6. Shoemark A, Frost E, Dixon M, Ollosson S, Kilpin K, Patel M, *et al*. Accuracy of immunofluorescence in the diagnosis of primary ciliary dyskinesia. *Am J Respir Crit Care Med* 2017;196:94–101.
7. Bolte S, Cordelières FP. A guided tour into subcellular colocalization analysis in light microscopy. *J Microsc* 2006;224:213–232.
8. Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis patients. *J Cyst Fibros* 2003;2:29–34.
9. Ortori CA, Dubern JF, Chhabra SR, Cámara M, Hardie K, Williams P, *et al*. Simultaneous quantitative profiling of N-acyl-L-homoserine lactone and 2-alkyl-4(1H)-quinolone families of quorum-sensing signaling molecules using LC-MS/MS. *Anal Bioanal Chem* 2011;399:839–850.
10. Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. *Science* 2009;325:1131–1134.
11. Yan CH, Hahn S, McMahon D, Bonislawski D, Kennedy DW, Adappa ND, *et al*. Nitric oxide production is stimulated by bitter taste receptors ubiquitously expressed in the sinonasal cavity. *Am J Rhinol Allergy* 2017;31:85–92.
12. Yang J, Liu X, Yue G, Adamian M, Bulgakov O, Li T. Rootletin, a novel coiled-coil protein, is a structural component of the ciliary rootlet. *J Cell Biol* 2002;159:431–440.
13. Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, *et al*.; ECFS Patient Registry Steering Group. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. *Eur Respir J* 2014;43:125–133.

H2 Receptor Antagonist Use and Mortality in Pulmonary Hypertension: Insight from the VA-CART Program

To the Editor:

Pulmonary hypertension (PH) is common and predicts or mediates poor outcomes in many medical disorders (1). Independent of the underlying etiology, persons affected by PH have increased right-ventricular load and often develop right-heart failure. Pulmonary vasodilators are beneficial in some forms of PH (e.g., pulmonary arterial hypertension), but they can be harmful or have no impact in other forms (2).

Histamine H2 receptor antagonism may be relevant in the myocardial stress response and beneficial in right-heart dysfunction and right-heart failure (3–6). To explore this possibility, we examined relationships between H2 receptor antagonist (H2RA) use and mortality in a cohort of veterans with PH confirmed at right-heart catheterization (RHC).

Supported by the NIH (1K08HL11207-01A1, KL2TR002317, R56HL131787, and 1R01HL139613-01), American Heart Association (AHA 15GRNT25080016 and AHA 17SDG33670199), Pulmonary Hypertension Association, Cardiovascular Medical Research and Education Fund, CHEST Foundation (Award in Pulmonary Arterial Hypertension), and Systemic Sclerosis Foundation.

Author Contributions: All authors participated in the conception and design of the research. E.H. and A.E.B. conducted the statistical analysis. G.C., B.A.M., R.T.Z., and T.L. developed the right-heart catheterization cohort of the VA-CART program. P.J.L. and T.L. interpreted the data and drafted the report. All authors reviewed, revised, and approved the final version of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201801-0048LE on February 13, 2018

Methods

We included veterans from the Veterans Affairs (VA) Clinical Assessment, Reporting, and Tracking (VA-CART) program who received RHC at a VA center between 2008 and 2014, had a mean pulmonary artery pressure (mPAP) of ⩾25 mm Hg, and had a pulmonary artery wedge pressure (PAWP) recorded. The Colorado Multiple Institutional Review Board approved this study (#14-1649).

Exposure. Participants were considered to have used an H2RA if an outpatient prescription was filled within 90 days of the RHC. Participants were excluded if they died within 90 days or had a hospitalization lasting longer than 60 days after catheterization. This provided at least 30 days to detect outpatient medication use.

Outcome. The outcome was the rate of all-cause mortality determined using the combined VA vital status file (97.6% exact agreement with the National Death Index) (7). Risk time accrued after the 90-day window that was used to establish exposure status. Exposure and outcome assessment did not temporally overlap in an effort to avoid immortal time bias.

Statistical Analysis

We used Cox proportional hazards models to estimate associations between H2RA use and mortality. In limited models, we adjusted for age, sex, race, and body mass index. In fully adjusted models, we also accounted for participants' markers of socioeconomic status and health behaviors. In separate models, we further adjusted for comorbid medical conditions or comedication use.

To account for confounding by indication, analyses were repeated in a restricted cohort comparing participants who used H2RAs with those who used proton pump inhibitors. In a second restricted cohort, propensity scores were used to match H2RA users with nonusers. Analyses were repeated in cohorts limited to participants with a diagnosis of heart failure or chronic obstructive pulmonary disease (COPD).

Careful phenotyping by World Health Organization group was not feasible; however, PAWP was available for all participants. PAWP was evaluated as an effect modifier of the relationship between H2RA use and mortality. A typical cutoff of 15 mm Hg and a more stringent cutoff of 12 mm Hg to exclude left-heart disease were used.

Analyses were performed using SAS 9.4 (SAS Institute) and R 3.3.1 (R Project for Statistical Computing).

Results

Participant characteristics are included in Table 1. A total of 589 H2RA users died in 4,719 person-years (12.5 deaths per 100 person-years) and 6,341 nonusers died in 46,129 person-years (13.7 deaths per 100 person-years). H2RA use within 90 days of RHC was associated with a 10% lower risk for all-cause mortality (adjusted hazard ratio, 0.90; 95% confidence interval, 0.83–0.98; $P = 0.02$; the proportional hazard assumption was not violated). This relationship was slightly stronger when we accounted for comedication use, accounted for comorbidity, compared H2RA users with users of proton pump inhibitors, and when we compared H2RA users with propensity-matched nonusers (Table 2). When associations were evaluated in cohorts limited to veterans with COPD or heart failure, estimates were similar to those obtained in the full cohort but less precise.

There was no evidence that PAWP modified relationships between H2RAs and mortality using either conventional (15 mm Hg;

Table 1. Characteristics of the Study Sample

	H2RA Users (*n* = 1,518)	Non-H2RA Users (*n* = 16,011)	PS Matched Nonusers (*n* = 1,518)
Age, yr	65.3 ± 12.1	66.4 ± 9.3	66.4 ± 9.8
Male, %	95.8	96.7	95.0
Race, %			
White	80.6	76.8	80.9
African American	17.5	21.1	16.7
Other	1.8	2.1	2.4
Body mass index, %			
Underweight, <18.5 kg/m^2	0.8	0.7	0.8
Normal, 18.5–25 kg/m^2	15.2	17.1	15.6
Overweight, 25–30 kg/m^2	30.4	28.8	30.3
Obese or severely obese, ⩾30 kg/m^2	53.6	53.4	53.3
Income, $10,000	49.0 ± 16.7	49.8 ± 17.4	49.1 ± 16.2
Marital status, %			
Single	13.7	13.6	14.5
Married	50.1	48.4	49.9
Divorced or widowed	36.2	38.0	35.5
Documented current/previous alcohol abuse, %	10.0	10.4	9.4
Documented current or previous smoking, %	61.9	60.7	60.5
Comorbidity, %			
Diabetes mellitus	55.7	51.7	56.1
End-stage renal disease/dialysis	35.3	33.2	34.4
Cirrhosis	6.3	7.2	5.8
Obstructive sleep apnea	14.4	14.6	14.0
Chronic obstructive pulmonary disease	40.6	37.3	40.5
Asthma	6.9	5.6	6.8
Interstitial lung disease	0.6	0.5	0.7
Prior MI, PCI, or CABG	48.7	39.9	47.3
Congestive heart failure	67.1	68.1	66.9
Valvular heart disease	40.6	38.7	41.2
Congenital heart disease	0.5	0.6	0.7
Atrial fibrillation/flutter	30.1	33.1	31.1
Hemodynamics at right-heart catheterization			
Systolic systemic blood pressure, mm Hg	130 ± 15	131 ± 16	132 ± 16
Diastolic systemic blood pressure, mm Hg	73 ± 10	74 ± 10	74 ± 10
Right atrial pressure, mm Hg	12 ± 6	12 ± 6	12 ± 6
Pulmonary artery systolic pressure, mm Hg	53 ± 14	53 ± 14	53 ± 14
Pulmonary artery diastolic pressure, mm Hg	24 ± 7	24 ± 7	24 ± 7
Mean pulmonary arterial pressure, mm Hg	35 ± 9	35 ± 9	35 ± 9
Pulmonary artery wedge pressure, mm Hg	22 ± 7	22 ± 8	22 ± 8
Cardiac output, L/min	5.2 ± 1.7	5.2 ± 1.9	5.1 ± 1.6
Pulmonary vascular resistance, Wood units*	2.8 ± 2.0	3.0 ± 2.1	3.0 ± 2.2

Definition of abbreviations: CABG = coronary artery bypass graft; H2RA = H2 receptor antagonist; MI = myocardial infarction; PCI = percutaneous coronary intervention; PS = propensity score.
Data are mean ± SD, unless otherwise specified.
*Pulmonary vascular resistance [(mean pulmonary artery pressure − wedge pressure)/cardiac output] was determined for each participant and then averaged.

P value for the interaction = 0.75) or conservative (12 mm Hg; *P* = 0.25) thresholds for left-heart disease.

Discussion

We observed that H2RA use was associated with a 10% lower risk for all-cause mortality in a large cohort with PH confirmed by RHC. Similar relationships were seen in unadjusted and adjusted analyses, and in restricted cohorts with specific participant characteristics.

Conventional treatment for PH focuses on the underlying cause of the PH (e.g., COPD or left-heart failure) and includes the use of pulmonary vasodilators in pulmonary arterial hypertension (2). VA-CART is not a pulmonary arterial hypertension cohort. Prior work suggested that H2RAs may exert a benefit by targeting the ventricle itself, rather than the pulmonary vasculature. We observed similar survival rates with H2RA use in veterans with COPD, those with heart failure, and when PAWP was above or below key thresholds. This finding is unusual for PH therapies, as treatment often improves mortality in selected groups with precapillary PH but may worsen mortality in those with postcapillary PH (2).

This report is consistent with converging lines of evidence concerning left-heart failure, which suggest that histaminic signaling may be important for cardiovascular health. A previous single-center, open-label, randomized trial demonstrated improvement in cardiac morphology, b-type natriuretic peptide, and functional class for participants with left-heart failure and reduced ejection

Table 2. Relationship of H2RA Use within 90 Days of Right-Heart Catheterization to Mortality in Veterans with Pulmonary Hypertension ($n = 17,529$)

	Adjusted Risk of Mortality in H2RA Users Relative to Nonusers		
	Hazard Ratio	**95% CI**	***P* Value**
Full cohort			
Unadjusted	0.90	0.83–0.98	0.02
Limited adjustment*	0.91	0.83–0.99	0.03
Full adjustment†	0.90	0.83–0.98	0.02
Full adjustment† + comedication use‡	0.88	0.80–0.96	0.003
Full adjustment† + comorbidity§	0.86	0.79–0.94	0.001
Restricted cohorts			
Restricted to H2RA users and PPI users‖ ($n = 7,967$)	0.86	0.79–0.94	0.001
Restricted to PS matched participants‖ ($n = 2,982$)	0.82	0.74–0.92	0.001
Restricted to participants with a diagnosis of COPD‖ ($n = 6,594$)	0.89	0.79–1.00	0.06
Restricted to participants with a diagnosis of CHF‖ ($n = 11,927$)	0.91	0.83–1.00	0.06

Definition of abbreviations: CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; H2RA = H2 receptor antagonist; PPI = proton pump inhibitor; PS = propensity score.
*Limited adjustment accounts for age, sex, race/ethnicity, and body mass index.
†Full adjustment accounts for the limited model and also includes income, tobacco use, alcohol abuse, and marital status.
‡Comedication use included aldosterone antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-receptor antagonists, calcium channel blockers, digoxin, diuretics, lipid-lowering medication, medications for asthma or chronic obstructive pulmonary disease, medications for diabetes mellitus, oral anticoagulants, platelet inhibitors, systemic vasodilators, and proton pump inhibitors.
§Comorbidity included the presence or absence of end-stage renal disease/dialysis, diabetes mellitus, cirrhosis, sleep-disordered breathing, chronic obstructive pulmonary disease or asthma, interstitial lung disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, congestive heart failure, valvular heart disease, congenital heart disease, atrial fibrillation, and/or atrial flutter.
‖Participants in the restricted cohorts were considered in models with full adjustment.

fraction treated with the H2RA famotidine (8). In addition, H2RA use was associated with a reduced incidence of heart failure in a previous observational study (9). These studies are reinforced by results from animal models suggesting plausible mechanisms for benefit. For example, modulating histaminic signaling in animal models can abrogate heart failure from tachycardia, doxorubicin, and aortic banding (3–5). Furthermore, H2 receptor activation has been shown to contribute to mitochondrial permeability and myocardial fibrosis in experimental models (10).

This study has several limitations. Confounding can complicate inference in observational studies, and occult left-heart disease or an imbalance of H2RA use between incident and prevalent cases may have contributed to our findings. The consistency of results across a range of adjustments and in several restricted cohorts is reassuring but not definitive. Generalizability will require analyses in sex-balanced populations. In addition, all-cause mortality, while expedient, relatively insensitive to misclassification, and inherently patient-oriented, is not "cause specific." Cause-specific mortality was not available, and the results could reflect outcomes from noncardiovascular causes. Finally, H2RAs are available over the counter and are poorly enumerated in an integrated medical record. It is likely that misclassification of H2RA use was present. True associations between H2RA use and mortality may be diluted by misclassification.

H2RAs are inexpensive and safe, and have a favorable side-effect profile. If our results are confirmed in prospective, randomized studies, H2RAs may represent an attractive treatment strategy for patients with PH. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank Michael Bristow, M.D., Ph.D., Gary Grunwald, Ph.D., and Claudius Mahr, D.O., for providing insights and suggestions that strengthened this work.

Peter J. Leary, M.D., M.S.
University of Washington
Seattle, Washington

Edward Hess, M.S.
Veterans Affairs Eastern Colorado Health Care System
Denver, Colorado

Anna E. Barón, Ph.D.
Veterans Affairs Eastern Colorado Health Care System
Denver, Colorado
and
Colorado School of Public Health
Denver, Colorado

Kelley R. Branch, M.D., M.S.
University of Washington
Seattle, Washington

Gaurav Choudhary, M.D.
Providence Veterans Affairs Medical Center
Providence, Rhode Island
and
Alpert Medical School of Brown University
Providence, Rhode Island

Catherine L. Hough, M.D., M.S.
University of Washington
Seattle, Washington

Bradley A. Maron, M.D.
Veterans Affairs Boston Healthcare System
Boston, Massachusetts

Brigham and Women's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

David D. Ralph, M.D.
University of Washington
Seattle, Washington

John J. Ryan, M.D.
University of Utah
Salt Lake City, Utah

Ryan J. Tedford, M.D.
Medical University of South Carolina
Charleston, South Carolina

Noel S. Weiss, M.D., Dr.P.H.
University of Washington
Seattle, Washington

Roham T. Zamanian, M.D.*
Stanford University
Stanford, California

Tim Lahm, M.D.*
Richard L. Roudebush Veterans Affairs Medical Center
Indianapolis, Indiana
and
Indiana University School of Medicine
Indianapolis, Indiana

*Co–senior authors

ORCID ID: 0000-0001-5716-248X (P.J.L.).

References

1. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, *et al*. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the veterans affairs clinical assessment, reporting, and tracking program. *Circulation* 2016;133:1240–1248.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34–D41.
3. Bristow MR, Kantrowitz NE, Harrison WD, Minobe WA, Sageman WS, Billingham ME. Mediation of subacute anthracycline cardiotoxicity in rabbits by cardiac histamine release. *J Cardiovasc Pharmacol* 1983;5:913–919.
4. Takahama H, Asanuma H, Sanada S, Fujita M, Sasaki H, Wakeno M, *et al*. A histamine H2 receptor blocker ameliorates development of heart failure in dogs independently of β-adrenergic receptor blockade. *Basic Res Cardiol* 2010;105:787–794.
5. Zeng Z, Shen L, Li X, Luo T, Wei X, Zhang J, *et al*. Disruption of histamine H2 receptor slows heart failure progression through reducing myocardial apoptosis and fibrosis. *Clin Sci (Lond)* 2014;127:448.
6. Leary PJ, Barr RG, Bluemke DA, Bristow MR, Kronmal RA, Lima JA, *et al*. H2 receptor antagonists and right ventricular morphology: the MESA right ventricle study. *Ann Am Thorac Soc* 2014;11:1386.
7. Sohn M-W, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr* 2006;4:2.
8. Kim J, Ogai A, Nakatani S, Hashimura K, Kanzaki H, Komamura K, *et al*. Impact of blockade of histamine H2 receptors on chronic heart failure revealed by retrospective and prospective randomized studies. *J Am Coll Cardiol* 2006;48:1378–1384.
9. Leary PJ, Tedford RJ, Bluemke DA, Bristow MR, Heckbert SR, Kawut SM, *et al*. Histamine H2 receptor antagonists, left ventricular morphology, and heart failure risk: the MESA Study. *J Am Coll Cardiol* 2016;67:1544–1552.
10. Luo T, Chen B, Zhao Z, He N, Zeng Z, Wu B, *et al*. Histamine H2 receptor activation exacerbates myocardial ischemia/reperfusion injury by disturbing mitochondrial and endothelial function. *Basic Res Cardiol* 2013;108:342.

Long-Acting β-Agonist/Inhaled Corticosteroid in Patients with Chronic Obstructive Pulmonary Disease with Cardiovascular Disease or Risk: A Factorial Analysis of the SUMMIT Clinical Trial

To the Editor:

Treatment with the combination of a long-acting β-agonist (LABA) and an inhaled corticosteroid (ICS) reduces the frequency of exacerbations and improves health status in patients with chronic obstructive pulmonary disease (COPD). In the TORCH (Towards a Revolution in COPD Health) trial, use of the combination of salmeterol and fluticasone propionate was associated with a slower rate of FEV_1 decline but no significant decrease in risk for death (1). On the basis of *post hoc* factorial analyses of the mortality data from TORCH, it was suggested that most of the benefit on the outcomes could be attributed to the LABA (salmeterol) benefit (2, 3). To test this concept, we undertook a prespecified factorial analysis of the SUMMIT (Study to Understand Mortality and Morbidity) trial evaluating the interactive contribution of the ICS fluticasone furoate (FF) and the β-agonist vilanterol (VI) on the study outcomes. Clinical trial registered with www.clinicaltrials.gov (NCT01313676).

Study Design

SUMMIT was a prospective, double-blind, placebo-controlled, parallel-group, event-driven randomized trial conducted in 43 countries that included 16,485 patients in the intent-to-treat–efficacy population (4). Patients were predominantly male (75%), aged 40–80 years (mean, 65 yr); 47% were current smokers, and 39% had an exacerbation in the year before the study. The mean postbronchodilator FEV_1 at screening was 60 ± 6% of predicted. Patients aged 40–80 years either had a history of cardiovascular disease or were ⩾60 years and had increased cardiovascular (CV)

This study was funded by GlaxoSmithKline (clinical trial registry NCT01313676, 113782).

Author Contributions: All authors contributed to the planning and conduction of the study, analysis of the data, and preparation of this manuscript. All authors have approved its content and agreed to the submission.

Originally Published in Press as DOI: 10.1164/rccm.201710-2052LE on February 7, 2018