answered in this single-center retrospective and speak to the study limitations. As previously mentioned, Tikkanen's group has a different protocol on the basis of pretransplant sensitization risk groups (8). Each group, on the basis of sensitization, receives different immunosuppression. They did account for these differences in their multivariate analysis; nonetheless, it still makes generalizability to other centers less applicable. Another limitation that Tikkanen and colleagues reveal is that during the study term there was no accepted definition of antibody-mediated rejection (AMR) in lung transplantation (8). Thus, there were only few cases of definitive AMR and no ability to associate dnDSA, AMR, and CLAD. Last, the follow-up time was relatively short (median of 764 d). Thus, there was no ability to gauge the rate of decline of lung function and allograft survival.

Tikkanen and colleagues have furthered our knowledge of HLA antibodies and their link to CLAD (8). Their data may alter the way some allocate their organs, particularly paying attention to DQ mismatching. However, further studies are needed to validate the results of Tikkanen and colleagues (8) and focus on how therapy alters dnDSA and if such manipulations alter the trajectory of CLAD. Future research should be directed toward prospective randomized trials that incorporate HLA testing, standardized surveillance of the allograft, and treatment protocols for CLAD. ■

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

Kartik V. Shenoy, M.D.
Department of Thoracic Medicine and Surgery
Temple University Lewis Katz School of Medicine
Philadelphia, Pennsylvania

ORCID ID: 0000-0001-5654-0629 (K.V.S.).

References

1. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. *Am J Transplant* 2011;11:1226–1235.
2. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Goldfarb SB, Levvey BJ, Lund LH, Meiser B, *et al*.; International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report–2014; focus theme: retransplantation. *J Heart Lung Transplant* 2014;33:1009–1024.
3. Verleden SE, Ruttens D, Vandermeulen E, Vaneylen A, Dupont LJ, Van Raemdonck DE, Verleden GM, Vanaudenaerde BM, Vos R. Bronchiolitis obliterans syndrome and restrictive allograft syndrome: do risk factors differ? *Transplantation* 2013;95:1167–1172.
4. Magnusson J, Westin J, Andersson LM, Brittain-Long R, Riise GC. The impact of viral respiratory tract infections on long-term morbidity and mortality following lung transplantation: a retrospective cohort study using a multiplex PCR panel. *Transplantation* 2013;95: 383–388.
5. Welsh CH, Wang TS, Lyu DM, Orr J, Meyer KC, Glanville AR, Verleden GM, Wilson KC, Thomson CC; The American Thoracic Society Implementation Task Force. An international ISHLT/ERS/ATS clinical practice guideline: summary for clinicians. Bronchiolitis obliterans syndrome complicating lung transplantation. *Ann Am Thorac Soc* 2015;12:118–119.
6. Lobo LJ, Aris RM, Schmitz J, Neuringer IP. Donor-specific antibodies are associated with antibody-mediated rejection, acute cellular rejection, bronchiolitis obliterans syndrome, and cystic fibrosis after lung transplantation. *J Heart Lung Transplant* 2013;32:70–77.
7. DeVos JM, Gaber AO, Knight RJ, Land GA, Suki WN, Gaber LW, Patel SJ. Donor-specific HLA-DQ antibodies may contribute to poor graft outcome after renal transplantation. *Kidney Int* 2012;82: 598–604.
8. Tikkanen JM, Singer LG, Kim SJ, Li Y, Binnie M, Chaparro C, Chow C-W, Martinu T, Azad S, Keshavjee S, *et al*. *De novo* DQ donor-specific antibodies are associated with chronic lung allograft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2016;194:596–606.
9. Palmer SM, Davis RD, Hadjiliadis D, Hertz MI, Howell DN, Ward FE, Savik K, Reinsmoen NL. Development of an antibody specific to major histocompatibility antigens detectable by flow cytometry after lung transplant is associated with bronchiolitis obliterans syndrome. *Transplantation* 2002;74: 799–804.
10. Hadjiliadis D, Chaparro C, Reinsmoen NL, Gutierrez C, Singer LG, Steele MP, Waddell TK, Davis RD, Hutcheon MA, Palmer SM, *et al*. Pre-transplant panel reactive antibody in lung transplant recipients is associated with significantly worse post-transplant survival in a multicenter study. *J Heart Lung Transplant* 2005;24: S249–S254.
11. Cypel M, Yeung J, Liu M, Anraku M, Chen F, Karolak W, Sato M, Laratta J, Azad S, Madonik M, *et al*. Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med* 2011;364: 1431–1440.
12. Cypel M, Aigner C, Sage E, *et al*. Three center experience with clinical normothermic ex vivo lung perfusion. *J Heart Lung Transplant* 2013; 32:S16.

The Positive and Negative about Positive Airway Pressure Therapy

Cardiovascular disease is the leading cause of death in the world, with an estimated 17.3 million deaths per year globally and more than 375,000 deaths annually in the United States alone (1). In the United States, the 2020 goal is to improve cardiovascular health by 20% and reduce deaths from cardiovascular diseases and stroke by 20%, but the list of targeted risk factors has generally not included improving sleep health or screening and treating sleep-disordered breathing (2). Specifically, the Life's Simple 7 are to not smoke, physical activity, healthy diet, body weight, and control of cholesterol, blood pressure, and blood sugar. The absence of a recommendation for widespread screening and treatment of sleep-disordered breathing, despite many observational data, stems from the lack of prospective randomized controlled trials (RCTs) of effective interventions aimed at improving clinical events, as opposed to surrogate end-points (3, 4). It is for this reason that the long-term

S.P. was supported by National Institutes of Health grants HL095799 and CA184920 and Patient-Centered Outcomes Research Institute award IHS-1306-02505) during the writing of this manuscript. The statements in this manuscript are solely the responsibility of the author and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its board of governors, or its methodology committee.

trial published in this issue of the *Journal* by Peker and colleagues (pp. 613–620) is most welcome (5).

Peker and colleagues report the effect of continuous positive airway pressure (CPAP) on long-term clinical events in adult patients with angiography-verified coronary artery disease who had recently (<6 mo) undergone a percutaneous coronary intervention or coronary artery bypass grafting with evidence for moderate obstructive sleep apnea (OSA) without significant sleepiness (5). The lack of sleepiness was operationalized as an Epworth sleepiness score less than 10, and participants were randomized to either automatic CPAP (autoCPAP) or no CPAP therapy. Over the course of 57 months of follow-up, the researchers measured tangible clinical events; specifically, a primary composite end-point of repeat revascularization, myocardial infarction, stroke, and cardiovascular mortality. Intention-to-treat analysis did not reveal any difference in the primary end-point, but on-treatment analysis showed a significant reduction in cardiovascular events in those who were adherent to CPAP (nightly usage, ⩾4 h) when compared with those who were nonadherent to CPAP or did not receive CPAP treatment. The researchers found that in such an enriched sample of patients with coronary artery disease who were not sleepy, treatment of OSA with CPAP did not lead to reduction of the primary composite endpoint in intention-to-treat analysis. However, on-treatment analysis revealed a greater than threefold reduction in the chance for the primary end-point in patients with OSA who were treated with CPAP when compared with patients who were not treated with such CPAP therapy.

There are many important takeaways from this study, and the authors should be commended for this long and arduous study. First, the cardiovascular benefit of CPAP therapy, based on on-treatment analysis, is unerringly similar in magnitude to prior observational studies, suggesting that if we were to improve CPAP adherence in our ongoing and future trials, we could conclusively answer the question as to whether treatment of OSA with PAP therapy can improve cardiovascular outcomes (6). Second, this study underscores that our quest to address the aforementioned knowledge gap hinges on our ability to promote CPAP adherence in research participants. Previous efforts to reduce attrition resulting from poor long-term CPAP adherence by instituting a placebo wash-in period for 1 week before randomization have met with less than desired levels of CPAP adherence (7). Such less-than-optimal long-term CPAP adherence brings into sharp focus the lack of high-quality evidence of educational, supportive, or behavioral interventions aimed at promoting CPAP adherence (8). Moreover, at this time, the optimal timing and duration and long-term effectiveness of interventions aimed at promoting CPAP adherence remain uncertain (8). More recently, a large trial of patients with heart failure and central sleep apnea revealed that 28% of participants in the intervention groups did not use a form of PAP therapy termed adaptive servo-ventilation (9). This led to concerns about the interpretation of the lack of benefit and the potential harms of the intervention when such a large proportion of participants were nonadherent to adaptive servo-ventilation (10, 11). As a community of scientists, patients, clinicians, and other stakeholders, we need to develop and successfully test and implement effective long-term interventions that can promote and sustain CPAP adherence. However, a search in ClinicalTrials.gov site reveals only six ongoing trials with a primary focus of promoting CPAP adherence. More needs to be done with regard to improving CPAP adherence both in trials and in the real world for research to translate into benefits to patients (12, 13).

The study by Peker and colleagues focused on nonsleepy apneics to avoid the ethical constraints of performing long-term RCTs against no treatment in symptomatic patients with OSA (5). Such a combination of circumstances could continue to plague our efforts to answer important questions unless we embark in a different direction. Specifically, we need to perform comparative effectiveness research between CPAP therapy and other treatment options, such as mandibular advancement devices in symptomatic patients, considering an accumulating body of evidence of cardiovascular benefits of such alternative treatments (14). Other promising treatment options would conceivably allow us to ethically undertake long-term trials in symptomatic patients (15). However, we may have to contend with differential drop-outs in comparator arms and the high cost and consequent feasibility of such trials. A third and very important aspect to the trial by Peker and colleagues is that the on-treatment analysis should be interpreted with caution, considering that such patients may be more adherent to other therapies, such as cardiovascular medications (16). We await the results of larger, ongoing trials, which could potentially provide conclusive answers of the effect of PAP therapies on cardiovascular outcomes: SAVE (Sleep Apnea Cardiovascular Endpoints Study), ADVENT-HF (Effects of Adaptive Servo Ventilation on Survival and Frequency of Cardiovascular Hospital Admissions in Patients with Heart Failure and Sleep Apnea), and ISAAC (Impact of CPAP on Patients with Acute Coronary Syndrome and Nonsleepy OSA) (7, 17). The study by Peker and colleagues sets the stage nicely for such studies. Whether these trials yield a conclusive positive or negative result with regard to the effect of CPAP therapy on cardiovascular outcomes hangs precariously on positive news regarding CPAP adherence in these trials. ■

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

Sairam Parthasarathy, M.D.
UAHS Center for Sleep and Circadian Sciences
University of Arizona
Tucson, Arizona

ORCID ID: 0000-0002-1128-3005 (S.P.).

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, *et al.*; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2016 update: a report from the American Heart Association. *Circulation* 2016;133:e38–e360.
2. American Heart Association. My life check: life's simple 7. Dallas, TX: American Heart Association; 2016 [accessed 2016 Mar 6]. Available from: http://www.heart.org/HEARTORG/Conditions/My-Life-Check—Lifes-Simple-7_UCM_471453_Article.jsp#.VtuYXPkrJD8
3. Gordon D, Taddei-Peters W, Mascette A, Antman M, Kaufmann PG, Lauer MS. Publication of trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med* 2013;369:1926–1934.
4. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, *et al*. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6:e1000132.

5. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.
6. Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nuñez N, Caballero-Martinez I, Catalan-Serra P, Almeida-Gonzalez CV. Role of sleep apnea and continuous positive airway pressure therapy in the incidence of stroke or coronary heart disease in women. *Am J Respir Crit Care Med* 2014;189:1544–1550.
7. Chai-Coetzer CL, Luo YM, Antic NA, Zhang XL, Chen BY, He QY, Heeley E, Huang SG, Anderson C, Zhong NS, *et al*. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep* 2013;36:1929–1937.
8. Wozniak DR, Lasserson TJ, Smith I. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev* 2014;1:CD007736.
9. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, *et al*. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373:1095–1105.
10. Bradley TD, Floras JS. Adaptive servo-ventilation for central sleep apnea in heart failure. *N Engl J Med* 2016;374:689.
11. Yamauchi M, Combs D, Parthasarathy S. Adaptive servo-ventilation for central sleep apnea in heart failure. *N Engl J Med* 2016;374:689.
12. Parthasarathy S, Subramanian S, Quan SF. A multicenter prospective comparative effectiveness study of the effect of physician certification and center accreditation on patient-centered outcomes in obstructive sleep apnea. *J Clin Sleep Med* 2014;10:243–249.
13. Parthasarathy S. CON: thoughtful steps informed by more comparative effectiveness research is needed in home testing. *J Clin Sleep Med* 2013;9:9–12.
14. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA* 2015;314:2280–2293.
15. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, *et al*.; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139–149.
16. Platt AB, Kuna ST, Field SH, Chen Z, Gupta R, Roche DF, Christie JD, Asch DA. Adherence to sleep apnea therapy and use of lipid-lowering drugs: a study of the healthy-user effect. *Chest* 2010;137:102–108.
17. Esquinas C, Sánchez-de-la Torre M, Aldomá A, Florés M, Martínez M, Barceló A, Barbé F; Spanish Sleep Network. Rationale and methodology of the impact of continuous positive airway pressure on patients with ACS and nonsleepy OSA: the ISAACC Trial. *Clin Cardiol* 2013;36:495–501.

Making Tuberculosis Care and Control Easy Again

First, the bad news: tuberculosis (TB) care and control will get harder before it gets easy again. Nearly 30 years ago, when the World Health Organization crafted the global TB control strategy called directly observed treatment (1), they proposed that TB could be controlled anywhere based on two simple "if/then" statements: if you saw acid-fast bacilli under the microscope, then you administered four drugs for 6 months, and if you still saw the bacteria after 2 months of therapy, you considered the possibility that the patient's organism was drug resistant. This strategy was so simple (or so the story went) that everyone would be within walking distance of a government sputum microscopy center. The few patients who had drug-resistant TB could be referred to a regional laboratory for culture and drug susceptibility testing.

In the past 2 decades, however, TB has made more progress than TB controllers. It has partnered with the global HIV epidemic to telescope the time interval between infection and illness from decades to months. It has exploited the chaos of mixed public and private health systems to confuse and delay a patient's pathway to cure. And it has evolved resistance to our best drugs in at least 3.5% of 9 million new cases that occurred last year (2). National prevalence surveys that are slowly being revealed to the general public are providing evidence that we are losing the global fight against TB. About a third of quality studies that are actually conducted find that reality is significantly worse than estimates.

The most concerning manifestation of our failure is the global epidemic of drug-resistant TB strains and the effect they are having on patients and public health budgets. Resistance to isoniazid and rifampin increases both the cost of therapy, from $14 to $3,000 per patient, and the duration of treatment, from 6 to 18 months. As a result, budgets become more constrained; some countries, such as India, now spend about half their TB resources on the fewer than 5% of patients who have drug-resistant disease. And even with treatment, about half these patients will die from drug-resistant TB (3).

Furthermore, the propensity of public health practitioners to oversimplify TB has hopelessly muddled even the language that describes drug resistance. In most of their minds, there are simply drug-susceptible and multiple-drug–resistant TB patients. This confuses the fact that we are talking about the bacteria, and not the patient. It overlooks the fact that most of the world's "drug-susceptible" TB has not undergone susceptibility testing. It obscures the fact that there are therapeutic implications to strains that have resistance to even one antibiotic. And it has spawned a new lexicon of obfuscation that even they cannot agree on, such as "pre–extensively drug-resistant TB."

Simply stated, it is time to modernize TB care and control. It is time to stop using our patients as bioassays for detecting drug resistance. It is time we start measuring what we need to know and describing it precisely. It is time to give our patients only those drugs we know will be effective against their strain of bacteria, or to use a more widely accepted phase in oncology, it is time to use therapies in the context of their accompanying diagnostic. Great progress was made toward this goal 7 years ago when the World Health Organization endorsed Cepheid's GeneXpert automated cartridge-based molecular diagnostic, but outside of South Africa, its uptake has been slowest where its need is greatest.

Two significant technical hurdles lie between us and modern TB control: We need a comprehensive list of mutations that confer resistance to our antibiotics, and we need a technique that can detect