“The association of severity of airflow limitation with adherence to oral medications in Veterans with hypertension and/or diabetes”

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ABSTRACT:

Rationale/Objectives: Diabetes and Hypertension are common among patients with Airflow Limitation and contribute to Cardiovascular (CV) mortality, one of the leading cause of death among patients with airflow limitation (AFL). We examined the association of severity of AFL with adherence to medications for hypertension and diabetes.

Methods: We identified 7,359 Veterans with hypertension and/or diabetes in the Veterans Integrated Service Network-20. Entry date into the cohort was defined as the date of a patient's first pulmonary function testing (PFT). Diagnostic codes (ICD-9), PFT, and pharmacy data were available via the electronic medical record or via direct interrogation of PFT equipment. Our primary exposure was AFL defined as an FEV1≥80% predicted (normal), FEV1 50-<80% predicted (mild/moderate), FEV1 30-<50% predicted (severe), and FEV1<30% predicted (very severe). We assessed adherence using a validated method based on electronic pharmacy refill data and defined adherence as ≥80% medication possession for the period 6-12 months after enrollment. Medications of interest included beta blockers (BBs), calcium channel blockers (CCBs), thiazides, and ACE inhibitors (ACEIs) for patients with hypertension, and metformin and sulfonylureas for patients with diabetes. We utilized logistic regression models to assess the association between severity of AFL and adherence, adjusted for demographics, health behaviors, and comorbidities.

Results: Overall adherence was poor (44.6-55.1%). Among patients with hypertension, when compared to subjects with normal FEV1, subjects with each category lower of FEV1 were less adherent to BBs, with OR of 0.87 [95% CI, 0.80-0.95], CCBs, with OR of 0.83 [95% CI, 0.74-0.93], and ACEIs with OR 0.91 [95% CI 0.84-0.99]. AFL was not associated with adherence to thiazides. Among patients with diabetes, we found no significant association of FEV1 with

adherence, though a similar lower trend with increasing AFL. In a sensitivity analysis limited to patients with COPD, we found a non-statistically significant trend for decreased adherence to BBs, CCBs and ACEIs in subjects with higher GOLD stage.

Conclusion: Severity of AFL is associated with decreased adherence to BBs, CCBs and ACEIs. The decreased adherence to these medications may be related to adverse effects on symptoms in patients with lung disease, and may partially explain excess CV mortality in these patients.

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1. INTRODUCTION AND BACKGROUND:

Patients with respiratory disorders, often defined by a diminished forced expiratory volume in one second (FEV1), commonly suffer from multiple chronic conditions such as hypertension, diabetes, and cardiovascular disease. (1-3) The presence of multiple medical conditions in a given patient is becoming the norm in primary care, and this "multimorbidity" is well-established to be associated with increased costs,(4) as well as worse outcomes in terms of mortality, admission rates,(5) and quality of life.(6) Additional chronic conditions complicate patients' pharmacy regimens, cause additional symptoms, and may lower adherence to treatments that are known to improve outcomes. Attenuation of risk for many of these chronic conditions is available only through intense lifestyle modification, and potentially through the use of pharmaceutical therapies. Patients with COPD in particular are more likely than matched peers to be diagnosed with multiple chronic diseases, particularly coronary artery disease.(3, 7) Patients with a diminished FEV1 are at high risk of death not only from respiratory diseases, but also from cardiovascular disease and stroke,(8-10) independent of smoking history, (2, 11) making them a high-priority group for treatment of risk factors for cardiovascular disease.

Poor medication adherence for chronic conditions is common among patients with respiratory diseases (12, 13) and may have important implications for outcomes for these patients. Increased adherence to medications for chronic conditions is associated with improved outcomes, including better objective control, decreased hospital admission rate, and improved long-term outcomes.(14-17) While physicians frequently prescribe multiple medications for several co-existing medical problems, rates of adherence are rarely assessed. Therefore, adherence to medications for multiple medical problems is a significant issue for patients, physicians, and payers. The reasons behind the variation in adherence to chronic medications

from patient to patient are largely unknown, and may include interactions between symptoms and medication complexity.

How the presence of airflow limitation affects adherence to medications for hypertension and diabetes is unknown. In this study, we sought to examine the association between airflow limitation, as measured by forced expiratory volume at one second (FEV1), and adherence to oral medications for hypertension and diabetes. We hypothesized that increased airflow limitation would be associated with decreased adherence to oral medications for these conditions.

2. METHODS:

2.1 Design, setting and participants:

We conducted a retrospective cohort study of patients who carried a diagnosis of hypertension and/or diabetes and were being treated with oral medications for these conditions among a larger cohort of patients who underwent spirometry within the Veterans Affairs (VA) Integrated Service Network (VISN)-20. The VISN-20 comprises the northwest portion of the United States, and encompasses a wide variety of practice settings. This study was approved by the VA Puget Sound Health Care System Institutional Review Board as minimal risk under a waiver of informed consent.

2.2 Data source:

We used clinical information from the VISN-20 data warehouse that routinely collects data using the VA electronic medical record including demographics, prescription medications, office visits, hospital admissions, hospital and outpatient diagnoses. Pulmonary function testing (PFT) data was available in the electronic medical record or via direct interrogation of

pulmonary function testing equipment to ensure accurate values. Pulmonary function testing at each site is standardized and is performed according to the ATS guidelines for reproducibility.

2.3 Cohort development:

We identified 14,541 Veterans who underwent pulmonary function testing as part of routine care at one of three VISN-20 medical centers located throughout the Pacific Northwest, between January, 2003 and December, 2007. We defined an index date that was the date spirometry was performed. Presence of hypertension or diabetes was determined administratively via ICD.9 diagnostic codes (ICD.9 code 401.X or ICD.9 diagnostic code 250.0x-250.3x) assessed at any visit in the year prior to the index date. Disease categories were not mutually exclusive. Patients were excluded if they lacked a value for forced expiratory volume in one second or were not prescribed any stud y medications of interest during the assessment period.

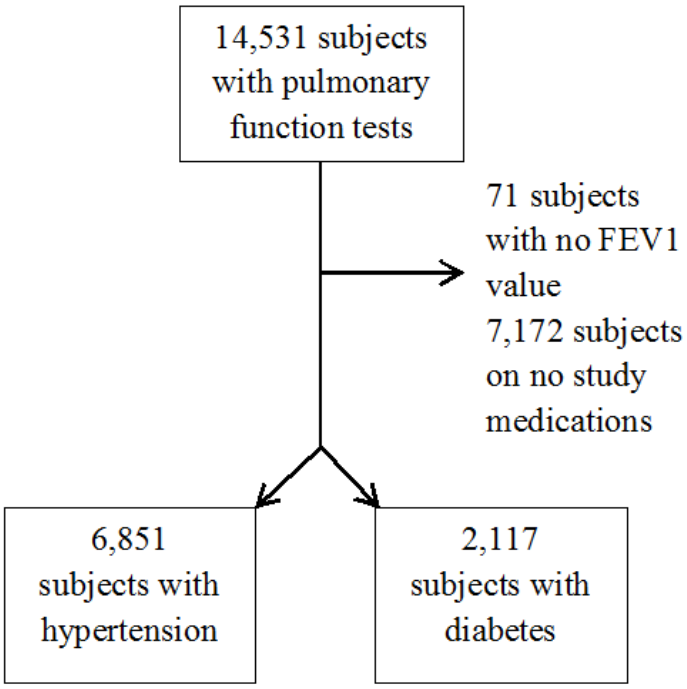

Figure 1: Results of cohort selection. All patients undergoing pulmonary function testing within the VA VISN-20 from 2003-2007 were screened for hypertension and/or diabetes and use of the study medications.

2.4 Outcome assessment:

The outcome of interest was adherence to oral medications for hypertension and diabetes. Medication adherence was assessed using ReComp, a previously validated method for assessing adherence based on electronic pharmacy data, validated with clinical outcomes.(18) Over longer

time windows, ReComp reflects the proportion of time a subject is in possession of medication and is equivalent to a medication possession ratio. Adherence to medication was defined as having a ≥80% score in the 6-12 months after index date. This threshold was selected due to previous studies demonstrating clinically meaningful benefit.(16, 19) We examined the use of beta blockers (BBs), calcium channel blockers (CCBs), thiazides, and angiotensin-converting-enzyme inhibitors (ACEIs) in the subjects with hypertension. Medications of interest were sulfonylureas and metformin in the subjects with diabetes.

2.5 Predictors of adherence:

Our primary exposure was the severity of airflow limitation as measured by pulmonary function testing. Categories of airflow limitation (AFL) were defined as FEV1≥80% predicted (normal), 80>FEV1≥50% predicted (mild to moderate limitation), 50>FEV1≥30% predicted (severe limitation), and FEV1<30% predicted (very severe limitation). The Crapo definitions for defining normal values were utilized.(20) As a secondary predictor, we examined the presence or absence of airflow obstruction.

2.6 Confounders:

Potential confounders known or expected to be associated with adherence were assessed administratively in the 1 year prior to index date. We collected patient information that we conceptually grouped into one of three categories: (1) demographics and health behaviors (age, BMI, race, sex, smoking status within the past year); (2) additional comorbid conditions by ICD.9 diagnostic code (congestive heart failure, acute coronary syndrome, lung cancer, depression, obstructive sleep apnea, schizophrenia) and complexity of medication regimen as described by a count of medication classes both oral and inhaled (including all study medications, statins, long-acting beta agonists, short-acting beta agonists, tiotroprium, and

ipratroprium), and (3) markers of lung disease severity (history of COPD exacerbation within the past year). Presence of a COPD exacerbation was defined administratively, either by a primary discharge diagnosis code of COPD, or by an outpatient visit for COPD accompanied within 48 hours by a prescription for an oral steroid or antibiotic, a previously validated method.(21) Airflow obstruction (AFO) was defined by the Global Initiative for Chronic obstructive Lung Disease criteria as FEV1/FVC ratio<0.70. These conceptual categories were chosen due to previous studies indicating that demographics, psychiatric conditions, health behaviors such as smoking, severity of pulmonary disease, and complexity of medication regimens were associated with medication adherence.

2.7 Statistical Analysis:

Using STATA 12 (College Station, TX) and SAS (SAS Institute Inc. 2011) software, we performed logistic regression to assess the effects of AFL on medication adherence. Bivariate descriptive statistics were calculated using the chi-squared test. We developed multivariable logistic regression models to adjust for potential confounding variables. We created separate models for each group of potential confounders as described above, with each model containing our primary exposure, degree of airflow limitation. To create a parsimonious final adjusted model, variables that achieved $p \leq 0.1$ in the preliminary models were included in the final model, with the exception of age, sex and race which were included in each final model. Test of linear trend was performed to assess the significance of advancing category of airflow limitation, our primary exposure, on medication adherence. Alpha level of <0.05 was considered significant.

2.8 Sensitivity Analysis:

We were interested to see whether patients with obstructive lung disease had a different adherence pattern when compared to patients with diminished FEV1 as a whole. We performed a sensitivity analysis restricted to patients with a post-bronchodilator FEV1/FVC ratio of <0.70. Patients having no airflow obstruction and/or an FEV1≥80% predicted served as the referent group for advancing GOLD stage. We utilized the same blocks of variables, outcomes, exposures, and methods as described above.

3. RESULTS

7,359 unique individuals were available for analysis. This resulted in 6,851 subjects with hypertension and 2,117 subjects with diabetes (Figure 1). Individuals were predominantly older white males. There were a number of significant differences observed between patients with and without airflow limitation. Among individuals with diabetes and individuals with hypertension, patients with airflow limitation were significantly older. A higher proportion of female patients with diabetes and with hypertension had no airflow limitation. A history of congestive heart failure and lung cancer were both more common in patients with airflow limitation. History of recent tobacco use was associated with airflow limitation among subjects with hypertension only. Subjects without airflow limitation were more likely to have a history of depression, but no difference was observed for a history of schizophrenia. We observed a very high proportion of obesity among all patients, particularly among those with diabetes. Patients were on a significant number of medications, averaging between 3 and 4 oral medications and 1 and 2 inhaled medications (Table 1).

Table 1: Characteristics of patients with hypertension and diabetes among Veterans who underwent pulmonary function testing in the VISN-20, by the presence or absence of airflow limitation

	Hypertension			Diabetes		
Variable*	**FEV1≥80% n=2026**	**FEV1<80% n=4825**	**p**	**FEV1≥80% n=571**	**FEV1<80% n=1546**	**p**
Age (years)	63.0 +/- 10.8	66.9 +/- 10.2	<0.001	63.1 +/- 9.7	65.5 +/- 9.8	<0.001
Male	1887 (93.2%)	4688 (97.2%)	<0.001	531 (93.0%)	1503 (97.2%)	<0.001
Race			<0.001			0.003
White	1443 (71.2%)	3529 (73.1%)		408 (71.5%)	1099 (71.1%)	
Non-white	125 (6.2%)	451 (9.3%)		39 (6.8%)	174 (11.3%)	
Unknown	458 (22.6%)	845 (17.5%)		124 (21.7%)	273 (17.7%)	
History of diabetes	570 (28.1%)	1634 (33.8%)	<0.001	-	-	
History of hypertension	-	-		451 (79.0%)	1222 (79.0%)	0.977
Smoker in the past year	629 (31.0%)	1708 (35.4%)	0.001	149 (26.1%)	465 (30.1%)	0.073
CHF	191 (8.9%)	1002 (20.7%)	<0.001	75 (13.1%)	382 (24.7%)	<0.001
History of lung cancer	18 (0.9%)	158 (3.2%)	<0.001	2 (0.35%)	48 (3.1%)	<0.001
History of ACS	62 (3.1%)	220 (4.6%)	0.004	20 (3.5%)	62 (4.0%)	0.591
History of OSA	238 (11.7%)	535 (11.1%)	0.431	101 (17.7%)	256 (16.6%)	0.538
History of depression	605 (29.9%)	1080 (22.4%)	<0.001	165 (28.7%)	369 (23.9%)	0.022
History of schizophrenia	32 (1.6%)	95 (1.9%)	0.275	11 (1.9%)	33 (2.1%)	0.766
Airflow obstruction on PFT	348 (17.2%)	2630 (54.5%)	<0.001	64 (11.2%)	656 (42.4%)	<0.001
FEV1‡						
50%≤FEV1<80%	-	3393 (70.3%)		-	1129 (73.0%)	
30%≤FEV1<50%	-	1120 (23.2%)		-	337 (21.8%)	
FEV1<30%	-	312 (6.5%)		-	80 (5.2%)	
History of COPD exacerbation in past year	60 (3.0%)	619 (12.8%)	<0.001	12 (2.1%)	158 (10.2%)	<0.001
BMI†			<0.001			0.407
25-30	656 (32.4%)	1475 (30.6%)		145 (25.4%)	367 (23.7%)	
>30	1118 (55.2%)	2380 (49.3%)		387 (67.8%)	1023 (66.2%)	
Number of oral medications	3.01 +/-1.34	3.12 +/- 1.37	0.002	4.19 +/-1.25	4.12 +/- 1.31	0.844
Number of respiratory medications	0.87 +/-1.10	1.67 +/-1.40	<0.001	0.84 +/-1.09	1.54 +/-1.37	<0.001

*Values presented are N (percent) with the exception of age (mean, SD)

‡ FEV1=forced expiratory volume in 1 second, presented at % predicted

† 60 subjects with missing BMI values

Abbreviations: CHF=congestive heart failure, ACS=acute coronary syndrome, OSA=obstructive sleep apnea, BMI=body mass index

3.1 Adherence to medications:

The proportion of patients adherent to medications for hypertension were low, ranging from 44.6 to 55.2%. Across several antihypertensive medications, adherence was lower as severity of AFL increased (Table 2). For example, among patients prescribed beta blockers, 54.5% of patients with mild to moderate airflow limitation were adherent, versus 50.0% of subjects with severe limitation, and 45.7% of patients with very severe limitation. Similarly, among those with mild to moderate airflow limitation who were prescribed calcium channel blockers, 55.1% of patients were adherent versus only 48.0% with severe limitation and 44.9% with very severe limitation. Likewise, patients with mild to moderate airflow limitation had a higher proportion adherent to ACE-I when compared to those with severe limitation (53.6% vs 47.5%). In contrast, adherence to thiazides did not vary by severity of AFL (47.9% mild to moderate vs 45.6% very severe limitation).

Table 2: Proportion of patients adherent to oral medications among Veterans with diabetes and hypertension, by severity of airflow limitation (unadjusted)

	FEV1 ≥80% Pred		50%≤FEV1<80%		30%≤FEV1<50%		FEV1<30%	
Medication	N	% Adherent	N	% Adherent	N	% Adherent	N	% Adherent
Antihypertensives								
Beta Blockers	1592	50.4%	2818	54.5%	938	50.0%	234	45.7%
Calcium Channel Blockers	869	52.8%	1632	55.1%	592	48.0%	176	44.9%
Thiazides	1159	48.0%	1777	46.9%	547	43.0%	158	45.6%
ACEIs*	1621	54.7%	2775	53.6%	939	52.1%	265	47.5%
Diabetes Medications								
Sulfonylureas	453	51.9%	911	54.1%	296	49.3%	73	42.5%
Metformin	471	50.5%	848	48.9%	209	45.0%	54	42.6%

*ACEIs: angiotensin converting enzyme inhibitors

Similar to what we observed for antihypertensive medications, adherence to anti-hyperglycemic medications was also low, ranging from 42.5 to 54.1%. There appeared to be a

trend for decreased adherence in subjects with very severe limitation, though adherence overall was not associated with airflow limitation (Table 2).

3.2 Association of airflow limitation with adherence:

In the adjusted models, test of linear trend indicated decreased odds of adherence with increasing severity of airflow limitation for beta blockers (OR 0.92, 95% CI, 0.85-0.99), calcium channel blockers (OR 0.84, 95% CI, 0.76-0.94) and ACEIs (OR 0.91, 95% CI 0.84-0.99). This association was not observed for thiazides (Table 3).

Among patients with diabetes, the presence or degree of airflow limitation was not predictive of a linear trend in adherence to metformin or sulfonylureas. However when analyzed by each individual category of severity in comparison to the referent group, there was a non-significant trend for decreased adherence among subjects with more severe airflow limitation, with significantly decreased adherence among patients with very severe airflow limitation who were taking sulfonylureas (Table 4).

Table 3: Adjusted odds ratios of adherence by severity of airflow limitation among Veterans with hypertension. Referent group is subjects with FEV1≥80% predicted (normal)

		Overall test of trend		50%≤FEV1<80%*		30%≤FEV1<50%*		FEV1<30%*	
Medication	N	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Beta blockers	4141	**0.87 (0.80, 0.95)**	**0.002**	1.06 (0.91,1.23)	0.439	0.78 (0.64, 0.95)	0.016	0.61 (0.43, 0.86)	0.005
Calcium Channel Blockers	2717	**0.83 (0.74, 0.93)**	**0.001**	1.01 (0.83, 1.22)	0.955	**0.65 (0.50, 0.84)**	**0.001**	**0.64** (0.42, 0.96)	**0.033**
Thiazides	3017	1.04 (0.94, 1.15)	0.421	1.03 (0.87, 1.22)	0.698	0.97 (0.76, 1.24)	0.823	**1.45 (0.95, 2.21)**	**0.086**
ACE Inhibitors	4449	**0.91** (0.94, 0.99)	**0.025**	0.92 (0.80, 1.06)	0.251	0.88 (0.72, 1.07)	0.195	**0.68** (0.50, 0.94)	**0.019**

*Forced expiratory volume in one second (FEV1) values expressed as % predicted
Each model adjusted per the results of model building considering for inclusion demographics, health behaviors, complexity of medication regimen, and medical and psychiatric comorbidities. Bold typeface indicates significance.

3.3 Association of airflow obstruction with adherence:

In a sensitivity analysis, we identified 3,281 patients with hypertension, and 1,059 patients with diabetes with airflow obstruction on PFTs, who qualified for a diagnosis of COPD. We examined the odds of adherence for each antihypertensive and diabetes medication. In the adjusted models, there was a similar but not statistically significant linear trend of association between severity of airflow obstruction and adherence for beta blockers (OR 0.92, 95% CI 0.83-1.01), CCBs (OR 0.93, 95% CI 0.83-1.05), thiazides (OR 1.1, 95% CI 0.99-1.23), ACEIs (OR 0.94, 95% CI 0.86-1.03) metformin (OR 0.89, 95% CI 0.76-1.05), or sulfonylureas (OR 0.88, 95% CI 0.76-1.03).

We found a similar but not statistically significant pattern of lower odds of adherence with very severe airflow limitation, which was observed for BBs (OR for adherence in GOLD stage IV: 0.71, 95% CI 0.48-1.04) and ACEIs (OR for adherence in GOLD stage: IV 0.77, 95% CI, 0.55-1.08). GOLD IV disease was associated with increased adherence for thiazides (OR 1.55 95% CI 1.00-2.53).

Table 4: Adjusted odds ratios of adherence to oral medications by severity of airflow limitation among Veterans with diabetes. Referent group is subjects with FEV≥80% predicted (normal)

		Overall test of trend		50%≤FEV1<80%*		30%≤FEV1<50%*		FEV1<30%*	
Medication	**N**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Metformin	1440	0.87 (0.76, 1.01)	0.068	0.93 (0.73, 1.18)	0.544	0.77 (0.54, 1.09	0.143	0.64 (0.35, 1.16)	0.142
Sulfonylureas	1554	0.88 (0.76, 1.01)	0.060	1.01 (0.79, 1.29)	0.951	0.86 (0.62, 1.20)	0.365	**0.52 (0.29, 0.92)**	**0.026**

*Forced expiratory volume in one second (FEV1) values expressed as % predicted
Each model adjusted per the results of model building considering for inclusion demographics, health behaviors, complexity of medication regimen, and medical and psychiatric comorbidities. Bold typeface indicates significance.

4. DISCUSSION

In this cohort of patients who underwent pulmonary function testing, we found that both hypertension and diabetes were common, but that overall adherence to antihypertensive or hypoglycemic medications was low. Previous studies of adherence to antihypertensive medications in the overall VA population have shown proportions of adherence of to be notably higher that what we describe. (22) Our cohort differs from previous VA cohorts assessed for adherence to chronic medications in that PFTs were ordered as part of clinical care, suggesting that these patients were symptomatic with dyspnea or other respiratory complaint. The low rates of adherence in our cohort in comparison to others suggest that patients with airflow limitation represent an important group to target for improved adherence, and may differ in important ways from patients with chronic conditions who are asymptomatic. Our primary predictor, severity of airflow limitation, was associated with lower adherence to several important medications including beta-blockers, calcium channel blockers, and ACEIs. Although we were unable to examine the reasons behind lower adherence to beta-blockers, calcium channel blockers and ACEIs, our results suggest that poor patient adherence may partially account for the worse cardiovascular outcomes associated with airflow limitation.

The lower adherence seen with beta blockers, calcium channel blockers, and ACEIs among subjects with increasing severity of airflow limitation may be due to several reasons, both biologic and behavioral. Non-adherence may be related to side effects associated with these medications. For example, while the likelihood of worsening bronchospasm may be low, beta blockers may predispose patients to fatigue as a side effect.(23) Beta blockers may also contribute to an inadequate heart rate response during exercise, which again may further limit exercise capacity in a patient already limited by lung disease. Patients suffering from fatigue or

dyspnea related to pulmonary disease may be particularly intolerant of this side effect, and may choose not to be adherent despite documented benefits on morbidity and mortality. Similarly, calcium channel blockers and ACEIs are generally well-tolerated classes of medications for hypertension. However, they too can contribute to dizziness and fatigue. Calcium channel blockers can cause bothersome leg swelling.(24) For patients with severe lung diseases who rely on hypoxic pulmonary vasoconstriction to maintain ventilation and perfusion matching, use of calcium channel blockers may in fact worsen hypoxemia, which may be more apparent with exercise, and which may lead patients to adhere to medications less often. ACE inhibitors cause cough in up to 10% of patients,(25) which may be more bothersome to patients with pre-existing airflow limitation.

From a behavioral standpoint, patients with increased airflow limitation may have other barriers that predispose to lower adherence. These patients may suffer from greater comorbidity, which carries with it higher symptom burden (6) and number of prescribed medications. Complex medication regimens (12) and inadequate time for doctor/patient communication about chronic medical conditions (26, 27) are both associated with decreased adherence in some studies. Conversely, other studies have found that increased numbers of medications prescribed are associated with increased adherence.(28-30) As airflow limitation becomes more severe, symptoms may worsen to the point that performing the tasks needed to obtain refills become more difficult. There was a significant trend for decreased adherence to sulfonylureas in the subjects with very severe airflow limitation. This trend may be explained by these complex behavioral interactions, rather than by symptomatic side effects. Poor lung function may be associated with other conditions such as lack of social support, homelessness, or alcohol use that may influence adherence, but were unmeasured in this study design. There was a suggestion of

increased adherence to thiazides in the subjects with very severe airflow limitation, which may suggest a therapeutic benefit to diuretics for patients with lung disease as has been seen in other studies.(31)

This study had several limitations. The data was obtained administratively and we did not know whether patients consumed the medications they received. The anticipated effect in this situation would be to overestimate adherence. We may not have captured all medication refills if they were performed outside the VA system, which may have induced bias if rates were differential with reference to the exposure. We believe that subsequently refilling medications outside the system is unlikely to be common, as the majority of patients receiving care within the VA use it as their primary pharmacy resource due to financial incentives.(32, 33) Pulmonary function testing in general has excellent test characteristics and reproducibility and is likely to provide accurate measures for the majority of patients. While clinically discouraged, some subjects may have undergone testing when they were acutely ill. Likewise, patients may have given poor effort, either of which may have caused misclassification in the exposure with an FEV1 not reflective of their true chronic lung function. This is anticipated to be rare, but is unable to be detected from the quality of the spirometry testing available. Data was collected within the VA system which may limit some of the generalizability outside of an integrated health care system. Despite being representative of the Veterans who seek care in the Pacific Northwest, there were relatively few women and minorities in our cohort, limiting the ability to generalize to these groups. If a patient was verbally instructed to discontinue a medication by their physician, without a change in the electronic order, we would not have been able to distinguish between non-use and non-adherence. Finally, despite adjustment for sociodemographic variables and additional comorbidities and predictors that are conceptually

anticipated to be associated with medication adherence, residual confounding may exist in the relationship between airflow limitation and adherence.

Our study has several strengths. We were able to examine a large cohort of patients with a wide range in FEV1 and high prevalence of comorbid conditions and medication usage. In addition, we included patients from a diverse set of VA settings including academically and non-academically affiliated centers. We performed an unbiased collection of patients, including all patients who had pulmonary function testing. We had access to excellent completeness of medications prescribed and filled collected within the VA system. We maintained a clear and unbiased approach to the assessment of the exposure as well as the outcome.

In summary, we found that overall prevalence of adherence to chronic oral medications was low among this population of Veterans with hypertension and/or diabetes, and airflow limitation. While improved medication adherence will not prevent all of the consequences of chronic diseases, it is an important target for improving health and the delivery of quality care. Patients with a diminished FEV1 are at high risk of death from cardiovascular disease and stroke,(8-10) independent of smoking history,(2, 11) making this an important group to target for modification of cardiovascular risk. Our data suggest that several key classes of medications may be associated with decreased adherence in these subjects, a finding that has important implications for prescribing patterns and counselling in these patients. Data suggests that a better understanding of the expected function of chronic medications can encourage patients to maintain compliance over time.(34) Focusing on the interplay between chronic diseases may be a target for improving adherence among patients with multiple conditions.

Melzer AC, Uman J, Au DH**.** Adherence to Oral Medications for Hypertension and Diabetes in Veterans with Comorbid Airflow Limitation. Ann Am Thorac Soc. 2015;12(6):831-7.

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