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Screening for Primary Aldosteronism is Underutilized in Patients with Obstructive Sleep Apnea

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Abstract

Background: Resistant hypertension is common in patients with primary aldosteronism and in those with obstructive sleep apnea. Primary aldosteronism treatment improves sleep apnea. Despite Endocrine Society guidelines' inclusion of sleep apnea and hypertension co-diagnosis as a primary aldosteronism screening indication, the state of screening implementation is unknown.

Methods: All hypertensive adult patients with obstructive sleep apnea (n=4,751) at one institution between 2012–2020 were compared to a control cohort without sleep apnea (n=117,815). We compared the association of primary aldosteronism diagnoses, risk factors, and screening between both groups. Patients were considered to have screening if they had a primary aldosteronism diagnosis or serum aldosterone or plasma renin activity evaluation.

Results: Obstructive sleep apnea patients were predominantly men and had higher BMI. On multivariable analysis, hypertensive sleep apnea patients had higher odds of drug-resistant hypertension (OR 2.70; p<0.001) and hypokalemia (OR 1.26; p<0.001) independent of BMI, sex, and number of anti-hypertensive medications. Overall, sleep apnea patients were more likely to be screened for primary aldosteronism (OR 1.45; p<0.001); however, few patients underwent screening whether they had sleep apnea or not (pre-guideline publication 7.8% v. 4.6%; post-guidelines 3.6% v. 4.6%; p<0.01). Screening among eligible sleep apnea patients remained low before and after guideline publication (4.4% v. 3.4%).

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Conclusions: Obstructive sleep apnea is associated with primary aldosteronism risk factors without formal diagnosis, suggesting screening underutilization and underdiagnosis. Strategies are needed to increase screening adherence, as patients may benefit from treatment of concomitant primary aldosteronism to reduce sleep apnea severity and its associated cardiopulmonary morbidity.

Keywords

Primary aldosteronism; obstructive sleep apnea; screening

INTRODUCTION

Primary aldosteronism is a potential causal link between obstructive sleep apnea and hypertension.[1] It is hypothesized that sodium and volume retention from primary aldosteronism leads to peripharyngeal edema, contributing to sleep apnea severity.[2, 3] Although primary aldosteronism is rare, its prevalence in patients with resistant hypertension, defined as blood pressure ≥140/90 despite adequate doses of three anti-hypertensive medications, is between 10–20%.[1, 4] Up to 85% of patients with drug-resistant hypertension also have sleep apnea.[5, 6] Among hypertensive patients, those with underlying primary aldosteronism are more likely to have sleep apnea.[7] Increased sleep apnea severity has been correlated with increased aldosterone levels, and both the medical and surgical treatment of primary aldosteronism reduce sleep apnea severity.[2, 3, 6, 8, 9]

In 2016, the Endocrine Society recommended primary aldosteronism screening in all patients with hypertension and sleep apnea co-diagnosis.[10] Other recommended screening indications include 1) moderate, severe, or resistant hypertension, 2) hypertension and hypokalemia, 3) hypertension and incidental adrenal mass, 4) a first-degree relative with primary aldosteronism, and 5) hypertension and family history of early-onset hypertension or stroke.[10–12] With an estimated 25% of the population having undiagnosed sleep apnea, which is associated with increased cardiovascular risk, it is imperative to identify patients who may benefit from treatment of concomitant primary aldosteronism.[2]

We aimed to clarify the association between sleep apnea, primary aldosteronism, and screening patterns to inform future practice recommendations. We hypothesized that formal sleep apnea diagnosis would be associated with primary aldosteronism and its risk factors and that screening would be underutilized.

METHODS

Study Design and Participants

We conducted a retrospective, case-control study of hypertensive adult patients with obstructive sleep apnea at one quaternary academic medical center between 2012–2020. Cases and controls were identified through electronic medical record (EMR) query. Data were extracted between July-August 2020. Institutional Review Board approval was granted (IRB#19–29146).

Cases were hypertensive (International Classification of Disease (ICD)-9 401.0, 401.1, 401.9, 402, 403, 404, 405, 796.2, ICD-10 I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9, I16.0, I16.9, R03.0) patients age ≥18 years who underwent polysomnography (Current Procedural Terminology (CPT) codes 95800, 95801, 95806, 95807, 95808, 95810, or 95811) and had a sleep apnea diagnosis (ICD-9 327.23 or ICD-10 G47.33).

Controls were hypertensive patients ≥18 years who presented for a new-patient primary care evaluation (CPT 99201, 99202, 99203, 99204, 99205). Controls were not matched to cases. Patients with a sleep apnea diagnosis or prior polysomnogram were excluded because they were more likely to have sleep apnea symptoms and false-negative studies.

Study Variables

Formal sleep apnea diagnosis was the outcome used to identify cases in this case-control study. Patients with both a CPT code for polysomnography and an ICD code for sleep apnea were considered to have a sleep apnea diagnosis. The primary predictor was primary aldosteronism diagnosis (ICD-9 255.10, 255.11, 255.14, ICD-10 E26.0, E26.9). Secondary predictors included hypokalemia (ICD-9 276.8 or ICD-10 E87.6) and drug-resistant hypertension. Subjects without a hypertension diagnosis code were excluded. The following data elements were extracted: age, sex, race, birth date, death date, BMI, diagnosis date, and first polysomnogram date. BMI classes were defined as follows: underweight (<18.5kg/m^2), normal (18.5–24.9kg/m^2), overweight (25–29.9kg/m^2), and obese (≥30kg/m^2). Laboratory values and dates for the following studies were extracted: aldosterone (Logical Observation Identifiers Names and Codes (LOINC) 1763–2), aldosterone/renin ratio (LOINC 30894–0), plasma renin activity (LOINC 2915–7), and potassium (LOINC 39789–3, 6298–4). All prescribed medications were extracted and the number of unique anti-hypertensive medications prescribed was determined. Patients with ≥3 anti-hypertensive medications were considered to have drug-resistant hypertension.

Subjects were considered to have a primary aldosteronism screening indication if they met any of the following criteria: 1) both hypertension and hypokalemia ICD codes, 2) drug-resistant hypertension, or 3) both hypertension and sleep apnea ICD codes. In 2016, the Endocrine Society published guidelines including sleep apnea and hypertension co-diagnosis as a primary aldosteronism screening indication.[10] Consequently, screening indication was characterized as original (pre-2016 guidelines) or updated (post-2016 guidelines). Patients met original screening criteria if they had hypertension and hypokalemia co-diagnosis or drug-resistant hypertension. Alternatively, patients met updated criteria if they had any of the above indications.

Subjects were considered to have undergone primary aldosteronism screening if they had one of the following: 1) primary aldosteronism diagnosis or evaluation of 2) serum aldosterone, 3) plasma renin activity, or 4) aldosterone-to-renin ratio. If their first primary aldosteronism diagnosis date or requisite laboratory test was prior to or during 2016, screening was classified as having been performed pre-2016. If their first primary aldosteronism diagnosis date or last requisite laboratory test was between 2017–2020,

subjects were considered to have a post-2016 primary aldosteronism-screening event. Some subjects were screened both pre- and post-2016.

The primary confounders were determined a priori to be drug-resistant hypertension, obesity, and male sex. Resistant hypertension is common in the general population, in sleep apnea patients, and in most patients with primary aldosteronism, our primary predictor. As such, we were unable to employ specification in our design strategy for this confounder. If we excluded patients with resistant hypertension, this would exclude the majority of the patients with primary aldosteronism, our primary predictor.

Statistical Analysis

Assuming the prevalence of primary aldosteronism in the general population is 3%[13, 14], a sample size of 572 subjects would provide 90% power to detect a statistically significant association between sleep apnea and primary aldosteronism if the true effect size is a 7% increase in primary aldosteronism prevalence to 10%[11, 12] in sleep apnea patients.

Continuous variables were summarized using means, medians, and standard deviations. Two-sample t-tests and Wilcoxon rank-sum tests were used to compare parametric and non-parametric continuous variables. Chi-squared tests were used to compare categorical variables. Multivariable logistic regression models controlling for BMI class, sex, and the number of anti-hypertensive medications were used to analyze odds of primary aldosteronism diagnosis, risk factor diagnosis, screening indication, and screening performance in cases and controls. The number of anti-hypertensive medications was used as a surrogate for hypertension severity because specific blood pressure measurements were not available. A two-sided alpha of 0.05 was used to determine statistical significance for all analyses. Data analysis was performed using Stata/IC v.16.1 (StataCorp LLC, College Station, TX).

RESULTS

Between 2012–2020, 4,751 hypertensive patients underwent polysomnography and had an obstructive sleep apnea diagnosis. 117,815 hypertensive control patients were identified who presented for a new patient evaluation without a sleep apnea diagnosis or polysomnogram.

Patient demographics are presented in Table 1. Sleep apnea patients were more likely to be male (59.6% v. 51.7%; $p<0.001$) and obese (mean BMI 32.3 v. 28.5 kg/m^2; $p<0.001$).

Association of Primary Aldosteronism and Risk Factors

Sleep apnea patients were more likely to have primary aldosteronism diagnoses (0.5% v. 0.3%; $p=0.02$) despite overall low rates. More sleep apnea patients had drug-resistant hypertension (34.8% v. 19.1%; $p<0.001$). Sleep apnea patients were prescribed more anti-hypertensive medications (mean, 2.2 v. 1.2 medications; $p<0.001$). Patients with sleep apnea were more likely to have hypertension/hypokalemia co-diagnosis (13.8% v. 8.5%; $p<0.001$) (Table 1).

After adjustment for sex, BMI class, and the number of anti-hypertensive medications, sleep apnea patients were at increased odds of hypokalemia (OR 1.26; 95% CI 1.14–1.40; p<0.001) and drug-resistant hypertension (OR 2.70; 95% CI 2.52–2.89; p<0.001) (Table 2). After further adjustment for thiazide and loop diuretic use, sleep apnea patients were still at increased odds of hypokalemia diagnosis (OR 1.26; 95% CI 1.13–1.39; p<0.001). After adjustment, there was no difference in the odds of formal primary aldosteronism diagnosis in sleep apnea patients compared to controls (OR 1.19; 95% CI 0.75–1.90; p=0.46).

Primary Aldosteronism Screening

Even when excluding hypertension and sleep apnea co-diagnosis as a primary aldosteronism screening indication (original guidelines), more sleep apnea patients had a screening indication (38.5% v. 23.2%; p<0.001). When considering updated guidelines, all hypertensive sleep apnea patients qualified for screening (100.0% v. 23.2%; p<0.001) (Table 3). After adjustment, sleep apnea patients were at increased odds of qualifying for screening (OR 1.30; 95% CI 1.09–1.56; p<0.01) (Table 4).

Primary aldosteronism screening was performed in very few patients, although sleep apnea patients were screened more frequently (3.6% v. 1.6%; p<0.001), regardless of indication (Table 3). Although screening rates were higher between 2017–2020 for all patient sub-groups, screening rates remained low, with <10% of patients undergoing screening. Of patients with an original screening indication, more sleep apnea patients were screened for primary aldosteronism in 2016 or earlier compared to controls (4.4% v. 2.2%; p<0.001). However, when considering the updated guidelines, more control patients underwent screening between 2017 and 2020 compared to sleep apnea patients (4.3% v. 3.4%; p<0.01) (Table 3). After adjustment, sleep apnea patients were at higher odds of having undergone primary aldosteronism screening regardless of indication (OR 1.45; 95% CI 1.20–1.74; p<0.001). Eligible sleep apnea patients were only at higher odds of undergoing screening if sleep apnea and hypertension co-diagnosis was excluded as an indication (OR 1.39; 95% CI 1.13–1.70; p<0.01). When considering updated indications, there was no difference in the odds of screening between eligible sleep apnea and control patients (OR 0.84; 95% CI 0.70–1.02; p=0.08) (Table 4).

DISCUSSION

In this retrospective, case-control study, obstructive sleep apnea was independently associated with primary aldosteronism risk factors. This association with primary aldosteronism risk factors in the setting of a lower primary aldosteronism frequency (0.3–0.5%) compared to the literature (10%)[4] and the lack of an association with formal primary aldosteronism diagnosis suggests underdiagnosis of primary aldosteronism. Despite most sleep apnea patients having a screening indication, all patients were under-screened for primary aldosteronism, with less than 8% of eligible patients receiving appropriate screening. Although sleep apnea patients were screened more frequently than controls (3.6% v. 1.6%), this 2% increase in screening is not clinically significant, particularly in the setting of an overall low absolute screening rate. Furthermore, there was no clinically significant increase in screening among hypertensive sleep apnea patients after publication of the 2016

Endocrine Society guidelines. To our knowledge, this is the first study examining primary aldosteronism screening practices among hypertensive sleep apnea patients both before and after updated guideline publication.

Historically, primary aldosteronism has been considered a rare cause of hypertension. Many physicians who traditionally care for hypertensive patients have not routinely considered primary aldosteronism as an underlying diagnosis. However, 10–20% of hypertensive patients have primary aldosteronism, a potentially surgically-curable form of hypertension.[4, 10, 15] Considering approximately 30% of Americans have hypertension and therefore substantial cardiovascular risk, primary aldosteronism emerges not as a rare footnote, but rather as a potentially significant public health issue.[10, 16]

Sleep apnea has long been associated with hypertension, but only in the last 10–15 years has its association with primary aldosteronism been recognized. Sleep apnea and primary aldosteronism co-diagnosis rates range from 9–34%.[11, 12, 17] Both the medical and surgical treatment of primary aldosteronism have been shown to reduce sleep apnea severity.[2, 9] A study of 207 hypertensive patients referred for polysomnography reported that 21% of patients with confirmed sleep apnea had a primary aldosteronism co-diagnosis compared to only 8% of hypertensive patients with a negative polysomnogram.[17] This is discordant with an earlier study of 203 hypertensive sleep apnea patients which demonstrated only a 9% primary aldosteronism co-diagnosis rate which was similar to their control cohort of hypertensive patients in the general population.[11] However, the control cohort in the latter study was not screened for obstructive sleep apnea and therefore may have lower external validity.

In the US, 10–25% of the population has sleep apnea, with nearly half also having hypertension and therefore meeting Endocrine Society guidelines' recommendation for primary aldosteronism screening.[18] Both patients with sleep apnea and those with primary aldosteronism are at increased risk for cardiovascular disease.[19–22] Although observational studies have shown continuous positive airway pressure (CPAP) use to be associated with improved cardiovascular outcomes in sleep apnea patients, an international, randomized controlled trial failed to demonstrate a reduction in cardiovascular events with CPAP use.[23] The authors hypothesized that this lack of efficacy may have been due to insufficient adherence. However, this study did not address the possibility of primary aldosteronism in this population. The contribution of primary aldosteronism to the cardiac morbidity in the sleep apnea population may have complicated the study outcome. For patients with sleep apnea and underlying primary aldosteronism, surgical cure or medical management of their primary aldosteronism and therefore reduction in their sleep apnea severity may lead to improved cardiovascular outcomes.

Despite the need to identify patients with primary aldosteronism, screening adherence remains low. In our study, eligible sleep apnea patients were only more likely to be screened compared to controls if their sleep apnea was not considered an indication. Among eligible sleep apnea patients, the rate of screening was lower after 2016 (3.4%) compared to before 2016 (4.4%). This observed lack of clinically significant increase in screening after guideline publication may be due to a delay in guideline implementation. New guideline

publication does not immediately lead to widespread practice change but does result in a large increase in the number of eligible patients and therefore lower overall screening rates. However, the low screening rates in our study are only marginally higher than in the literature. Ruhle et al. reported a primary aldosteronism screening rate of 2.7% in hypertensive hypokalemic patients compared to 3.0% in hypertensive sleep apnea patients.[24] Among hypertensive hypokalemic patients, those who were prescribed ≥5 anti-hypertensive medications or had a severe hypertension diagnosis code were more likely to be screened. Similarly, another study of hypertensive patients demonstrated that although 43.8% met screening criteria, only 1.3% had an aldosterone-to-renin ratio reported in the EMR.[25] Those with hypertension and an incidental adrenal mass were more likely to be screened, although only 18.2% underwent screening. In contrast, only 1.2% of hypertensive hypokalemic patients and 1.7% of hypertensive sleep apnea patients were screened.

This failure to implement recommended screening in primary aldosteronism mirrors challenges reported among patients with primary hyperparathyroidism, a similarly common "rare" endocrine disorder. Primary hyperparathyroidism screening remains underutilized, with only 20–30% of eligible patients undergoing screening.[26–28] Factors associated with increased screening include higher calcium elevation, which is analogous to greater primary aldosteronism screening among patients with severe hypertension or higher anti-hypertensive medication requirements.[24, 27] In primary hyperparathyroidism, specialist referral is associated with higher likelihood of screening.[27] Although this has not been demonstrated among patients with primary aldosteronism, it is likely that referral to an endocrinologist or specialized hypertension center would result in increased guideline adherence.

As in primary hyperparathyroidism, strategies are needed to improve primary aldosteronism screening adherence. Primary care physicians are on the frontlines of screening implementation and should be considered in strategies for improving adherence. A questionnaire sent to 500 primary care physicians revealed that only 53–59% were aware of primary aldosteronism screening guidelines.[29] Recognizing this gap, the 2016 Endocrine Society guidelines were accompanied by a desk reference for primary care physicians in an effort to increase screening.[10] EMR-based approaches have been suggested, where diagnostic algorithms trigger an alert to consider screening.[26, 28] For example, upon entering a sleep apnea diagnosis code in a hypertensive patient's record, the physician might be alerted that this patient meets primary aldosteronism screening criteria. To help with alert fatigue, polysomnography reports confirming a sleep apnea diagnosis could include a reminder to consider screening.

Our study has several limitations. This observational, retrospective, case-control study cannot draw any conclusions regarding the prevalence of primary aldosteronism diagnosis or screening among sleep apnea patients; rather, we can only determine the association between these diagnoses and screening practices. Our study is reliant on EMR query, which has the potential for missing or unreliable data, particularly for screening. We do not know if screening was recommended and patients declined; screening performed at another hospital would not be captured. Although we determined screening performance dates, we did not have access to medication initiation dates and were unable to determine

when a subject became eligible for screening. This retrospective study was performed at a single academic medical center, which limits the generalizability of these findings because we were unable to determine how screening rates in this cohort compared to other centers. For example, this analysis may overestimate screening practices because providers at a high-volume academic center might be more familiar with current recommendations. Specific blood pressure measurement and medication dosage data were unavailable in this study, which limited our ability to determine which patients on ≥3 maximally-dosed anti-hypertensive medications remained hypertensive, which is a more precise indication for primary aldosteronism screening. In our multivariable analysis, we adjusted for the number of anti-hypertensive medications as a surrogate for hypertension severity, an important confounder, but this was an imperfect adjustment. Inclusion of blood pressure measurements and hypertensive medication dosage would be important in future prospective studies.

Requiring both the polysomnogram and formal sleep apnea diagnosis for inclusion increased the likelihood that we captured patients with true sleep apnea because many patients have a sleep apnea diagnosis without a confirmatory polysomnogram. However, this risked missing patients who either had the polysomnogram at a different institution or had not yet had one. A sleep apnea diagnosis code may have been entered to proceed with the polysomnogram but the study result may have been negative.

The controls were designed to be primary care patients, with the rationale that they would be more likely to have diagnoses entered in the EMR, presumably during their new-patient visit. In contrast, incomplete records would be more likely in a random sample. However, it is not possible to ensure all relevant history and prior examinations are captured. This sample may not be representative of the general population, as patients in our primary care may have more complex conditions at baseline because our institution is an academic center.

In this study, we demonstrated that obstructive sleep apnea is associated with primary aldosteronism risk factors without formal primary aldosteronism diagnosis, suggesting underdiagnosis. Guidelines recommend primary aldosteronism screening to reduce the cardiopulmonary morbidity and mortality associated with the potentially surgically-curable resistant hypertension resulting from primary aldosteronism as well as complications that stem from sleep apnea. Despite these recommendations, few eligible patients undergo screening. Strategies are needed to improve primary aldosteronism screening adherence.

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Conflicts of Interest:

KCHM is a consultant for Prescient Surgical. **IS** is a consultant for Medtronic, Prescient Surgical. **JAS** is a member of the Data Monitoring Committee of the Medullary Thyroid Cancer Consortium Registry supported by GlaxoSmithKline, Novo Nordisk, Astra Zeneca, Eli Lilly. She receives institutional research funding from Exelixis and Eli Lilly.

Data Availability:

The datasets used are available from the authors on reasonable request.

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Table 1:

Demographic and Clinical Characteristics of Patients with and without Obstructive Sleep Apnea

	No. (%)		
	Obstructive Sleep Apnea (n = 4,751)	**Non-Obstructive Sleep Apnea (n = 117,815)**	***P* value**
Demographic Variables			
Patient age, mean (SD), years	60.1 (14.2)	60.1 (15.5)	0.94
Male	2,832 (59.6)	60,927 (51.7)	<0.001
Race			
White	2,372 (49.9)	64,477 (54.7)	<0.001
Black	537 (11.3)	9,209 (7.8)	
Asian	797 (16.8)	17,717 (15.0)	
Unknown/Other	1,045 (22.0)	26,412 (22.4)	
BMI, mean, kg/m ^{2}	32.3	28.5	<0.001
Clinical Variables			
Primary Aldosteronism	22 (0.5)	322 (0.3)	0.02
Hypertension	4,751 (100.0)	117,815 (100.0)	N/A
Drug-Resistant Hypertension	1,654 (34.8)	22,546 (19.1)	<0.001
Hypertensive medications, mean (SD), number	2.2 (2.8)	1.2 (1.9)	<0.001
Hypertension and Hypokalemia	654 (13.8)	9,968 (8.5)	<0.001

Table 2:

Adjusted* Odds of Primary Aldosteronism and Risk Factors for Primary Aldosteronism in Patients with Obstructive Sleep Apnea

	Odds Ratio (95% CI)	*P* value
Primary Aldosteronism	1.19 (0.75 – 1.90)	0.46
Hypokalemia	1.26 (1.14 – 1.40)	<0.001
Drug-Resistant Hypertension **	2.70 (2.52 – 2.89)	<0.001

*Adjusted for sex, BMI class, and number of anti-hypertensive medications.

**Adjusted for sex and BMI class

Table 3:

Primary Aldosteronism Screening Indications and Practices

	No. (%)		
	Obstructive Sleep Apnea (n = 4,751)	**Non-Obstructive Sleep Apnea (n = 117,815)**	***P* value**
Screening Indications			
Original Guidelines			
Hypertension and Hypokalemia *or* Drug-Resistant Hypertension	1,828 (38.5)	27,377 (23.2)	<0.001
Updated Guidelines			
Hypertension and Hypokalemia *or* Drug-Resistant Hypertension *or* Hypertension and Obstructive Sleep Apnea	4,751 (100.0)	27,377 (23.2)	<0.001
Screening Practices			
Screening Performed - Regardless of Indication			
Pre-2016	95 (2.0)	922 (0.8)	<0.001
Post-2016	160 (3.4)	1,797 (1.5)	<0.001
Either pre- or post-2016	170 (3.6)	1,929 (1.6)	<0.001
Screening Performed – Original Indication	(n = 1,828)	(n = 27,377)	
Pre-2016	80 (4.4)	605 (2.2)	<0.001
Post-2016	134 (7.3)	1,167 (4.3)	<0.001
Either pre- or post-2016	142 (7.8)	1,256 (4.6)	<0.001
Screening Performed – Updated Indication	(n = 4,751)	(n = 27,377)	
Pre-2016	95 (2.0)	605 (2.2)	0.36
Post-2016	160 (3.4)	1,167 (4.3)	<0.01
Either pre- or post-2016	170 (3.6)	1,256 (4.6)	<0.01

Table 4:

Adjusted* Odds of Primary Aldosteronism Screening Indications and Performance in Patients with Obstructive Sleep Apnea

	Odds Ratio (95% CI)	*P* value
Screening Indication		
Original Guidelines		
Hypertension and Hypokalemia *or* Drug-Resistant Hypertension	1.30 (1.09 – 1.56)	<0.01
Screening Performance		
Screening Performed – Regardless of Indication	1.45 (1.20 – 1.74)	<0.001
Screening Performed – Original Indication	1.39 (1.13 – 1.70)	<0.01
Screening Performed – Updated Indication	0.84 (0.70 – 1.02)	0.08

*Adjusted for sex, BMI class, and number of anti-hypertensive medications.