Quality of Life 3 and 12 Months After Acute Pulmonary Embolism Analysis From a Prospective Multicenter Cohort Study (New Hope for Outcomes Envy)
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We sit and stew. Stuck in our tarpit of outcomes envy. After all, those brain researchers have their Rankin Score. The endocrinologists have their hemoglobin A1c. Cardiologists have the thrombolysis in myocardial infarction flow grades, and major adverse cardiac events. Pulmonary hypertension researchers have the 6-minute walk test. But with pulmonary embolism (PE), experts entrenched in its study and treatment convene 2-day-long meetings and futilely argue over the question: what nonlethal end point can define success in the treatment of PE?1

The concept that PE causes persistent symptoms has been recognized for decades, but only in the past few years has the symptom complex gained a fairly well-recognized name—the post-PE syndrome.2,3 Charakterized by a mix of physical and psychological symptoms, defining this syndrome to some extent requires the wisdom expressed by Supreme Court Justice Potter Stewart, who said in Jacobellis v. Ohio (1964) about another topic, "[I can’t define it]…but I know it when I see it.”

The post-PE syndrome, more or less, includes varying combinations and intensity of exercise intolerance, fatigue, dyspnea, and some degree of anxiety, rumination, hopelessness, and loss of autonomy. Prior work has suggested this syndrome results from persistent right ventricular overload or dysfunction,4,5 deconditioning,6,7 obesity,6,8 and from the psychological stress imposed by constant worry about clot recurrence and the feeling of having been "snake bitten” by genetic predisposition.10,11 This combination degrades quality of life for a substantial minority of PE patients.12

The patient experience may offer an alternative to mortality as an outcome in the study of treatments. In clinical trials of higher-risk PE, after the informed consent process—with its eight-page consent form, replete with mandatory scary language about all possible bad things that might happen, and the three-page authorization of release of medical records—has weeded out many of the most sick PE patients, the mortality rate directly attributable to PE is less than 2%.13 Thus, with this low rate, the ability to detect a significant reduction on mortality, even with a magical treatment that could afford a whopping 50% effect size (mortality decrease from 2% to 1%), would require a sample size of over 1,000 patients. Enrolling 1,000 patients is a daunting task, given that interventional randomized trials of intermediate-risk PE patients in the United States have required the screening of more than 10 patients with PE for every patient who was successfully enrolled.14,15

Within this context—that a sometimes disabling, but poorly characterized syndrome often follows PE, and that mortality poses an impractical end point—the work by Valero et al16 in this issue of CHEST provides much needed descriptive information about outcomes from PE. This article has several firsts that advance the field of PE research. First, this paper administered psychometric measurements twice, separated by a fairly long period (3 and 12 months after diagnosis) and in a large patient sample. Second, at both time points, the authors administered both a generic quality of life survey and a more PE-specific survey to help tease out the natural effect of time and the unnatural effect of PE. Third, using mixed-models regression, the authors provide adjusted estimates of the influence of possible confounders and mediators on patient-reported quality

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of life. Fourth, the author team converted the findings into beautiful and innovative figures that clearly convey the change in the cohort’s overall perception of wellness. The money slide that lecturers will likely choose is Figure 3, an alluvial plot that shows the story: namely, that approximately two thirds of patients’ conditions improved, often by a large magnitude, from month 3 to month 12, but approximately 10% of patients became significantly worse during that time. For the clinical trialist, these novel data light the way toward better prediction of which patients will be part of this 10%, because that will be the subgroup most likely to benefit from novel treatments.

Further toward this goal, Table 2 from Valero et al16 provides the beta coefficients and CIs from the mixed-models regression, thereby estimating the magnitude of influence of 19 other clinical variables on the score of the psychometric surveys. This analysis considers the effect of variables on quality of life at 3 months, and then for the change in quality of life from 3 to 12 months. This table provides several surprises that must be interpreted with due consideration of change over time. One unexpected finding was that a higher BMI, interacting with time, predicted a higher quality of life. It is important to recognize that the interaction with time may mean that patients who had a high initial BMI and lost weight had the largest improvements. In other words, obese patients had the most quality of life to gain with weight loss. Another unexpected finding is that prior VTE had a nonsignificant negative coefficient at diagnosis (tending to influence the quality of life in a good way), but a significantly positive coefficient (influencing the qualitative of life in a bad way) when assessed over time.

The finding that women have a worse quality of life after PE has been suggested previously, and data in Table 2 allow hypothesis-generation to address this concerning finding.7 For example, given that the average age of participants was 61 years, and the mixed-models regression showed a negative effect of age, one could hypothesize that PE is particularly hard on postmenopausal women, or women with low estrogen for other reasons, given that estrogen has protective effects on right ventricular function in other causes of pulmonary hypertension.17 Alternatively, sex-based differences in illness perception and reporting biases (eg, the “social desirability” hypothesis) may have contributed to the lower scores.18,19 Previous work has suggested that when compared with men, women tend to report higher levels of persistent anxiety and depression and generally lower perception of wellness after diagnosis and treatment of acute arterial thrombotic diseases.20-22 Accordingly, the possible influence of sex-based response biases in survey assessments after PE need to be considered when interpreting sex-based results from surveys.

The findings from Valero et al16 allow new thoughts about patient-centered outcomes for PE in research and practice. For example, authors of placebo-controlled trials of reperfusion therapy should at least consider the variables in Table 2 when devising inclusion criteria to ensure representation of patients most likely to worsen over the next year with placebo, and inclusion of psychometric tests to assess treatment efficacy or effectiveness. In everyday practice, patient counseling should emphasize the value of weight loss after diagnosis.

The current work does not report the confounding or mediating effects of reperfusion therapy at diagnosis, nor the choice and duration of oral anticoagulation over the next year. The latter choice may affect patient-reported quality of life, especially for patients with DVT and post-thrombotic syndrome, which is also not reported.23,24 The cohort was derived from Germany, and perhaps as a result, 99% of participants were of White race, and the findings may not translate to people of color. The data show dynamic and relatively large changes in work-related problems, but do not assess the impact of financial toxicity, which associates with lower self-reported quality of life in other disease states.25,26 Also, these data only speak to the “acute reactionary period” in the first year after new PE diagnosis, during which time patients may initiate positive lifestyle changes, described in interviews as “living in the moment,” including weight loss and exercise. These lifestyle changes, and their positive effect on surveys, may diminish after 1 year, only to be followed by frustration, caused by many factors, including need for lifelong anticoagulation and associated limitations.10,11

The findings by Valero et al16 will help resolve our end-point envy, and shorten those 2-day arguments, by enabling a pathway toward a nonlethal, patient-reported outcome to improve the impact of future clinical trials designed to help patients with PE.

References


