3. Goldberg DS, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, *et al.* Trial of transplantation of HCV-infected kidneys into uninfected recipients. *N Engl J Med* 2017;376:2394–2395.
4. Levitsky J, Formica RN, Bloom RD, Charlton M, Curry M, Friedewald J, *et al.* The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. *Am J Transplant* 2017;17:2790–2802.
5. Khan B, Singer LG, Lilly LB, Chaparro C, Martinu T, Juvet S, *et al.* Successful lung transplantation from hepatitis C positive donor to seronegative recipient. *Am J Transplant* 2017;17:1129–1131.

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Disproportionate Right Ventricular Dysfunction and Poor Survival in Group 3 Pulmonary Hypertension

To the Editor:

Pulmonary hypertension (PH) due to chronic lung disease, classified as World Health Organization (WHO) group 3 PH (1), is the second most common cause of PH after left-heart disease (2). Group 3 patients have a lower quality of life, higher medical costs, and worse survival compared with patients with chronic lung disease but without PH (3). Despite the large clinical burden and poor prognosis of group 3 PH, its long-term outcomes and clinical, echocardiographic, and hemodynamic characteristics are not well described. Furthermore, despite the large clinical burden of this disease, there are no approved therapies for patients with group 3 PH. Thus, we need to better understand the clinical characteristics and outcomes of group 3 PH to identify possible therapeutic targets.

We examined 122 patients with group 3 PH and 155 patients with group 1 PH from the University of Minnesota Pulmonary Hypertension Repository (4). Group 3 PH and group 1 PH were defined according to the WHO classification criteria (1, 5). In the group 3 population, PH was associated with interstitial lung disease in 55 patients, chronic obstructive pulmonary disease (COPD) in 45, obstructive sleep apnea or obesity-hypoventilation syndrome in 11, and combined pulmonary fibrosis and emphysema in 11. The etiology of PH in the group 1 population included idiopathic, heritable, or drug-induced disease ($n = 48$), connective tissue disease ($n = 59$), liver disease ($n = 24$), congenital heart disease ($n = 18$), human immunodeficiency virus infection ($n = 2$), and other causes ($n = 4$). Fifty-two group 3 patients (43%) and 65 group 1 patients (42%) were incident cases.

Compared with group 1, the group 3 cohort was older, had a higher proportion of males, and had more comorbidities, including hypertension, diabetes, hyperlipidemia, coronary artery

disease, obesity, and atrial fibrillation, resulting in a significantly higher Charlson comorbidity score (Table 1). There was no difference in WHO functional class between the groups. At the time of referral, group 3 patients were more likely to be on supplemental oxygen and digoxin, and less likely to be on pulmonary vasodilator therapy. Use of diuretics did not differ between the groups. Group 3 patients had lower 6-minute-walk distances and more exercise-induced hypoxemia. On pulmonary function tests, group 3 patients had lower lung volumes and lower DL_{CO} values. There were no intergroup differences in serum N-terminal pro-B-type natriuretic peptide levels or serum creatinine (Table 1).

Group 3 patients had higher left ventricular mass and end-diastolic diameters (Table 1). There was no difference in right ventricular (RV) dimensions (Table 1), but group 3 patients had lower RV fractional area change (RVFAC) values (Figure 1A, top). When RVFAC was plotted against mean pulmonary artery pressure (mPAP), the rate of decline in RVFAC with increasing mPAP was similar between the two PH groups (Figure 1A, bottom). However, group 3 patients had lower RVFAC values for any given mPAP than group 1 patients (Figure 1A, bottom). Despite the lower RVFAC values, group 3 patients had a lower prevalence of right atrial enlargement and pericardial effusion than group 1 patients.

A hemodynamic evaluation showed that group 3 patients had lower mPAP and pulmonary vascular resistance, with higher pulmonary arterial compliance, pulmonary capillary wedge pressure, and cardiac output when compared with group 1 patients. Right atrial pressure and cardiac index did not differ between the two PH populations (Table 1).

The patients were followed routinely in the clinic every 3–6 months. Vital statistics were obtained from the Minnesota death index and chart review. No patient was lost to follow-up. There were 59 deaths in group 3 and 52 deaths in group 1 over a median follow-up of 2.3 years. Survival was significantly worse in group 3 patients compared with group 1 patients. The 1-, 3-, and 5-year survival rates in group 3 and group 1 patients were 80% and 95%, 48% and 82%, and 30% and 62%, respectively (hazard ratio [HR], 2.5 [95% confidence interval (CI), 1.7–3.7; $P < 0.001$]; Figure 1B, top). This remained significant after adjusting for age, sex, and Charlson comorbidity index (HR, 1.5 [95% CI, 1.0–2.3; $P = 0.046$]). The 1- and 2-year survival rates in the incident cohort were also worse in group 3 PH compared with group 1 PH (80% vs. 90%, and 55% vs. 82%, respectively; HR, 2.5 [95% CI, 1.1–5.6; $P = 0.026$]; Figure 1B, bottom). In the group 3 PH population, there was no difference in survival when COPD PH was compared with interstitial lung disease PH.

Consequently, although they had less severe pulmonary vascular disease, group 3 patients had worse RV function, reduced exercise capacity, and worse survival than group 1 patients. The mechanisms underlying the worse RV function in group 3 PH are unclear, but there are several possible explanations. First, patients with COPD but without PH have impaired RV function (6). This afterload-independent RV dysfunction is hypothesized to result from hypoxemia, inflammation, lung hyperinflation, and/or endothelial dysfunction (6). Thus, patients with group 3 PH may have additional, nonhemodynamic insults to the RV resulting in RV dysfunction that is disproportionate to the PH severity. Another possible reason for the worse RV function in group 3 patients is the higher proportion of males in this group. Consistent with this hypothesis, healthy males were found to have lower cardiac magnetic resonance–calculated RV ejection fraction values than females in the MESA (Multi-Ethnic

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Table 1. Comparison of Clinical, Echocardiographic, and Hemodynamic Characteristics of Patients with Group 3 and Group 1 Pulmonary Hypertension

Characteristics	Group 3 PH (n = 122)	Group 1 PH (n = 155)	P Value
Age, yr	65 ± 11	53 ± 17	<0.001
Female, n (%)	64 (53)	116 (75)	<0.001
Body mass index, kg/m ²	30 ± 7	28 ± 7	0.015
WHO functional class (n = 230), n (%)			0.151
I	0 (0)	3 (2)	
II	8 (8)	19 (15)	
III	79 (77)	87 (68)	
IV	15 (15)	19 (15)	
Comorbidities, n (%)			
Hypertension	86 (70)	63 (41)	<0.001
Diabetes	36 (30)	28 (18)	0.025
Hyperlipidemia	65 (53)	37 (24)	<0.001
Coronary artery disease	39 (32)	16 (10)	<0.001
Atrial fibrillation	25 (20)	9 (6)	<0.001
Charlson comorbidity index	5.1 ± 2.3	3.9 ± 3.1	<0.001
Medications, n (%)			
Oxygen	82 (67)	28 (18)	<0.001
Diuretics	64 (52)	72 (46)	0.321
Digoxin	12 (10)	5 (3)	0.023
Coumadin	19 (16)	28 (18)	0.583
Calcium channel blockers	23 (19)	30 (19)	0.916
Phosphodiesterase-5 inhibitors	12 (10)	42 (27)	<0.001
Endothelin receptor antagonists	1 (1)	9 (6)	0.046
Prostacyclins	0 (0)	10 (6)	0.003
Six-minute-walk test			
Distance, m (n = 162)	237 ± 108 (n = 73)	335 ± 136 (n = 89)	<0.001
Rest oxygen saturation, % (n = 151)	97 ± 2 (n = 71)	97 ± 3 (n = 80)	0.494
Nadir exercise oxygen saturation, % (n = 152)	87 ± 5 (n = 70)	90 ± 6 (n = 82)	0.001
Pulmonary function test, % predicted			
FEV ₁ (n = 196)	56 ± 23 (n = 99)	75 ± 19 (n = 97)	<0.001
FVC (n = 190)	64 ± 23 (n = 98)	78 ± 19 (n = 92)	<0.001
FEV ₁ /FVC (n = 191)	69 ± 19 (n = 98)	77 ± 9 (n = 93)	<0.001
TLC (n = 127)	80 ± 25 (n = 61)	87 ± 15 (n = 66)	0.078
D _{LCO} (n = 165)	35 ± 19 (n = 80)	60 ± 26 (n = 85)	<0.001
Lab			
Serum hemoglobin, g/dl (n = 272)	13.5 ± 2.1 (n = 121)	13.4 ± 2.7 (n = 151)	0.752
Serum creatinine, mg/dl (n = 274)	0.9 (0.7–1.1) (n = 121)	0.9 (0.7–1.1) (n = 153)	0.802
Serum NT-proBNP, pg/dl (n = 230)	1,324 (223–3,350) (n = 102)	806 (238–2,628) (n = 128)	0.393
Echocardiography			
Left ventricular ejection fraction, % (n = 247)	60 ± 10 (n = 116)	60 ± 8 (n = 131)	0.885
Left ventricular mass index, g/m ² (n = 182)	158 ± 57 (n = 88)	130 ± 48 (n = 94)	<0.001
Left ventricular end diastolic diameter, cm (n = 218)	4.3 ± 0.8 (n = 101)	4.0 ± 0.8 (n = 117)	0.014
Left atrial diameter, mm (n = 185)	4.0 ± 0.9 (n = 81)	3.8 ± 1.0 (n = 104)	0.221
Right ventricular enlargement, n (%) (n = 251)	83 (73) (n = 114)	108 (79) (n = 137)	0.265
Right atrial enlargement, n (%) (n = 247)	68 (60) (n = 113)	98 (73) (n = 134)	0.031
Right ventricular FAC, % (n = 190)	28 ± 10 (n = 85)	33 ± 11 (n = 105)	0.006
Right ventricular FAC <35%, n (%) (n = 190)	58 (68) (n = 85)	55 (52) (n = 105)	0.027
Pericardial effusion, n (%) (n = 251)	12 (10) (n = 115)	41 (30) (n = 136)	<0.001
Hemodynamics			
Heart rate, beats/min (n = 229)	79 ± 16 (n = 98)	77 ± 16 (n = 131)	0.347
Mean right atrial, mm Hg (n = 273)	7 ± 4 (n = 121)	8 ± 5 (n = 152)	0.244
Mean PAP, mm Hg (n = 277)	40 ± 10 (n = 122)	47 ± 14 (n = 155)	<0.001
PCWP, mm Hg (n = 277)	10 ± 3 (n = 122)	9 ± 3 (n = 155)	0.029
Cardiac output, L/min (n = 265)	4.8 ± 1.5 (n = 121)	4.2 ± 1.5 (n = 144)	0.006
Cardiac index, L/min/m ² (n = 189)	2.6 ± 0.7 (n = 92)	2.4 ± 0.8 (n = 97)	0.093
PVR, Wood units (n = 265)	6.9 ± 3.4 (n = 121)	10.3 ± 5.6 (n = 144)	<0.001
Diastolic pulmonary gradient, mm Hg (n = 277)	15 ± 8 (n = 122)	21 ± 12 (n = 155)	<0.001
PAC, ml/mm Hg (n = 224)	2.0 ± 1.1 (n = 97)	1.5 ± 1.0 (n = 127)	<0.001
Vasodilator response, n (%) (n = 277)	4 (3) (n = 122)	8 (5) (n = 155)	0.559

Definition of abbreviations: FAC = fractional area change; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAC = pulmonary arterial compliance; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WHO = World Health Organization.

Data are presented as n (%) for categorical variables and as mean ± SD or median (25th to 75th percentiles) for continuous variables.

Figure 1. Worse right ventricular (RV) function and increased mortality in group 3 pulmonary hypertension (PH). (A) Top: reduced RV fractional area change (RVFAC) in group 3 PH compared with group 1 PH ($28 \pm 10\%$ vs. $33 \pm 11\%$, $P = 0.006$). Bottom: plot of RVFAC versus mean pulmonary artery pressure (mPAP) in group 1 and group 3 patients. Group 3 patients had worse RV function at all mPAPs, as demonstrated by a significantly different y intercept (group 3: 44.2 ± 4.3 , group 1: 47.9 ± 4.2 , $P < 0.0001$). However, there was an equivalent response to increasing afterload, as shown by the similar slope of best-fit regression lines (group 3: -0.38 ± 0.10 , group 1: -0.33 ± 0.09 , $P = 0.70$). $*P < 0.05$ (t test). (B) Survival analysis shows significantly worse survival for group 3 PH in the total cohort (top) and incident cohort (bottom). CI = confidence interval; WHO = World Health Organization.

Study of Atherosclerosis) cohort (7). Further studies are needed to define the mechanisms that underlie the RV dysfunction in group 3 PH, as therapies that improve RV function may benefit these patients. This is particularly important because current pulmonary arterial hypertension-specific therapies neither improve symptom burden nor increase exercise capacity in group 3 patients (8).

Our study has several limitations. This was a single-center study and most patients were entered retrospectively. However, we collected the baseline variables at the time of the referral to our practice rather than at the time of enrollment in the registry, which reduces survival bias. Although we adjusted for age, sex, and Charlson comorbidity index, we did not adjust for all characteristics that were different between group 3 and group 1 PH in the survival analysis.

In conclusion, patients with group 3 PH have greater functional limitations, worse RV function, and increased mortality compared

with those with group 1 PH. These data highlight the requirement for further exploration of RV dysfunction in group 3 PH and the need for effective therapies to improve survival for this vulnerable patient population. ■

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References

1. Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, *et al.* Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013;62(25, Suppl):D109–D116.
2. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, *et al.* Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart* 2012;98:1805–1811.
3. Barberà JA, Blanco I. Gaining insights into pulmonary hypertension in respiratory diseases. *Eur Respir J* 2015;46:1247–1250.
4. Prins KW, Weir EK, Archer SL, Markowitz J, Rose L, Pritzker M, *et al.* Pulmonary pulse wave transit time is associated with right ventricular-pulmonary artery coupling in pulmonary arterial hypertension. *Pulm Circ* 2016;6:576–585.
5. 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(25, Suppl):D34–D41.
6. Hilde JM, Skjærten I, Grøtta OJ, Hansteen V, Melsom MN, Hisdal J, *et al.* Right ventricular dysfunction and remodeling in chronic obstructive pulmonary disease without pulmonary hypertension. *J Am Coll Cardiol* 2013;62:1103–1111.
7. Kawut SM, Lima JA, Barr RG, Chahal H, Jain A, Tandri H, *et al.* Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. *Circulation* 2011;123:2542–2551.
8. Prins KW, Duval S, Markowitz J, Pritzker M, Thenappan T. Chronic use of PAH-specific therapy in World Health Organization Group III pulmonary hypertension: a systematic review and meta-analysis. *Pulm Circ* 2017;7:145–155.

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Have We Not Learned from Past Mistakes?

To the Editor:

Schoenberg and colleagues propose an “expert opinion” and consensus-based Delphi method to increase the efficiency of guideline development (1). Although we welcome the exploration of new methodologies to improve and expedite the process of guideline development, we have great concerns about such an approach.

Let’s remember some of the lessons we should have learned and think about why recommendations informed by systematic reviews instead of consensus-based “expert opinion” recommendations are needed. In the past, experts failed patients when they did not systematically synthesize the evidence. For example, when Antman and colleagues in 1992 conducted a cumulative meta-analysis of randomized trials of thrombolytics in acute myocardial infarction (2), it was clear that the experts’ recommendations lagged more than a decade behind

the evidence, and more than 40,000 additional patients were randomized (and not benefited) when evidence had clearly supported the use of thrombolytics since the mid-1970s. Furthermore, experts failed patients when they did not systematically assess and explicitly state the quality of evidence. Between the 1960s and 1990s, hormone replacement therapy was widely recommended despite the very low quality of the evidence supporting its use. With the publication of the Women’s Health Initiative in the 2000s, it became clear that the widely recommended hormone replacement therapy could cause considerable harms, which subsequently led to a change in the recommendation. However, despite the new evidence, there was still a significant lag period before physicians and consumers were able to understand the harms involved in such therapy (3).

Guideline panels and clinical experts are known to have intrinsic conflicts, and relying solely on expert opinions has been associated with biased judgments (4). This is a serious issue that is not addressed by the methods suggested by Schoenberg and colleagues, especially when implementing a system that forces agreement. The true test of the potential effects of following an exclusive “expert opinion” approach does not lie in the percentage agreement or concordance between two methods. It is paramount to recognize that even one or two misinformed or biased recommendations are not acceptable and undermine the credibility of the entire guideline document. Finally, the confidence that guideline users place in a recommendation stems not only from the quality of the evidence but also from the transparency of the process used to move from the evidence to a recommendation. This transparency is what allows health professionals and patients to be informed by recommendations for individualized decisions, especially when dealing with the vast majority of weak (conditional) recommendations.

The Delphi method has been criticized on the grounds that the evidence regarding its reliability is controversial. If we had two or more panels of experts applying this approach, there is no guarantee that they would obtain the same results (5). On the other hand, the reliability of Grading of Recommendations, Assessment, Development, and Evaluation (GRADE; the system Schoenberg and colleagues compared with Delphi) has been assessed and proven in multiple studies and among different users with a wide variety of expertise, including guideline developers (6).

In summary, there is a historical track record documenting that expert opinion and consensus-based approaches have delayed implementation of appropriate therapies, duplicated research efforts, wasted resources, and allowed patient harm, even when these methods are supported by high-quality evidence. We must not repeat the mistakes of the past. We urge the guideline community to focus on identifying ways to use new developments in technology and methods to enhance the efficiency of the systematic-review process. Machine learning techniques, living systematic-review initiatives, and increased use of rapid reviews are just a few of the newer strategies that can improve efficiency while maintaining rigor. The price is simply too high for us to go back to the “expert opinion” era. We strongly discourage the use of Convergence of Opinion on Recommendations and Evidence (CORE), as the process is biased at its own core, regardless of its results. ■

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