rigorous procedural competency assessment for internal medicine residents performing central line placement in the simulation laboratory. However, the 24-point checklist focused on the steps needed to complete the procedure, from sterilizing the field to confirming venous puncture. We recommend implementing a competency assessment in the simulation laboratory that includes testing clinical judgement, not just technical skill. Given that the minority of claims in this study was from academic medical centers, focusing efforts in nonacademic medical centers makes sense.

The study has several limitations. First, the majority of claims originated from the Northeast. This could be due to the legal environment in the Northeast and/or the hospitals that are contributing claims to the database. Our national data source is one of the largest compendia of claims, and so represents the best data available. Second, the sample size for thoracentesis-related claims was small, so several analyses were not possible, including: *1*) an in-depth trend analysis; and *2*) the impact of specialized procedural services on the frequency of procedural malpractice claims.

In conclusion, we provide granular information about preventing future patient harm events related to chest procedures, specifically intubation, because of its high frequency, and thoracentesis, because of its high severity of harm.

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How Closely Do Clinical Trial Participants Resemble "Real-World" Patients with Groups 2 and 3 Pulmonary Hypertension? A Structured Review

To the Editor:

Randomized controlled trials (RCTs) of pulmonary vasodilators in the most common forms of pulmonary hypertension (PH)—those secondary to left heart disease (group 2 PH) and chronic lung disease (group 3 PH)—have failed to show consistent benefits, and some have shown a signal of harm (1, 2). Pulmonary vasodilators are costly; none are approved by the U.S. Food and Drug Administration for use in groups 2 or 3 PH; and guidelines recommend against their routine use in this context (3, 4). Despite this, use in "real-world" practice is common and rising over time (5, 6).

Guideline-discordant use of pulmonary vasodilators in some patients with groups 2 and 3 PH may be driven by a perception that nontrial patients may experience a more favorable balance of benefits to harms from treatment than observed in RCTs. Understanding how characteristics of patients with groups 2 and 3 PH in nontrial settings compare with RCT participants may help anticipate the risk/benefit ratio of using pulmonary vasodilators in groups 2/3 PH in a real-world population. We sought to compare baseline characteristics of participants in sentinel groups 2 and 3 PH RCTs with those of patients in the Veterans Health Administration, the largest national integrated healthcare system in the United States. We hypothesized that nontrial patients would

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Table 1. Study design details of groups 2 and 3 pulmonary hypertension randomized clinical trials

Trial	Study Drug	Population Studied	Exclusion Criteria	Primary Endpoint	Result
Group 2 PH clinical trials					
Bonderman (11) ($n = 201$)	Riociguat	HFrEF (EF, ⩽40%)	1. Other PH causes 2. Cardiac decompensation in preceding 30 d 3. Baseline systolic blood pressure <100 mm Hg 4. Severe renal impairment (GFR, <30 ml/min) 5. Cardiac ischemia with planned percutaneous coronary intervention or bypass surgery	Mean PAP	No change
Bermejo (1) ($n = 200$)	Sildenafil	Corrected valvular heart disease	1. Persistent significant valvular dysfunction 2. Myocardial infarction, stroke, or life-threatening arrhythmia in preceding 6 mo 3. Baseline systolic blood pressure <90 mm Hg 4. Severe renal impairment (GFR, <30 ml/min) or liver dysfunction 5. Life expectancy <2 yr	Composite clinical score*	Worsening in treated group
Kaluski (12) ($n = 87$)	Bosentan	HFrEF (EF, <35%), NYHA FC IIIb–IV	1. Baseline systolic blood pressure <100 mm Hg	Systolic PAP	No change; more frequent adverse events in treated group requiring drug discontinuation
Vachiéry (13) ($n = 63$)	Macitentan	HFpEF (EF, ⩾30%), NYHA FC II–III	1. Baseline blood pressure >180/100 mm Hg or systolic blood pressure <90 mm Hg 2. Uncontrolled heart rate from atrial fibrillation 3. Severe renal impairment (GFR, <30 ml/min) or liver dysfunction 4. Unstable coronary artery disease or myocardial infarction within 6 mo 5. Severe obstructive or moderate to severe restrictive lung disease 6. Oxygen saturation <90% on room air 7. Anemia (hemoglobin <10 g/dl) 8. Other PH causes	Composite of fluid retention or worsening NYHA FC	Increased fluid retention in treated group
Hoendermis (14) ($n = 52$)	Sildenafil	HFpEF (EF, ⩾45%), NYHA FC II–IV	1. Severe noncardiac exercise limitation 2. Other PH causes 3. Myocardial infarction or coronary ischemia in preceding 6 mo 4. Blood pressure <90/50 mm Hg 5. Significant mitral or aortic valvular dysfunction 6. Severe liver dysfunction	Mean PAP	No change

(Continued)

Table 1. (*Continued*)

Trial	Study Drug	Population Studied	Exclusion Criteria	Primary Endpoint	Result
Group 3 PH clinical trials					
Nathan (2) (*n* = 147)	Riociguat	Idiopathic interstitial pneumonia	1. Systolic blood pressure <95 mm Hg 2. Forced vital capacity <45% 3. Active smoking	6MWD	Stopped early; increased harm in treated group
Goudie (15) (*n* = 120)	Tadalafil	COPD	1. Left ventricular systolic dysfunction (EF, <45%) 2. Systolic blood pressure <90 mm Hg 3. Recent stroke or unstable angina 4. COPD exacerbation within 1 mo	6MWD	No change
Raghu (16) (*n* = 68)	Ambrisentan	Idiopathic pulmonary fibrosis	1. NYHA FC III–IV 2. EF <40% 3. Coexisting obstructive airflow or emphysema on computed tomography 4. Hospitalization or respiratory infection within 60 d	Disease progression†	Unfavorable trend; more hospitalizations in treated group

Definition of abbreviations: 6MWD = 6-minute-walk distance; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; GFR = glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NYHA FC = New York Heart Association functional class; PAP = pulmonary arterial pressure; PH = pulmonary hypertension.
*Combination of death, hospitalization for heart failure, change in NYHA FC, and patient global self-assessment.
†Composite endpoint of *1*) decline in functional vital capacity and diffusing capacity of the lung for carbon monoxide, *2*) respiratory hospitalization event, and *3*) death of any cause.

have a higher burden of comorbid conditions than RCT participants.

Methods

We selected RCTs evaluating use of pulmonary vasodilators in PH due to left heart disease or lung disease. RCTs were eligible for comparison if they met the following criteria: *1*) studied the target population of group 2 or 3 PH, *2*) were full-length articles, *3*) included at least 50 study participants, and *4*) reported baseline comorbidities. From the selected RCTs, we abstracted study details (first author, study drug, key exclusion criteria, endpoint studied, and primary results) and baseline participant characteristics (age, sex, race and ethnicity, and pertinent comorbid conditions). We contacted authors to obtain baseline characteristics if not reported. We calculated pooled estimates for each of the variables using available data. For comparison, we created a national cohort of patients with groups 2 and 3 PH in nontrial settings by linking patient-level data from the Veterans Health Administration and Centers for Medicare and Medicaid Services, as previously described (5). The Edith Nourse Rogers Memorial Veterans Hospital Institutional Review Board approved this study.

Results

We identified eight RCTs meeting inclusion criteria, with a pooled sample size of 938 patients. Table 1 shows trial details, including the study drug, population studied, key exclusion criteria, endpoints studied, and primary results. Many trials excluded patients with common conditions, including kidney or liver impairment, ischemic heart disease, and atrial fibrillation. Three group 2 PH trials excluded participants with lung disease, and two group 3 PH trials excluded participants with heart disease. We identified 136,670 patients with groups 2/3 PH in our nontrial cohort; 2,813 (2.1%) received pulmonary vasodilators. In our nontrial cohort, 21.6% had group 2 PH only, 8.4% had group 3 PH only, and 70.0% had conditions associated with both groups 2 and 3 PH. Patients in the nontrial cohort were elderly and had high rates of comorbid illnesses (Table 2). Compared with groups 2 and 3 PH trial participants, nontrial patients with groups 2/3 PH were older (76.8 vs. 67.1 yr) and more racially diverse. Nontrial patients with PH had a greater burden of comorbid illnesses, including a higher prevalence of diabetes (49.7% vs. 29.4%), hypertension (92.9% vs. 61.7%), hyperlipidemia (81.7% vs. 33.7%), chronic kidney disease (40.1% vs. 6.6%), and arrhythmia (63.1% vs. 34.1%) at the time of PH diagnosis.

Discussion

Many groups 2 and 3 PH RCTs had extensive exclusion criteria, limiting patients with common comorbid conditions and resulting in an overall healthier population. At least 70% of our nontrial cohort would have been ineligible for inclusion in these trials because they carried diagnoses associated with both groups 2 and 3 PH. This high rate of ineligibility is not unique to PH; the elderly and those with significant comorbidities are groups frequently excluded from clinical trials of cardiovascular disease (7, 8).

Patients with groups 2 and 3 PH in real-world practice were older and had a higher burden of comorbid disease than trial participants. Importantly, key differences between our nontrial cohort and trial participants, such as higher prevalence of chronic kidney disease and arrhythmias, may further reduce both the

Table 2. Comparison of baseline characteristics of nontrial patients with participants enrolled in select group 2 and group 3 pulmonary hypertension randomized clinical trials

Cohort Characteristic	Nontrial Cohort	Trial cohort*	Group 2 PH Trials					Group 3 PH Trials		
			Bonderman (11)	Bermejo (1)	Kaluski (12)	Vachiéry (13)	Hoendermis (14)	Nathan (2)	Goudie (15)	Raghu (16)
n	136,670	938	201	200	87	63	52	147	120	68
Age, yr, mean (SD)	76.8 (9.5)	67.1[†]	58.1[‡]	70.0[‡]	69.5 (9.4)	70.0[‡]	74.0 (9.9)	68.5 (8.0)	69.0 (7.6)	68.0 (6.1)
Female sex	2.5%	42.3%	14.4%	77.0%	28.7%	65.1%	71.2%	35.4%	31.7%	30.9%
Race/ethnicity										
White	85.3%	95.1%	—	100%	98.9%	—	96.2%	85.7%	100%	86.8%
Black	9.4%	1.2%	—	0%	1.1%[§]	—	3.8%[§]	2.7%	0%	1.5%
Hispanic	1.9%	0.9%	—	0%	—	—	—	3.4%	0%	0%
Comorbid conditions										
Diabetes	49.7%	29.4%	43.3%	29.0%	36.8%	42.9%	34.6%	29.9%	8.3%	—
Smoking	41.8%	34.6%	—	6.5%	—	—	—	4.1%	100%	67.6%
Hypertension	92.9%	61.7%	—	64.0%	66.7%	90.5%	90.4%	55.8%	34.2%	—
Hyperlipidemia	81.7%	33.7%	—	42.5%	54.0%	7.9%	51.9%	14.3%	—	—
Chronic kidney disease	40.1%	6.6%	0%[‖]	0%[‖]	—	39.7%	—	8.2%	9.2%	—
Cerebrovascular disease	17.4%	8.5%	—	—	—	—	15.4%	6.8%	7.5%	—
Heart disease	67.9%	20.7%	0%[‖]	13.5%	72.4%	—	32.7%	34.7%	7.5%	—
Arrhythmia	63.1%	34.1%	12.9%	77.0%	20.7%	73.0%	61.5%	10.2%	5.0%	—

Definition of abbreviations: PH = pulmonary hypertension; SD = standard deviation.
Data are presented as percentages unless otherwise noted; data not available from authors is designated as —.
*Pooled estimate calculated on the basis of available data.
[†]Pooled SD unable to be calculated because SD was not provided for all studies.
[‡]SD not provided.
[§]Maximum value possible based on prevalence of other races.
[‖]Assumed on the basis of trial exclusion criteria.

anticipated efficacy and safety profile of these drugs in nontrial settings. Although no RCT has directly evaluated outcomes of pulmonary vasodilators in older, sicker patients with groups 2/3 PH, a subgroup analysis in a trial of vasodilators in group 2 PH (1) suggested that older patients and those with worse functional class may experience an even greater harm/benefit ratio. In addition, evidence in group 1 PH suggests that patients with cardiovascular risk factors such as hypertension, diabetes, or atrial fibrillation experience reduced efficacy and higher rates of adverse events compared with those without such risk factors when treated with pulmonary vasodilators (9, 10).

Our study has limitations. Many of the trials did not report complete baseline characteristics, and, despite our efforts, we were unable to obtain these missing data from the authors. Thus, our comparisons may be valid only for the studies with complete data. Our cohort of veterans with PH does not represent all real-world practice settings. In addition, the granularity of our data did not allow comparisons of functional class or hemodynamics between the trial and nontrial cohorts. As such, we were unable to discern the role of disease severity in the decision to prescribe outside of guideline recommendations.

This comparison of RCT participants with groups 2 and 3 PH with nontrial patients with PH reveals significant differences in these populations, with the latter experiencing a greater degree of multimorbidity. RCTs demonstrate that pulmonary vasodilators offer limited benefit and potential for harm among the younger, healthier participants with groups 2 and 3 PH enrolled in these studies, and it is even more likely that the more medically complex patients seen in real-world practice will experience harm. Thus, our findings support the call in guidelines to limit the use of pulmonary vasodilators in patients with groups 2 and 3 PH in clinical practice.

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Comment on "From Air Pollution to the Anthropocene and Planetary Health. Implications for Clinicians, Researchers, and Society"

To the Editor:

I read with great interest the eloquent perspective by Hu entitled "From Air Pollution to the Anthropocene and Planetary Health. Implications for Clinicians, Researchers, and Society" (1).

Unfortunately, the world is divided about whether climate change is happening, and even people who agree on that point are divided in their views about what is causing it and how to "fix" it.

As with many similar complex situations where the answers to many questions are not precisely known and the consequences of interventions are difficult to predict, we need to use the art of conflict resolution and positive action to find common ground on which all parties can agree.

The profound impact of air pollution on human health is indisputable and extensively documented in many publications, including the paper by Hu (1). Given the prevalence of respiratory and other diseases caused or significantly exacerbated by air pollution, almost everyone is affected either directly or by the misery and death of people close to them.

We therefore have a real chance to persuade the general public as well as politicians and other decision makers to accelerate efforts to reduce air pollution, be it "man-made," such as that due to fossil fuel use, or "natural," such as that caused by the recent catastrophic bushfires in Australia.

Although reductions in air pollution may not be viewed by everyone as measures that would be necessary or effective in terms of an impact on global climate, an agreement on the need for such reductions would likely be achievable and would positively impact global health in the foreseeable future. We as individuals and our professional respiratory societies could provide very trustworthy leadership on this front.

Postscript: It is one of a few positive consequences in the current COVID-19 pandemic that the global air pollution has been drastically reduced. Perhaps, we can find a way to "normalcy" without return to the poor air quality.