increased morbidity and mortality associated with COPD,[12] and COPD accounts for more than 80% of total deaths from chronic respiratory disease globally.[5] A primary goal of the outpatient management of COPD is to prevent future AECOPD. A treatment approach that is proactive and prevents future AECOPD will improve health status, reduce health care utilization and reduce mortality.[41,42]

Patient Values and Preferences

We placed high value on the prevention of AECOPD as a treatment goal. Given the significance that AECOPD has on an individual (both short- and long-term outcomes) and the health care system, a proactive approach to reduce exacerbation is necessary.

Review of Evidence by Outcomes

Moderate to Severe Exacerbations: COPD exacerbation is either symptom-based requiring a change of at least one major symptom (dyspnea, sputum purulence, sputum volume), or event-based requiring a change of at least one major symptom and use of antibiotics and/or systemic corticosteroids (moderate exacerbation) or event based requiring a change of hospital admission (severe exacerbation).[55] The best way of identifying subjects susceptible to exacerbations is through their exacerbation history, where frequent exacerbations predict risk of future events.[56] Exacerbations of COPD have profound impact on patients' health status, functional capacity, and lung function.[57,58] The frequency and severity of exacerbations varies, and high risk exacerbations which has been used as operational definition in many large clinical trials has been defined as either frequent moderate exacerbations (exacerbations requiring antibiotic and/or prednisone treatment) or severe exacerbations (resulting in emergency department or hospital admission).[29] Severe exacerbations have a poor prognosis with increased mortality,[59] significantly impaired health status, and increased risk of further exacerbations.[60,61] Patients who have been admitted to hospital for a severe exacerbation of COPD are at substantial risk of rehospitalization.[9] Therefore, targeted interventions aimed at preventing or reducing the frequency and severity of exacerbations should be a priority for improving patients' prognoses.

Recommendations and Changes From Last CTS COPD Guideline in 2019 With Respect to Moderate to Severe Exacerbations (Table 2): In stable individuals at a low risk of exacerbations and with moderate to high symptom burden, health status impairment (mMRC $\geq$ 2, CAT $\geq$ 10) and FEV_1 < 80% predicted, based on updated evidence, there is a change from 2019, with a recommendation to start LAMA/LABA dual therapy as initial maintenance therapy (**rec. PICO P.2.A.**). This aligns with the recommendation P.1.B made in PICO 1. Furthermore, LAMA/LABA dual therapy is preferred to ICS/LABA combination therapy due to significant improvement in lung function and lower rates of adverse effects (eg, pneumonia). However, ICS/LABA combination therapy is preferred to LAMA/LABA dual therapy in individuals with both COPD and concomitant asthma.

Additionally, in stable individuals with COPD at a high risk of exacerbations, with a high symptom burden, health status impairment (mMRC $\geq$ 2, CAT $\geq$ 10) and FEV_1 < 80% predicted, based on updated evidence as previously described, there is a change from 2019, with a strong recommendation to start LAMA/LABA/ICS triple combination therapy as initial maintenance therapy (**rec. PICO P.2.B.**). For symptomatic individuals with impaired health status meeting the definition of having a high AECOPD risk (see Fig 3), two large RCTs, IMPACT[42] and ETHOS,[41] demonstrated the benefits of triple inhaled LAMA/LABA/ICS (administered in a single inhaler) versus dual inhaled LAMA/LABA or ICS/LABA. In IMPACT, LAMA/LABA/ICS triple combination therapy was associated with a significantly lower annual rate of moderate or severe exacerbations during treatment than ICS/LABA combination therapy or LAMA/LABA dual therapy (0.91 vs 1.07 vs 1.21 exacerbations/year, respectively). LAMA/LABA/ICS triple combination therapy was also associated with a significantly lower risk of severe exacerbations compared to LAMA/LABA dual therapy (0.13 vs 0.19 severe exacerbations/year; rate ratio, 0.66, 95% CI, 0.56-0.78). In the ETHOS trial, the annual rate of moderate or severe exacerbations was 24% lower with 320 μg budesonide LAMA/LABA/ICS triple combination therapy compared with LAMA/LABA dual therapy, and 13% lower compared to ICS/LABA combination therapy. Similarly, the annual rate of moderate or severe exacerbation was significantly lower with 160 μg budesonide LAMA/LABA/ICS triple combination therapy compared with LAMA/LABA dual therapy and ICS/LABA combination therapy. No difference in annual rate of moderate or severe exacerbation (or time to first moderate or severe exacerbation) was observed between LAMA/LABA/ICS groups with differing ICS doses (rate ratio, 1.00; 95% CI, 0.91-1.10).