patients with pre-existing hypertension, those with OSA had a higher likelihood of developing MACCE when they had grade 3 hypertension (HR=1.54, 95% CI 1.12 to 2.13, p=0.008; figure 2). However, no significant differences in MACCE rates were observed between the OSA and non-OSA groups in patients with grade 1 or 2 hypertension (figure 2).
Table 1 Baseline characteristics and sleep information

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n=1927)</th>
<th>Hypertension (n=1247)</th>
<th>Non-OSA(n=556)</th>
<th>P value</th>
<th>Non-hypertension (n=680)</th>
<th>OSA (n=323)</th>
<th>Non-OSA (n=357)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Age, mean±SD, years</td>
<td>56.4±10.5</td>
<td>57.1±10.8</td>
<td>57.1±10.6</td>
<td>0.91</td>
<td>55.3±9.9</td>
<td>54.9±10.0</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Male</td>
<td>1629 (84.5)</td>
<td>585 (46.7)</td>
<td>422 (75.9)</td>
<td>&lt;0.001</td>
<td>301 (93.2)</td>
<td>321 (89.9)</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>BMI, mean±SD, kg/m²</td>
<td>27.1±3.6</td>
<td>28.4±3.6</td>
<td>26.2±3.5</td>
<td>&lt;0.001</td>
<td>27.3±3.4</td>
<td>25.7±3.3</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neck circumference, median (IQR), cm</td>
<td>41 (38–43)</td>
<td>42 (39–44)</td>
<td>40 (37–42)</td>
<td>&lt;0.001</td>
<td>41 (39–43)</td>
<td>40 (38–42)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip, median (IQR), cm</td>
<td>0.98 (0.95–1.02)</td>
<td>0.99 (0.96–1.03)</td>
<td>0.97 (0.94–1.00)</td>
<td>&lt;0.001</td>
<td>0.99 (0.96–1.02)</td>
<td>0.97 (0.93–1.00)</td>
<td>&lt;0.001</td>
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<tr>
<td>Systolic BP, median (IQR), mm Hg</td>
<td>126 (117–138)</td>
<td>130 (120–140)</td>
<td>130 (120–140)</td>
<td>0.90</td>
<td>120 (110–130)</td>
<td>120 (111–130)</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Diastolic BP, median (IQR), mm Hg</td>
<td>76.0 (70.0–84.0)</td>
<td>79.0 (70.0–87.0)</td>
<td>76.5 (70.0–85.0)</td>
<td>0.002</td>
<td>73.0 (69.0–80.0)</td>
<td>72.0 (68.0–80.0)</td>
<td></td>
<td>0.14</td>
</tr>
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<td>Medical history</td>
<td></td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>609 (31.6)</td>
<td>243 (35.2)</td>
<td>205 (36.9)</td>
<td>0.53</td>
<td>76 (23.5)</td>
<td>85 (23.8)</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>637 (33.1)</td>
<td>259 (37.5)</td>
<td>199 (35.8)</td>
<td>0.54</td>
<td>84 (26.0)</td>
<td>95 (26.6)</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>Prior MI</td>
<td>316 (16.4)</td>
<td>123 (17.8)</td>
<td>81 (14.6)</td>
<td>0.13</td>
<td>54 (16.7)</td>
<td>58 (16.2)</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>207 (10.7)</td>
<td>103 (14.9)</td>
<td>68 (12.2)</td>
<td>0.17</td>
<td>18 (5.6)</td>
<td>18 (5.0)</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>399 (20.7)</td>
<td>177 (25.6)</td>
<td>109 (19.6)</td>
<td>0.01</td>
<td>57 (17.6)</td>
<td>56 (15.7)</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>29 (1.5)</td>
<td>13 (1.9)</td>
<td>6 (1.1)</td>
<td>0.25</td>
<td>5 (1.5)</td>
<td>5 (1.4)</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Current drinking</td>
<td>1181 (61.3)</td>
<td>247 (35.7)</td>
<td>153 (27.5)</td>
<td>0.002</td>
<td>110 (34.1)</td>
<td>127 (35.6)</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoking</td>
<td>913 (47.4)</td>
<td>320 (46.3)</td>
<td>226 (40.6)</td>
<td>0.045</td>
<td>179 (55.4)</td>
<td>193 (54.1)</td>
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<td>0.72</td>
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<tr>
<td>Laboratory data</td>
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<tr>
<td>Creatinine, median (IQR), µmol/L</td>
<td>73.7 (64.8–83.9)</td>
<td>76.1 (66.5–86.7)</td>
<td>73.6 (63.0–85.4)</td>
<td>0.007</td>
<td>72.7 (64.1–81.9)</td>
<td>70.7 (63.9–79.6)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Hs-CRP, median (IQR), mg/L</td>
<td>2.0 (0.8–6.1)</td>
<td>2.5 (1.0–6.8)</td>
<td>1.5 (0.6–4.4)</td>
<td>&lt;0.001</td>
<td>2.4 (1.0–8.5)</td>
<td>1.4 (0.6–4.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>LVEF, median (IQR), %</td>
<td>61 (56–65)</td>
<td>61 (56–65)</td>
<td>63 (58–66)</td>
<td>0.046</td>
<td>60 (54–65)</td>
<td>61 (55–65)</td>
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<td>0.02</td>
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<tr>
<td>LDL-C, median (IQR), mmol/L</td>
<td>2.4 (1.9–3.1)</td>
<td>2.4 (1.9–3.0)</td>
<td>2.3 (1.8–3.0)</td>
<td>0.09</td>
<td>2.6 (2.0–3.2)</td>
<td>2.5 (2.0–3.3)</td>
<td>0.70</td>
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<tr>
<td>TC, median (IQR), mmol/L</td>
<td>4.1 (3.5–4.9)</td>
<td>4.1 (3.5–4.8)</td>
<td>4.0 (3.4–4.9)</td>
<td>0.23</td>
<td>4.2 (3.6–5.0)</td>
<td>4.2 (3.5–5.1)</td>
<td>0.99</td>
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<tr>
<td>TG, median (IQR), mmol/L</td>
<td>1.5 (1.1–2.2)</td>
<td>1.6 (1.1–2.3)</td>
<td>1.5 (1.1–2.2)</td>
<td>0.08</td>
<td>1.6 (1.1–2.2)</td>
<td>1.4 (1.1–2.0)</td>
<td>0.03</td>
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<tr>
<td>Sleep information</td>
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<tr>
<td>AHI, median (IQR), events·h⁻¹</td>
<td>16.0 (8.0–30.0)</td>
<td>30.4 (21.4–44.1)</td>
<td>7.8 (4.2–10.8)</td>
<td>&lt;0.001</td>
<td>27.2 (19.9–39.1)</td>
<td>7.2 (4.0–10.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ODI, median (IQR), events·h⁻¹</td>
<td>16.2 (8.8–28.6)</td>
<td>28.8 (20.9–41.0)</td>
<td>8.9 (5.1–12.0)</td>
<td>&lt;0.001</td>
<td>25.6 (18.9–36.4)</td>
<td>8.1 (4.5–11.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean SaO₂, median (IQR), %</td>
<td>94.0 (93.0–95.0)</td>
<td>93.0 (92.0–94.0)</td>
<td>94.0 (93.0–95.0)</td>
<td>&lt;0.001</td>
<td>93.3 (92.0–94.6)</td>
<td>94.0 (93.0–95.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Minimum SaO₂, median (IQR), %</td>
<td>85 (81–88)</td>
<td>82 (77–89)</td>
<td>87 (84–89)</td>
<td>&lt;0.001</td>
<td>84 (79–87)</td>
<td>88 (85–90)</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>TSA90, median (IQR), %</td>
<td>2.3 (0.4–10.0)</td>
<td>7.5 (2.3–18.7)</td>
<td>0.6 (0.1–3.0)</td>
<td>&lt;0.001</td>
<td>4.0 (1.0–13.0)</td>
<td>0.5 (0.0–3.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ESS, median (IQR)</td>
<td>7.0 (4.0–11.0)</td>
<td>8.0 (4.0–12.0)</td>
<td>6.0 (3.0–11.0)</td>
<td>0.001</td>
<td>8.0 (5.0–12.0)</td>
<td>6.0 (3.0–10.0)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

AHI, apnoea-hypopnoea index; BMI, body mass index; CABG, coronary artery bypass grafting; Hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infraction; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PCI, percutaneous coronary intervention; SaO₂, arterial oxygen saturation; TC, total cholesterol; TG, triglyceride; TSA90, time with SaO₂<90%.
Sensitivity analyses

To further confirm the robustness of our findings, we performed a sensitivity analysis by using ODI (≥15 vs <15) as a diagnostic parameter of OSA instead of AHI. The results showed that the presence of OSA remained associated with MACCE in patients with hypertension (ODI ≥15 vs ODI <15, HR=1.30, 95% CI 1.01 to 1.67, p=0.04), while there was no significant association between OSA and MACCE in patients without hypertension (HR=1.05, 95% CI 0.73 to 1.52, p=0.79) (online supplemental figure S2). Moreover, we compared the primary outcome in patients with AHI ≥20 vs AHI <10 among those with or without hypertension and found similar results. Specifically, among patients with hypertension, there was a higher risk of MACCE in the group with AHI ≥20 (HR=1.41, 95% CI 1.06 to 1.87, p=0.018), while among patients without hypertension, there was no significant difference in MACCE rates between the two groups (HR=1.21, 95% CI 0.78 to 1.88, p=0.39).

DISCUSSION

The present study showed that OSA was associated with an increased risk of MACCE in patients with hypertension, although no significant hypertension by OSA interaction was noted. This risk is particularly pronounced among patients who already have severe hypertension. Conversely, among patients who do not have hypertension, there was no significant difference in the incidence of MACCE between those with and without OSA.

Previous observational studies and meta-analyses have consistently demonstrated a robust association between moderate-to-severe OSA and an increased risk of cardiac events following ACS.23 24 Yet recent randomised controlled studies have found no benefit from CPAP for secondary cardiovascular prevention. Building on this existing research, our study sought to explore the effect of moderate-to-severe OSA on MACCE, specifically in the high-risk subgroup of patients with hypertension following ACS onset. This study was motivated by epidemiological data, indicating that hypertension is present in approximately half of OSA patients, and that the incidence of OSA is elevated in hypertensive patients.25 Both of these conditions are known to contribute to endothelial dysfunction and accelerate the progression of atherosclerotic plaque,24 thereby increasing the likelihood of recurrent cardiovascular events after ACS. Our study findings align with this body of knowledge, 1247 (64.7%) patients had hypertension and 1014 (52.6%) patients had OSA, revealing that OSA is significantly associated with recurrent cardiovascular events among hypertensive patients, but not among those without hypertension. Moreover, we found that patients with preexisting severe hypertension who also had OSA were at particularly high risk for MACCE, while this relationship was not observed...
in patients with grade 1 or 2 hypertension. No significant signal of interaction was observed between OSA and hypertension for cardiovascular events. This could be due to the limited statistical power, resulting from the relatively small sample size and the low event rates during the relatively short follow-up period. Therefore, the results should be interpreted with caution and require further verification with larger cohorts.

A growing body of evidence suggests a close association between OSA and hypertension, with OSA potentially playing an active role in the development of hypertension. The underlying mechanism may involve OSA-mediated intermittent hypoxemia and sympathetic nervous system activation, which can contribute to the development of hypertension. Moreover, the cyclical hypoxemia-reoxygenation associated with OSA can promote oxidative stress, systemic vascular inflammation and endothelial dysfunction, all of which can further contribute to the development of hypertension. Notably, OSA and hypertension exhibit a bidirectional relationship, and together, they may synergistically accelerate the progression of atherosclerosis and increase the risk of adverse cardiovascular events. Our study found that the presence of OSA and hypertension was associated with a higher rate of PCI due to severe coronary lesions. Furthermore, we observed a greater incidence of ischaemia-driven revascularisation in patients with OSA and hypertension, compared with those without OSA. This association was only observed in patients with hypertension and not in those without hypertension.

Current evidence suggests that CPAP has a neutral effect on secondary cardiovascular prevention. In the ISAACC trial, non-sleepy patients with ACS and OSA were randomly assigned to receive either CPAP treatment plus usual care or usual care alone. Over an average follow-up of 3.35 years, no significant difference was observed in the composite primary outcomes. However, further studies are needed to confirm these findings.

### Table 3: Clinical outcomes in OSA versus non-OSA groups according to hypertension status

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertension</th>
<th>Non-hypertension</th>
<th>Unadjusted HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE</td>
<td>1.41 (1.11 to 1.81)</td>
<td>0.006</td>
<td>1.35 (1.04 to 1.75)</td>
<td>0.02</td>
<td>1.15 (0.80 to 1.65)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.26 (0.57 to 2.51)</td>
<td>0.07</td>
<td>1.09 (0.46 to 2.59)</td>
<td>0.44</td>
<td>0.99 (0.30 to 2.69)</td>
<td>0.85</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.14 (1.06 to 4.22)</td>
<td>0.03</td>
<td>0.90 (0.89 to 2.60)</td>
<td>0.10</td>
<td>0.90 (0.89 to 2.60)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.33 (0.66 to 2.60)</td>
<td>0.22</td>
<td>1.30 (0.61 to 2.66)</td>
<td>0.30</td>
<td>1.30 (0.61 to 2.66)</td>
<td>0.30</td>
</tr>
<tr>
<td>Ischaemia-driven revascularisation</td>
<td>1.71 (1.14 to 2.56)</td>
<td>0.01</td>
<td>1.61 (1.04 to 2.50)</td>
<td>0.03</td>
<td>1.61 (1.04 to 2.50)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalisation for unstable angina</td>
<td>1.35 (1.00 to 1.81)</td>
<td>0.05</td>
<td>1.27 (0.92 to 1.74)</td>
<td>0.14</td>
<td>1.27 (0.92 to 1.74)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>0.50 (0.18 to 1.39)</td>
<td>0.12</td>
<td>0.34 (0.11 to 1.00)</td>
<td>0.37</td>
<td>0.34 (0.11 to 1.00)</td>
<td>0.37</td>
</tr>
<tr>
<td>All repeat revascularisation</td>
<td>1.48 (1.10 to 2.00)</td>
<td>0.01</td>
<td>1.40 (1.02 to 1.93)</td>
<td>0.04</td>
<td>1.40 (1.02 to 1.93)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Note:** Adjusted HR: age, sex, body mass index, diabetes mellitus, smoking, dyslipidaemia, prior stroke, prior myocardial infarction, left ventricular ejection fraction, creatinine, elective PCI, clinical presentation (ST-segment elevation myocardial infarction vs Non-ST-segment elevation acute coronary syndrome).

**Figure 1:** Kaplan-Meier curves for MACCE in OSA versus non-OSA groups according to hypertension status. HT, hypertension; MACCE, major adverse cardiovascular and cerebrovascular events; OSA, obstructive sleep apnoea.
endpoint of cardiovascular death or non-fatal events. However, adherence to CPAP treatment was poor, with an average use of only 2.78 hours per night.\textsuperscript{4} Subgroup analyses showed no significant difference in primary outcomes between CPAP treatment and usual care in patients with OSA after ACS (with or without hypertension). Nonetheless, the number of adverse events was numerically lower in patients with hypertension who received CPAP treatment (18.86\% vs 22.41\%).\textsuperscript{4} Our study found that only patients with both OSA and hypertension had a greater risk of adverse events after suffering ACS, indicating that this high-risk subgroup is likely to benefit from treatment. Conversely, the prognosis of patients with hypertension but without OSA was similar to those without hypertension (with or without OSA). OSA appears to be a crucial modifiable factor responsible for the adverse impact of hypertension on ACS. Therefore, screening for OSA in patients with hypertension and ACS is essential, and a modest intervention may be required. Further trials are needed to prove the efficacy of such interventions in this high-risk subgroup.

CONCLUSIONS
In this present study, OSA was associated with an increased risk of subsequent cardiovascular events following ACS in patients with hypertension, especially for patients with pre-existing severe hypertension. The significance of identifying OSA in ACS patients with hypertension is emphasised by these findings. Further trials are necessary to investigate the efficacy of OSA treatment in high-risk patients with ACS and hypertension.

Limitations
First, the diagnosis of OSA was based on portable cardiorespiratory polygraphy, which may underestimate AHI compared with full polysomnography. However, this method is a safe and straightforward way to monitor OSA in high-risk patients, and there is evidence of its validity.\textsuperscript{30} Second, the severity of OSA could potentially change in the weeks after ACS,\textsuperscript{31,32} suggesting that OSA identified after ACS may be a temporary phenomenon. Nevertheless, this is true for OSA evaluation in the setting of any acute disease, including heart failure. Also, sleep studies were conducted after clinical stabilisation in this study to minimise potential bias. Third, although we excluded patients with diagnosed secondary hypertension, it is possible that there are patients with unidentified secondary hypertension, which may affect the accuracy of the results to some extent. Fourthmore, it is unknown whether our results can be extrapolated to the women or obese population as the majority of participants were men and non-obese. Last but not least, this study primarily recruited East-Asian patients, and our findings cannot be generalised to patients from other ethnicities.

Figure 2 Kaplan-Meier curves for MACCE in OSA versus non-OSA groups according to hypertension stage. The cumulative incidences of MACCE are shown in OSA and non-OSA groups, grade 1 hypertension (HT) (A); grade 2 hypertension (B); grade 3 hypertension (C). MACCE, major adverse cardiovascular and cerebrovascular events; OSA, obstructive sleep apnoea.

CONCLUSIONS
In this present study, OSA was associated with an increased risk of subsequent cardiovascular events following ACS in patients with hypertension, especially for patients with pre-existing severe hypertension. The significance of identifying OSA in ACS patients with hypertension is emphasised by these findings. Further trials are necessary to investigate the efficacy of OSA treatment in high-risk patients with ACS and hypertension.

Contributors GW, HM, XW and SN analysed and interpreted the data, and contributed to writing and revising the draft of the manuscript; HW and GZ analysed the data and reviewed the manuscript. YY, WG, JYF, HA and BQ reviewed the manuscript and provided opinions. XW and SN were responsible for the overall content as the guarantors. All authors reviewed and approved the final manuscript.

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Competing interests SN: research grants to the institution from Boston Scientific, Abbott, Jiangsu Hengrui Pharmaceuticals, China Resources Sanjiu Medical & Pharmaceuticals, and East China Pharmaceuticals.

Patient consent for publication Not applicable.

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