loop system. There was one episode of ketoacidosis in the closed-loop group, due to pump infusion set failure, and no serious hypoglycemic events occurred in either group.

These results are impressive and clinically relevant, since it has been shown that for each 10% reduction in the time spent in the glucose target range, the risk of development or progression of retinopathy increases by 64% and the risk of development of microalbuminuria by 40%.[5] Furthermore, the fact that these results were obtained in patients of different ages and degrees of diabetes control adds robustness to the data. However, the trial was performed in university-based diabetes centers, and the baseline use of sensors and insulin pumps was higher than in the general population of patients with diabetes. Furthermore, the insulin pumps used in the group with the sensor-augmented pump lacked the ability to suspend insulin for predicted hypoglycemia.

The closed-loop system is becoming a mature technology ready for practical use, but there are a variety of barriers to a fully automated closed-loop system, including slow subcutaneous absorption of insulin, low stability of present glucagon formulations, insufficient sensor accuracy, and algorithms that are not yet flexible enough for everyday needs.[6] Whether closed-loop systems can be used in higher-risk patients, such as those with impaired awareness of hypoglycemia, also remains a pressing issue. Cost-effectiveness, user acceptance, and training of both patients and health care professionals also need to be addressed. It is clear that patients would appreciate wearing devices that require minimal interaction, leading to a more carefree lifestyle. We are not there yet, but the trial by Brown et al. offers an almost fingerstick-free option, providing a big step toward a brighter future for patients.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Understanding Progressive Fibrosing Interstitial Lung Disease through Therapeutic Trials

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In the era before antifibrotic therapy, idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias, had a survival rate of 20 to 30% at 5 years,[1] a poorer outcome than that of many common forms of cancer. Patients with IPF still have a progressive course that is either gradual and predictable or defined by sudden episodes of acute worsening. The lethality of this disease has stimulated substantial interest in identifying new therapeutic options for its management, with two new therapies showing clinical benefit in the past 5 years.[2,3]

Similar patterns of decline have also been observed in other forms of diffuse parenchymal lung disease. This finding has led to the description of chronic fibrosing interstitial lung disease as a distinct category of advanced lung disease.[4,5] In survey data, this phenotype is thought to have a poor prognosis, similar to that of IPF,[6] although epidemiologic studies of this cohort are limited. Treatment efficacy in this group is un-

known. These circumstances create a need to define the mechanisms of disease development — are they distinct or similar to those in IPF? — and appropriate management options.

However, one limitation in our understanding of the epidemiology, natural history, and treatment strategies in fibrosing interstitial lung disease is the very fact of its identification as a common phenotype in a broad array of disease states, including autoimmune disease, granulomatous lung disease, and idiopathic interstitial pneumonias other than IPF.[7] Even though the diseases associated with fibrosing interstitial lung disease have some similar clinical features, they have divergent physiological mechanisms, which makes the determination of common therapeutic targets challenging and intriguing. In addition, the manifestations of fibrosing interstitial lung disease that are associated with these diseases can overlap substantially with IPF, with radiographic and histologic patterns that meet the criteria for usual interstitial pneumonia, which was once considered the hallmark of IPF.

Given the lack of a diagnostic marker that would distinguish fibrosing interstitial lung disease from IPF, the design of definitive research studies in this patient population becomes all the more complex. Whether fibrosing interstitial lung disease should be approached as a distinct disease state or as a final common pathway for a heterogeneous array of parenchymal lung diseases with overlapping features remains to be determined. Similar questions have been raised in the approach to the study of IPF, which has been described as a product of a variety of molecular pathways overlying a diverse genetic background.[8] Some investigators have suggested that IPF should be viewed as one manifestation of a spectrum of molecular endotypes that lead to fibrotic lung disease.[9]

Flaherty et al.[10] now report in the *Journal* a significant slowing of the decline in the forced vital capacity (FVC) in patients with fibrosing interstitial lung disease who were treated with nintedanib, a tyrosine kinase inhibitor that was previously shown to have efficacy in patients with IPF. The authors report an absolute difference of 107 ml in the annual rate of decrease in the FVC after 52 weeks of treatment between patients who received nintedanib and those who received placebo. The magnitude of this benefit is similar to that previously described in the IPF population. This finding is remarkable in the context of the trial population, which included patients with a variety of underlying interstitial lung diseases. (Some of these patients were enrolled from my clinic, but I had no other involvement with the trial.) The inclusion of this heterogeneous population of patients might be expected to make it difficult to determine therapeutic efficacy, given the variable physiological mechanisms that were probably initiated and then ultimately led to fibrosis in the cohort. However, the criteria for enrollment mandated that computed tomography of the chest show at least 10% fibrotic involvement of the lung and that there be a 2:1 ratio of patients with features of usual interstitial pneumonia to patients with other patterns of fibrosis. This design ensured that there were enough similarities among the patients and features common to IPF to suggest the potential efficacy of the trial intervention.

Past therapeutic trials involving patients with IPF have been vulnerable to the limitations of enrollment of heterogeneous patient populations, because of the spectrum of disease that can be seen in the IPF population and the overlap of IPF with other fibrotic lung diseases. The investigators in the current trial do not shy away from this risk but rather embrace the consideration of a phenotypic or endotypic approach to the study of therapeutic agents in fibrosing interstitial lung disease. Their apparent success in this trial suggests a final common pathway to fibrosis. Although knowledge of the exact cause of fibrosing lung disease may not be needed to derive a therapeutic benefit on the slowing of the decline in the FVC, it stands to reason that preventing each of these diseases from gaining a foothold will probably require an understanding of the disease-specific mechanisms at play. The use of nintedanib may slow the disease progression, but our challenge for the future is to design studies that identify earlier targets to prevent the establishment of this still highly morbid condition.

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