UC Irvine

UC Irvine Previously Published Works

Title

Comparisons of sleep apnoea rate and outcomes among patients with resistant and non-resistant hypertension.

Permalink

<https://escholarship.org/uc/item/7rm9j6z8>

Journal

Respirology (Carlton, Vic.), 21(8)

ISSN

1323-7799

Authors

Bhandari, Simran K
Shi, Jiaxiao
Molnar, Miklos Z
[et al.](#)

Publication Date

2016-11-01

DOI

10.1111/resp.12840

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

ORIGINAL ARTICLE

Comparisons of sleep apnoea rate and outcomes among patients with resistant and non-resistant hypertension

SIMRAN K. BHANDARI,¹ JIAXIAO SHI,² MIKLOS Z. MOLNAR,³ SCOTT A. RASGON,¹ STEPHEN F. DEROSE,² CSABA P. KOVESDY,³ DAVID A. CALHOUN,⁴ KAMYAR KALANTAR-ZADEH,⁵ STEVEN J. JACOBSEN² AND JOHN J. SIM¹

¹Division of Nephrology and Hypertension, Kaiser Permanente Los Angeles Medical Center, Los Angeles, ²Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, ³Division of Nephrology and Hypertension, University of California Irvine Medical Center, Irvine, California, ⁴Division of Nephrology, University of Tennessee Health Science Center, Memphis, Tennessee and ⁵Department of Cardiovascular Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

ABSTRACT

Background and objective: We directly compared sleep apnoea (SA) rates and risk of cardiovascular and mortality outcomes among SA patients with resistant hypertension (RH) and non-RH within a large diverse hypertension population.

Methods: A retrospective cohort study between 1 January 2006 and 31 December 2010 among hypertensive adults (age ≥ 18 years) was performed within an integrated health system. Rates of SA in RH and non-RH were determined. Multivariable logistic regression analyses were used to calculate OR for SA. Cox proportional hazard modelling was used to estimate hazard ratios (HRs) for cardiovascular and mortality outcomes between SA in RH versus SA in non-RH adjusting for age, gender, race, BMI, chronic kidney disease and other comorbidities.

Results: SA was identified in 33 682 (7.2%) from 470 386 hypertensive individuals. SA in RH accounted for 5806 (9.6%) compared to SA in non-RH 27 876 individuals (6.8%). Multivariable OR (95% CI) for SA was 1.16 (1.12, 1.19), 3.57 (3.47, 3.66) and 2.20 (2.15, 2.25) for RH versus non-RH, BMI ≥ 30 , and males, respectively. Compared to SA in non-RH individuals, SA in RH had a multivariable adjusted HR (95% CI) of 1.24 (1.13, 1.36), 1.43 (1.28, 1.61), 0.98 (0.85, 1.12) and 1.04 (0.95, 1.14) for ischaemic heart event (IHE), congestive heart failure (CHF), stroke and mortality, respectively.

Conclusion: We observed a modest increase in likelihood for SA among RH compared to non-RH patients. Risks for IHE and CHF were higher for SA in RH compared to SA in non-RH patients; however, there were no differences in risk for stroke and mortality.

SUMMARY AT A GLANCE

The risk for ischaemic heart events and congestive heart failure were increased in a large ethnically diverse hypertension (HTN) population with sleep apnoea (SA) and resistant versus non-resistant HTN. However, there were no differences in risk for stroke and mortality in SA and resistant HTN versus SA and non-resistant HTN.

Key words: epidemiology, outcomes, resistant hypertension, sleep apnoea.

Abbreviations: BiPAP, bi-level PAP; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; CPAP, continuous PAP; CPT, current procedural terminology; CVA, cerebrovascular accident; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HR, hazard ratio; HTN, hypertension; ICD-9, International statistical classification of diseases, ninth revision; IHE, ischaemic heart event; KPSC, Kaiser Permanente Southern California; PAP, positive airway pressure; RH, resistant hypertension; SA, sleep apnoea; SBP, systolic blood pressure.

INTRODUCTION

Sleep apnoea (SA) has been identified as one of the most common comorbidities associated with the development of resistant hypertension (RH).¹⁻⁴ While SA is believed to occur in up to 5-20% of the adult population, rates as high as 37-56% have been described in the hypertensive population.⁵⁻⁸ The severity of hypertension (HTN) has been shown to increase with the severity of SA.⁹⁻¹¹ Furthermore, treatment of SA has been shown to improve blood pressure among hypertensive populations.¹²⁻¹⁴

The prevalence and prognosis of SA among RH compared to non-RH has not been well described. Prior estimates on the prevalence of SA among RH have

Correspondence: Simran K. Bhandari, MD, Division of Nephrology and Hypertension, Kaiser Permanente Los Angeles Medical Center, 4700 Sunset Building, Los Angeles, CA 90027, USA. E-mail: simran.x.bhandari@kp.org

Received 29 March 2016; invited to revise 10 May 2016; revised 18 May 2016; accepted 18 May 2016 (Associate Editor: David Barnes).

been derived from smaller specialized populations and from tertiary referral centres which are likely to have higher rates of both RH and SA than the general hypertensive population.^{1–4,15} Direct comparison of outcomes in individuals with SA and RH to those with SA and non-RH is lacking.

We previously characterized and described an RH cohort within a large, ethnically diverse HTN population using an electronic health record (EHR) approach.^{16,17} Using this RH and non-RH cohort, we sought to compare the rates and characteristics of SA in RH versus SA in non-RH and study their comparative risk of cardiovascular and mortality outcomes.

METHODS

Study population

A retrospective cohort study of Kaiser Permanente Southern California (KPSC) members was performed between 1 January 2006 and 31 December 2010. This study was approved by the KPSC institutional review board (Approval #5932) and exempted from informed consent. The KPSC healthcare system is a prepaid integrated health plan currently providing comprehensive care to over 4.0 million members throughout Southern California. The patient population is racially/ethnically and socioeconomically diverse, reflecting the general population of Southern California.^{17,18} All KPSC members have similar benefits and access to healthcare services, clinic visits, procedures and copays for medications.

Details of the study population have been previously described.^{16,17} Individuals 18 years and older with HTN and a documented blood pressure measurement were identified in the time period between 1 January 2006 and 31 December 2010. Individuals were followed up until they experienced any outcome or until the end of the observation period (31 December 2010).

Data collection and laboratory measurements

All laboratory data, vital sign assessments (including blood pressure measurements) and diagnostic and procedure codes are collected in the EHR as part of routine clinical care encounters. Comorbidities, including diabetes mellitus (DM), coronary artery disease, congestive heart failure (CHF) and cerebrovascular disease, were assessed based on inpatient and outpatient International statistical classification of diseases (ICD)-9 diagnoses coding. Chronic kidney disease (CKD) was identified and defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m² estimated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration Equation.¹⁹ End stage renal disease was defined as requiring haemodialysis, peritoneal dialysis or renal transplantation. Data on hospitalizations and diagnoses that occurred outside the healthcare system were available through administrative claims records. Antihypertensive medication use was retrieved from KPSC internal pharmacy dispensing records.

Definitions of RH

HTN was identified by inpatient and outpatient ICD-9 diagnoses codes specific to HTN (codes 401.xx, 402.xx, 403.xx, 404.xx and 405.xx). To be included in this study, all individuals were required to have a minimum of two outpatient separately dated ICD-9 codes for HTN. The date of the second ICD-9 HTN code was used as the index date. Outpatient blood pressure values closest in date to the index date were used. Individuals who did not have a blood pressure measurement or those who were diagnosed with secondary HTN, specifically individuals with ICD-9 codes for renovascular disease, adrenal disorders, Cushing's syndrome, aortic coarctation and secondary HTN not specified, were excluded from the study cohort. Hyperaldosteronism was not an exclusion criteria. Although hyperaldosteronism is a form of secondary HTN, there is a known overlap with obesity and inappropriate aldosterone secretion with clinicians often coding for hyperaldosteronism based on serum studies alone.

Individuals were classified as having RH if their systolic blood pressure was ≥ 140 mm Hg and/or their diastolic blood pressure was ≥ 90 mm Hg while prescribed three or more different antihypertensive medications concomitantly, or when they were prescribed four or more medications concomitantly regardless of blood pressure. All other hypertensive individuals were categorized as having non-RH.

Identification of SA

SA was identified using inpatient and outpatient ICD-9 diagnoses codes for SA (327.20, 327.21, 327.23, 780.51, 780.53 and 780.57) and/or by current procedural terminology (CPT) coding for dispensation of continuous positive airway pressure (CPAP) or bi-level PAP (BiPAP) devices (94660, E0470, E0471 and E0601) (Table S1, Supplementary information). SA patients were identified during the period 1 January 2006 to 31 December 2010 and thus they may be identified before or after the RH diagnosis. We were unable to distinguish obstructive from central SA.

Outcomes

The primary outcomes evaluated were ischaemic heart event (IHE), CHF, cerebrovascular accident (CVA) and all-cause mortality as separate competing outcomes. Any hospitalization with the primary or secondary diagnoses of IHE, CHF and CVA were used to identify these outcomes (Table S2, Supplementary information). Mortality information for the cohort was obtained from internal health systems databases. 31 December 2010 was used to censor follow-up. Each event was followed up separately without competing outcomes. Individuals were followed up until the occurrence of that particular event, disenrolment from the health plan, end of the study period (31 December 2010) or death. Follow-up was not censored when another event occurred, with the exception of death.

Statistical analysis

The prevalence of SA among the non-RH and RH populations was determined in the study cohort. The demographic characteristics and comorbidities of individuals who met the criteria for SA and RH were compared with those with SA and non-RH. Chi-square test was used for comparison of ordinal variables and the nonparametric Kruskal-Wallis test was used for continuous variables. Multivariable logistic regression analyses were used to calculate OR and 95% CI for SA, with adjustment for age, sex, race, BMI, systolic blood pressure ≥ 140 and the presence of comorbidities, including DM, CKD, ischaemic heart disease, CHF and cerebrovascular disease.

The primary analysis was to compare the risk of IHE, CHF, CVA and all-cause mortality among SA in RH and SA in non-RH. Cox proportional hazards regression modelling was used to estimate hazard ratios (HRs) for each outcome separately for SA in RH and SA in non-RH. HRs were also calculated for each outcome separately among SA subjects with a positive airway pressure (PAP) device prescription versus no PAP device prescription. Multivariable HRs were calculated with adjustment for potential confounders including age, sex, race, BMI, systolic blood pressure ≥ 140 , whether or not they were prescribed PAP (either CPAP or BiPAP), and pre-existing comorbidities including DM, CKD, ischaemic heart disease, CHF and cerebrovascular disease.

All statistical analyses were generated using the SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). Results with $P < 0.05$ were considered statistically significant.

63% males, 54% whites, 14% blacks, 19% Hispanics and had a mean age of 62 years. Average blood pressure of the SA population was 132/75 mm Hg and 32% of the SA population was noted to have CPAP/BiPAP prescribed. RH was identified in 60 327 (12.8%) of hypertensive individuals of whom 5806 (9.6%) were found to have SA. Of the non-RH population, 27 876 (6.8%) were noted to have SA ($P < 0.001$ when compared to SA in RH).

SA in RH patients had an average blood pressure of 139/75 mm Hg compared to 130/75 mm Hg in SA in non-RH. SA in RH compared to SA in non-RH was more frequent in males (67% vs 63%), were those older in age (65 years vs 62 years), were more likely obese (80% vs 71%) and were more likely to be on anticoagulation medications (10.1% vs 5.1%) and antithrombotic medications (8.5% vs 3.9%) (Table S3, Supplementary information). SA in RH were also more likely to have CPAP/BiPAP prescribed (65.1% vs 62.4%) compared to the SA in non-RH. Classes of antihypertensive medications were similar between both SA in RH and SA in non-RH. Diuretics were the most frequently prescribed class of medications for both the groups. Average number of antihypertensive medications was 4.1 for individuals with SA in RH compared to 1.5 medicines for those with SA in non-RH.

Compared with the SA in non-RH population, the SA in RH population had a greater prevalence of comorbid conditions including DM (59% vs 38%), CKD (41% vs 22%), ischaemic heart disease (50% vs 31%), atrial tachycardia (4.0% vs 1.1%), CHF (33% vs 14%) and cerebrovascular disease (17% vs 10%; $P < 0.001$ for all) (Table 1).

RESULTS

Cohort characteristics

A total of 470 386 individuals were identified for the study cohort (Fig. 1), as described previously.^{16,17} SA was identified in 33 682 patients (7.2%) of the HTN population (Table 1). The SA cohort was comprised of

Regression analyses: SA risk

In multivariable logistic regression analyses adjusting for age, sex, race, BMI and the presence of comorbidities, the OR (95% CI) for SA in RH compared to non-RH was 1.16 (1.12–1.19) (Table 2). In crude and adjusted analyses, both BMI of ≥ 30 and male gender had increased risk of SA. Every 5-year age decrease had

Figure 1 During the period 1 January 2006 through 31 December 2010, 470 386 individuals were identified with hypertension. Resistant hypertension (RH) was identified in 60 327 individuals (12.8%). Sleep apnoea (SA) was identified in 7.17% (33 682) of the hypertensive subjects with 5806 subjects having SA and RH and 27 876 having SA and non-RH.

Table 1 Baseline characteristics of the study cohort by hypertension category and SA status

Characteristics	HTN cohort				SA cohort		
	All HTN	HTN without SA	HTN with SA	P-value	SA and non-RH	SA and RH	P-value
n (%)	470 386 (100)	436 704 (92.8)	33 682 (7.2)	<0.001	27 876 (5.9)	5806 (1.2)	<0.001
Age, mean (SD)	65 (11)	65 (11)	62 (9)	<0.001	62 (9)	65 (9)	<0.001
Female, %	55	56	37	<0.001	37	33	<0.001
Race, %							<0.001
White	43	42	54	<0.001	53	51	
Black	13	13	14		12	20	
Hispanic	21	21	19		19	17	
Asian/Pacific	8	8	5		5	4	
Other	16	16	11		11	8	
SBP, mean (SD)	133 (18)	134 (18)	132 (17)	<0.001	130 (16)	139 (20)	<0.001
DBP, mean (SD)	75 (11)	75 (11)	75 (11)	0.320	75 (11)	75 (13)	0.270
BMI ≥ 30, %	43	41	73	<0.001	71	80	<0.001
Mean creatinine (SD), mg/dL	1.1 (0.7)	1.1 (0.6)	1.1 (0.8)	0.137	1.1 (0.7)	1.3 (1.0)	<0.001
Mean eGFR (SD), mL/min/1.73 m ²	73 (21)	73 (21)	73 (21)	0.152	75 (20)	65 (23)	<0.001
Anticoagulation u, % [†]	3.8	3.6	5.9	<0.001	5.1	10.1	<0.001
Antithrombotic usage, % [†]	3.6	3.5	4.7	<0.001	3.9	8.5	<0.001
Chronic kidney disease, % [‡]	26 [§]	27	25	0.016	62.4	65.1	<0.001
Diabetes mellitus, %	32	31	42	<0.001	22	41	<0.001
Atrial tachycardia, % [¶]	0.88	0.83	1.59	<0.001	38	59	<0.001
Ischaemic heart disease, %	25	24	34	<0.001	1.08	4.03	<0.001
Congestive heart failure, %	9	9	17	<0.001	31	50	<0.001
Cerebrovascular disease, %	10	10	11	<0.001	14	33	<0.001

[†]Medication defined as anticoagulation and antithrombotic listed in Table S3 (Supplementary information).

[‡]Defined as eGFR <60 mL/min/1.73 m².

[§]1.7% of cohort found to have end stage renal disease.

[¶]Atrial tachycardia identified by ICD coding listed in Table S2 (Supplementary information).

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; ICD, International statistical classification of diseases; RH, resistant hypertension; SA, sleep apnoea; SBP, systolic blood pressure; SD, standard deviation.

Table 2 Unadjusted and adjusted logistic regression analyses for sleep apnoea

Variable	OR (95% CI)	
	Unadjusted	Adjusted
Resistant hypertension	1.46 (1.41, 1.50)	1.16 (1.12, 1.19)
Age, 5 year increase	0.88 (0.87, 0.88)	0.87 (0.87, 0.88)
Male vs female	2.21 (2.16, 2.26)	2.20 (2.15, 2.25)
Race		
White	—	—
Hispanic	0.71 (0.69, 0.73)	0.61 (0.60, 0.63)
Black	0.86 (0.83, 0.89)	0.76 (0.73, 0.79)
Asian	0.49 (0.47, 0.52)	0.69 (0.65, 0.73)
BMI ≥ 30 vs 0–29	3.89 (3.80, 3.99)	3.57 (3.47, 3.66)
CKD: eGFR <60 vs ≥ 60 mL/min/1.73 m ²	0.92 (0.89, 0.94)	0.99 (0.96, 1.02)
Diabetes mellitus	1.57 (1.53, 1.60)	1.22 (1.19, 1.25)
Ischaemic heart disease	1.64 (1.60, 1.68)	1.34 (1.30, 1.37)
Congestive heart failure	2.18 (2.11, 2.24)	1.83 (1.76, 1.90)
Cerebrovascular disease	1.18 (1.13, 1.22)	1.19 (1.14, 1.24)

P < 0.001 for all.

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

an OR of 1.15 (95% CI: 1.14–1.15) for SA. White race compared to blacks, Asians and Hispanics was associated with greater likelihood of SA.

Regression analyses: Outcomes

Overall, 7245 events occurred among the SA and HTN cohort with 21.5% experiencing at least one event (Table 3). The overall mortality rate was 8.3% (2801 individuals). The total number of outcomes was 5218 in the SA in non-RH population and 2027 in the SA in RH. SA in RH had a greater proportion of individuals who reached any outcome (34.9% vs 18.7%) compared to SA in non-RH ($P < 0.001$). When compared to SA in non-RH, SA in RH had higher rates of IHE (13.5% vs 7.1%), CHF (10.4% vs 3.3%), CVA (5.4% vs 3.4%) and mortality (13.5% vs 7.2%; $P < 0.001$ for all).

In crude models, SA in RH was at greater risk for all outcomes compared with SA in non-RH. In adjusted models, compared with SA in non-RH, SA in RH individuals was at greater risk for IHE and CHF. Risks for CVA and all-cause mortality were similar between those with SA in non-RH and SA in RH. Overall, SA individuals prescribed CPAP/BiPAP compared to those not prescribed CPAP/BiPAP had lower risk for mortality in adjusted models (HR, 0.70 (0.65–0.76)) but higher

Table 3 Event rates among the study population and by RH status

Outcome	All SA subjects			SA and non-RH			SA and RH		
	n = 33 682			n = 27 876			n = 5806		
	Person years	n (%)	Rate per 1000 person years (95% CI)	Person years	n (%)	Rate per 1000 person years	Person years	n (%)	Rate per 1000 person years
Ischaemic heart event	131 093	2758 (8.19)	21.0 (20.3, 21.8)	108 695	1972 (7.07)	18.1 (17.4, 19.0)	22 399	786 (13.54)	35.1 (32.7, 37.6)
Congestive heart failure	134 538	1520 (4.51)	11.3 (10.7, 11.9)	111 586	919 (3.30)	8.2 (7.7, 8.8)	22 952	601 (10.35)	26.2 (24.1, 28.4)
Cerebrovascular accident	135 201	1257 (3.73)	9.3 (8.8, 9.8)	111 517	945 (3.39)	8.5 (7.9, 9.0)	23 685	312 (5.37)	13.2 (11.8, 14.7)
Death	137 901	2801 (8.32)	20.3 (19.6, 21.1)	113 583	2015 (7.23)	17.7 (17.0, 18.5)	24 318	786 (13.54)	32.3 (30.1, 34.7)
Individuals with any event	123 108	7245 (21.51)	58.9 (57.5, 60.2)	103 193	5218 (18.72)	50.6 (49.2, 52.0)	19 914	2027 (34.91)	101.8 (97.4, 106.3)

CI, confidence interval; RH, resistant hypertension; SA, sleep apnoea.

Table 4 Hazard ratio for ischaemic heart event, congestive heart failure, cerebrovascular event or death in RH versus non-RH individuals with SA

Outcome	HR (95% CI)					
	RH with SA (n = 5806) vs non-RH with SA (n = 27 876)			CPAP use (n = 21 165) vs non-use (n = 12 517)		
	Unadjusted	Adjusted	P-value	Unadjusted	Adjusted	P-value
IHE	1.93 (1.77, 2.09)	1.24 (1.13, 1.36)	<0.001	1.08 (1.00, 1.17)	1.18 (1.09, 1.28)	<0.001
CHF	3.19 (2.88, 3.55)	1.43 (1.28, 1.61)	<0.001	1.07 (0.96, 1.19)	1.20 (1.08, 1.34)	<0.001
Cerebrovascular event	1.55 (1.36, 1.77)	0.98 (0.85, 1.12)	0.74	0.94 (0.84, 1.05)	1.04 (0.93, 1.17)	0.47
Mortality	1.78 (1.64, 1.93)	1.04 (0.95, 1.14)	0.40	0.61 (0.57, 0.66)	0.70 (0.65, 0.76)	<0.001

Multivariable HRs were calculated with adjustment for potential confounders including age, sex, race/ethnicity, BMI, systolic blood pressure ≥ 140 , Charlson's comorbidity index and pre-existing comorbidities including diabetes mellitus, chronic kidney disease, ischaemic heart disease, CHF, cerebrovascular disease and the use of PAP device (CPAP and BiPAP usage).

BiPAP, bi-level PAP; CHF, congestive heart failure; CI, confidence interval; CPAP, continuous PAP; HR, hazard ratio; IHE, ischaemic heart event; PAP, positive airway pressure; RH, resistant hypertension; SA, sleep apnoea.

risk for IHE (HR, 1.18 (1.09–1.28)) and CHF (HR, 1.20 (1.08–1.34)). Compared to SA in non-RH, SA in RH HRs was 1.24 (1.13–1.36), 1.43 (1.28–1.61), 0.98 (0.85–1.12) and 1.04 (0.95–1.14) for IHE, CHF, CVA, and all-cause mortality, respectively (Table 4).

DISCUSSION

SA and HTN have been closely linked conditions based on pooled information from various observations. In this study, we found that the risk for cardiovascular outcomes was increased in SA subjects with RH compared with those with non-RH. The SA in RH individuals had a 24% increased risk for IHE and 43% increased risk for CHF. Our study within a single population of over 450 000 hypertensive individuals is one of the first studies to directly compare the cardiovascular risk associated with SA in RH population to the risk of SA in non-RH population. While the risk for IHE and

CHF remained higher in SA in RH subjects compared to the SA in non-RH subjects, mortality and CVA risk were not greater in SA in RH. Furthermore, in evaluating SA versus no SA, we found that among the RH population, SA was associated with an HR (95% CI) of 1.08 (1.03–1.14) for all events compared to no SA. Among the non-RH population, SA was associated with HR (95% CI) of 1.05 (1.02–1.08) for all events compared to no SA (results not shown).

We found a higher rate of SA among RH compared to SA among non-RH (9.6% vs 6.8%). RH has been previously described to have a strong association with SA with prevalence rates ranging from 70% to 85%.^{2,4,15,20} However, the majority of prior studies on the RA and SA populations included RH patients from specialty HTN clinics and thus less generalizable to the routine HTN environment. Conversely, our study identified SA in 7.2% of our HTN population. We believe that our lower rate drawn from a real-world practice environment is representative of the under-screening and

under-detection of SA that routinely occurs. Despite the growing prevalence of SA, it is well known that SA in the majority of patients remains undiagnosed. We feel that SA may have been under-reported in our analysis. Thus, the true prevalence of SA in HTN likely falls somewhere between our observation and rates described from specialized populations.

The RH population remains an important subset of the hypertensive population with described rates that are continually increasing.^{21,22} People with RH have increased cardiovascular and mortality risks compared to those with non-RH.^{17,23} Given the increased risk, identification and treatment of secondary causes of RH may help to better control blood pressure and ultimately improve outcomes. SA has been identified as a common secondary cause associated with the development of RH.¹

The treatment of SA has been shown to suppress sympathetic activation and also improve blood pressure particularly in the RH population.²⁴ Long-term adherence to PAP therapy has been shown to suppress sympathetic activity and improve blood pressure in patients with RH.^{25–28} In our study, we found an 18% increased risk for IHE and a 20% increased risk for CHF among SA subjects with CPAP/BiPAP prescription versus SA subjects without CPAP/BiPAP prescription. A confounder on progression to IHE and CHF is the competing risk of death in the SA population. The increased risk for IHE and CHF may speak to the fact that the SA population with CPAP/BiPAP prescription was less likely to die and thus more likely to reach another outcome. We found a 43% reduction in mortality among SA patients who were prescribed CPAP/BiPAP, underscoring the importance of SA identification and treatment.

There are several potential limitations that may confound our study findings and interpretations. We identified SA using ICD-9 and CPT codes only. Polysomnography results for each SA patient were not available including apnoea-hypopnoea indexes. To validate the accuracy of the coding, a random chart review of those coded with SA revealed that 88% of patients who had coded for SA had a documented polysomnography or were being treated for SA with CPAP or BiPAP.²⁹ Although we defined RH based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and American Heart Association guidelines, our definition remains imperfect.^{30,31} We did not require the use of a diuretic; however, 97% of the RH population were on a diuretic. We used two blood pressure measurements to determine RH versus non-RH status without being able to take into consideration blood pressure variation with time. In contrast to the real-world phenomenon where blood pressures vary over time, we somewhat arbitrarily identified a cohort as RH. The assumption was that once subjects were identified as RH or non-RH, they would remain so during the observation period.

In conclusion, in a large ethnically diverse and gender-balanced HTN population, there was a modest increase in risk for SA in the RH population compared to non-RH. Risk for IHEs and CHF were increased in those with SA in RH compared to SA in non-RH. However, there were no differences in risk for stroke and mortality in SA in RH

versus SA in non-RH. Our EHR-based study and cohort has the potential to provide valuable insights into management strategies for both the SA and the RH populations in addition to studying the natural history of these co-existing conditions.

Acknowledgements

This study was funded and supported by Kaiser Permanente Southern California Research. Support was also provided by a research grant from the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health (R21 DK103104) to S.F.D.

REFERENCES

- Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD *et al.* Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* 2011; **58**: 811–7.
- Muxfeldt ES, Margallo VS, Guimaraes GM, Salles GF. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. *Am. J. Hypertens.* 2014; **27**: 1069–78.
- Demede M, Pandey A, Zizi F, Bachmann R, Donat M, McFarlane SI, Jean-Louis G, Ogedegbe G. Resistant hypertension and obstructive sleep apnea in the primary-care setting. *Int. J. Hypertens.* 2011; **2011**: 340929.
- Goncalves SC, Martinez D, Gus M, de Abreu-Silva EO, Bertoluci C, Dutra I, Branchi T, Moreira LB, Fuchs SC, de Oliveira AC *et al.* Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest* 2007; **132**: 1858–62.
- Drager LF, Genta PR, Pedrosa RP, Nerbass FB, Gonzaga CC, Krieger EM, Lorenzi-Filho G. Characteristics and predictors of obstructive sleep apnea in patients with systemic hypertension. *Am. J. Cardiol.* 2010; **105**: 1135–9.
- Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am. J. Epidemiol.* 2013; **177**: 1006–14.
- Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004; **291**: 2013–6.
- Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc. Am. Thorac. Soc.* 2008; **5**: 136–43.
- Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A. Association of hypertension and sleep-disordered breathing. *Arch. Intern. Med.* 2000; **160**: 2289–95.
- Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N. Engl. J. Med.* 2000; **342**: 1378–84.
- Sim JJ, Rasgon SA, Derose SF. Sleep apnea and hypertension: prevalence in chronic kidney disease. *J. Clin. Hypertens. (Greenwich)* 2007; **9**: 837–41.
- Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 2007; **50**: 417–23.
- Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerdts S, Poppe K, Dupont A, Velkeniers B. The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. *Arch. Intern. Med.* 2007; **167**: 757–64.
- Dudenbostel T, Calhoun DA. Resistant hypertension, obstructive sleep apnoea and aldosterone. *J. Hum. Hypertens.* 2012; **26**: 281–7.
- Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, Leung RS, Bradley TD. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J. Hypertens.* 2001; **19**: 2271–7.
- Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun DA, McGlynn EA, Kalantar-Zadeh K, Jacobsen SJ. Characteristics of resistant

- hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin. Proc.* 2013; **88**: 1099–107.
- 17 Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. *Kidney Int.* 2015; **88**: 622–32.
 - 18 Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, Chen W, Jacobsen SJ. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm. J.* 2012; **16**: 37–41.
 - 19 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T *et al.* A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* 2009; **150**: 604–12.
 - 20 Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest* 2007; **131**: 453–9.
 - 21 Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension* 2011; **57**: 1076–80.
 - 22 Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation* 2011; **124**: 1046–58.
 - 23 Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, Caldarella MP, Neri M, Cuccurullo F, Mezzetti A. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. *Am. J. Hypertens.* 2005; **18**: 1422–8.
 - 24 Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation* 1999; **100**: 2332–5.
 - 25 Huang Z, Liu Z, Luo Q, Zhao Q, Zhao Z, Ma X, Liu W, Yang D. Long-term effects of continuous positive airway pressure on blood pressure and prognosis in hypertensive patients with coronary heart disease and obstructive sleep apnea: a randomized controlled trial. *Am. J. Hypertens.* 2015; **28**: 300–6.
 - 26 Pedrosa RP, Drager LF, de Paula LK, Amaro AC, Bortolotto LA, Lorenzi-Filho G. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. *Chest* 2013; **144**: 1487–94.
 - 27 Martinez-Garcia MA, Gomez-Aldaravi R, Soler-Cataluna JJ, Martinez TG, Bernacer-Alpera B, Roman-Sanchez P. Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. *Eur. Respir. J.* 2007; **29**: 951–7.
 - 28 Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, Bradley TD. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. *Eur. Respir. J.* 2003; **21**: 241–7.
 - 29 Sim JJ, Rasgon SA, Kujubu DA, Kumar VA, Liu IL, Shi JM, Pham TT, Derose SF. Sleep apnea in early and advanced chronic kidney disease: Kaiser Permanente Southern California cohort. *Chest* 2009; **135**: 710–6.
 - 30 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr, Jones DW, Materson BJ, Oparil S, Wright JT, Jr, *et al.* National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72.
 - 31 Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, *et al.* American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; **117**: e510–26.

Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website:

Table S1 ICD-9 codes used to capture sleep apnoea.

Table S2 ICD-9 codes used to capture outcomes/events during hospitalizations.

Table S3 Anticoagulation and antithrombotic medications evaluated.