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Modeled reductions in COPD exacerbation rates, mortality, and related medical costs due to increased SITT adoption: PROMETHEUS Italy

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Abstract

Introduction COPD is a leading cause of death and significant healthcare burden in Italy. The ETHOS (NCT02465567||5/2015) and IMPACT (NCT02164513||6/2014) randomized controlled trials (RCTs) have evaluated single-inhaler triple therapy (SITT) and have shown SITT efficacy and safety in reducing exacerbations and all-cause mortality in COPD patients. Despite benefits seen in RCTs, there are currently no studies that evaluate the long-term implications of broader and appropriate SITT use in Italy. We therefore evaluated the potential impact of broader SITT adoption on mortality, exacerbations, and related medical costs in Italy.

Methods We developed a 10-year (2025–2034) microsimulation model using literature-based patient demographic and clinical characteristics, incidence, therapy distribution and changes, COPD severity changes, mortality, and exacerbations to simulate the Italian COPD population. We modeled two scenarios: "status quo" and "increased SITT," and used patients' airflow limitation and exacerbation history (per GOLD guidelines) to choose patients for SITT. The model simulated annual changes in patient characteristics and related changes in medication therapy over 10-years. Patients' progression reflected reductions in % of FEV1 predicted and annual clinical characteristics. Flagged patients were those that qualified for SITT.

Results A starting population of approximately 1,550,000 diagnosed prevalent and incident COPD patients were included in the analysis. Based on our modeled "increased SITT" simulation and medication transition algorithm, at the end of the 10-year projection, the prevalent and incident COPD population in Italy increased to 1,881,000 patients, of which 45.4% received SITT. Over 10 years, modeled increased SITT treatment reduced severe and moderate Exacerbations by 12% and 13%, respectively, and all-cause mortality by 14%, avoiding 40,000 deaths, compared to status quo treatment for flagged COPD patients. Consequently, higher than current SITT adoption could reduce associated medical costs by €646 million for flagged COPD patients.

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Conclusion Assuming RCTs effects and adherence translate to clinical practice, our model shows that higher than current SITT use in the Italian COPD population may lead to lower mortality rates and exacerbations, ensuring a substantial savings in associated medical costs. The results of this modeling study could provide rationale to modify existing practices on SITT prescribing with the aim of alleviating the burden of COPD.

Keywords COPD, Single-inhaler triple therapy, Population model

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition usually progressive primarily caused by inhalation of lung irritants such as pollution and cigarette smoke as well as other factors including genetics [1]. Patients with COPD are at an increased risk of other chronic conditions such as cardiovascular and metabolic diseases, anemia, osteoporosis, and sleep and mental health conditions [2].

Standards of care for patients with COPD include a combination of maintenance inhalers with use of short-acting rescue medications, as well as lifestyle changes, including smoking cessation [3]. The management of COPD involves continuous evaluation of the response to treatment, with possible adjustments based on the evolution of the disease. Maintenance therapy includes long-acting beta 2- agonists (LABA), long-acting anticholinergics (LAMA), and inhaled corticosteroids (ICS) [3]. The natural history of the disease is punctuated by acute worsening episodes termed exacerbations, impacting on medium and long terms outcomes as well as deterioration of concomitant conditions (in particular cardiovascular [4]). Indeed, exacerbations are not only associated with acute inflammation, but they are also linked to a decline in lung function, functional status, a higher risk of mortality, and higher direct medical costs and hospital resource utilization.

The 2023 GOLD guidelines places an emphasis on the role of exacerbations in COPD. The initial treatment algorithm was modified to create a new group, called GOLD E (or GOLD Exacerbator) which represents those patients that have experienced ≥ 2 moderate or ≥ 1 severe exacerbation (an exacerbation leading to hospitalization) annually [3].

Triple therapy, or therapy with a LABA, LAMA, and ICS, is recommended in patients with frequent exacerbations and high a blood eosinophil count. Triple therapy can be utilized with either a multiple inhale strategy (multiple inhaler triple therapy, or MITT), or by combining all three agents into a single inhaler (single inhaler triple therapy, or SITT), which is preferred by GOLD guidelines. There is evidence suggesting that SITT improves medication compliance [5–7] and multiple inhaler treatment are discouraged by GOLD. Both the ETHOS (NCT02465567) and IMPACT (NCT02164513) RCTs demonstrated that SITT therapy resulted in lower rates of mortality and exacerbation compared to patients receiving dual therapies [8, 9].

The prevalence of COPD in Italy is 3.59% in males and 2.47% in females [10]. COPD was the 5th leading cause of death in Italy in 2021 and was responsible for 59.46 deaths per 100,000 people [11].

The Gulp study, a recently published retrospective observational cohort study, evaluated the burden of exacerbations and the all-cause mortality of COPD in Italy [12]. They found that even among those patients without a prior history of Exacerbations, 45.5% experienced an Exacerbation during the 3-year follow-up period and 13% died. This study demonstrates that even patients with a low baseline risk of exacerbations have an overall high risk of experiencing subsequent exacerbations, along with an associated increased risk of mortality.

The cost burden of COPD in Italy is relevant; a study evaluating the annual cost of COPD found that the mean cost per patient year in 2015 was €3291 [13]. Much of the costs were due to both Exacerbations and related hospitalizations, with hospitalization costs alone accounting for 59.9% of the total costs [13].

To optimize healthcare resources, effective strategies for better COPD management are urgently needed. Since SITT therapy has been shown to be underutilized in Italy, the objective of the present study was to estimate the potential implications in the real-world of appropriate broader SITT use on the Italian COPD population by utilizing a multi-year stochastic microsimulation model [14].

Methods

Model approach

The base structure of this model was adapted from the PROMETHEUS study conducted in the United States based [15]. Our multi-year stochastic microsimulation model projects outcomes over 10-years by starting with a base population of Italian COPD patients and incorporating new entrants (incident cases) annually. Literature-based assumptions were generated to create a population that represents the current Italian COPD population by assigning characteristics such as age, gender, COPD incidence rates, yearly changes in airflow restriction, baseline treatments as well as treatment modifications, mortality rates, and exacerbation rates (for both moderate and severe exacerbations). We describe the literature sources used for each characteristic in the supplemental

materials. If an Italian source was available, it was used for inclusion with preference given to sources that were more recent in order to best represent the current Italian COPD population. In cases where there was no Italian data source, we utilized other available data as outlined. The percent of predicted forced exhalation volume in 1 s (FEV_1) was then utilized to assign patients to a GOLD stage, 1–4. We then applied annual declines in FEV_1 to model the progressive nature of the disease. Additional penalties were also applied if a patient was deemed to be a smoker.

A baseline (or status quo) model was created by integrating population growth in accordance with the projected increase of the Italian population over the 10-year forecast period.

Simulation overview, model populations, and simulation scenarios

After defining the baseline "Status Quo" model, we modeled 1,000 simulations over 10 years from 2025 to 2034. Each year, we applied probabilistic changes to the COPD patient characteristics. Changes included FEV_1 decline, as mentioned above, smoking cessation rates, changes in COPD treatments, all-cause mortality, and occurrence of moderate and severe exacerbations. Any patient that did not quit smoking or those that experienced exacerbations was given a higher probability of COPD progression/FEV_1 decline, which is in line with disease pathophysiology. We also linked medication therapy utilization to Exacerbations, based on available data on varying Exacerbation rates among patients on different therapies. Lastly, in addition to annually adding newly diagnosed incident COPD patients, patients were removed from the model either by dying or by reaching 100 years of age.

We modeled two scenarios – "Status Quo" and "Increased SITT".

- "Status Quo" (Baseline): this model was a simulation of the current Italian COPD population without applying any changes in current SITT prescribing patterns (Fig. 1).
- "Increased SITT": this model assumed a higher SITT prescribing practice occurring over the modeled 10-years based on GOLD prescribing guidelines (Fig. 2). The key difference between the "*Increased SITT*" and the "*Status Quo*" modeled populations was that the "Increased SITT" model modified the annual medication algorithm, resulting in a higher transition of patients to SITT.

We utilized data from the AVOIDEx study to map the probability of treatment changes in our status quo population [16]. Our treatment algorithm is based on both GOLD guidelines as well as key inclusion criteria from the ETHOS study. Our results are reported for two different populations within each scenario: the Total and Flagged populations. The flagged population represents the subset of the total population that met GOLD recommendation criteria for SITT prescribing, independent of the actual modeled medication use for those patients. These patients represent the more severe subset within the total population. Both the total and flagged

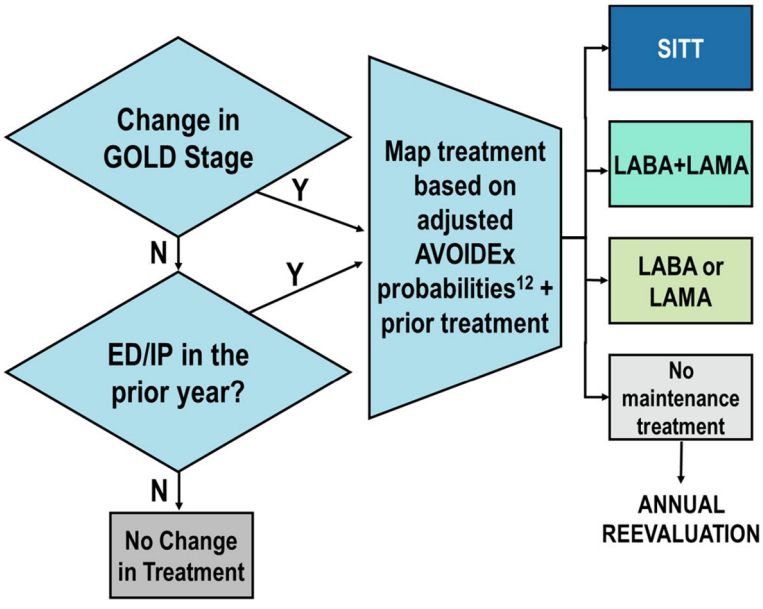

Fig. 1 "Status Quo" medication transition
If a patient started on *SITT*, no further transitions were made, *ED* emergency department, *IP* inpatient admission, *SITT* single inhaler triple therapy, *LABA* long-acting beta 2- agonists, *LAMA* long-acting anticholinergics

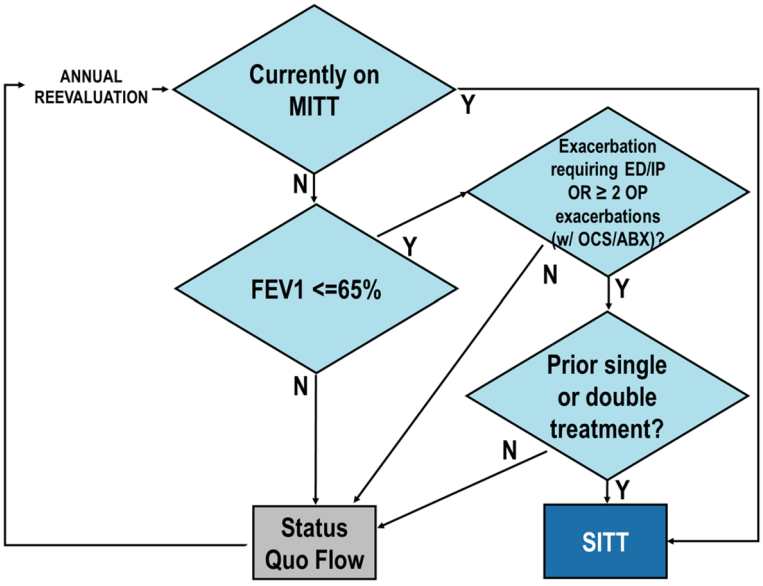

Fig. 2 "Increased SITT" medication transition based on GOLD 2023 guidelines and key inclusion criteria for ETHOS study
If a patient started on *SITT*, no further transitions were made *MITT* multiple inhaler triple therapy, *FEV1* forced expiratory volume in 1 s, *ED* emergency department, *IP* inpatient admission, *OP* outpatient visit, *OCS* oral corticosteroids, *ABX* antibiotics, *SITT* single inhaler triple therapy

populations were sampled and simulated separately from each other and therefore there may be variation in the patient counts and outcomes for the non-flagged population. The exacerbation rates were an important assumption in our modeling. To determine the baseline rate, we utilized the Gulp study and then utilized additional literature to determine the difference in rates [12, 17]. This approach was used to avoid over emphasizing the benefits of SITT compared to MITT in a real-world population on the exacerbation rate.

We estimated the number of life-years extended for both the total and flagged populations under higher SITT adoption scenarios compared to status quo. Initially, we calculated the expected years of life by using standard mortality tables and considering the age and sex distribution. Subsequently, we adjusted the standard mortality rates to reflect the increased mortality associated with COPD and estimated the expected future years of life for each population.

Outcomes and statistical analyses

Over our 10-year model, we determined the simulated severe and moderate exacerbation rates and counts as well as the all-cause mortality rate and death counts for both the total population as well as the flagged population under both the "Status Quo" and the "Increased SITT" models. We also calculate the change in mortality, the life years extended and the difference in the exacerbation rates and counts between both models (for both the total and flagged populations, separately). Of note, the flagged population drives much of the numerical difference in mortality and morbidity observed in the total population. Lastly, we calculated the number needed to treat (NNT) to increase life expectancy by one year for the "Increased SITT" model. We also calculated the number of remaining life years in the flagged population under both the "Increased SITT" and "Status Quo" models over a 10 year-period. This was done to quantify the impact of increased SITT on the life expectancy of each COPD patient.

We utilized Python PySpark and the following statistical analyses were included: (1) use of a stochastic microsimulation model, (2) descriptive statistics including means for continuous variables, and (3) frequency percentages for categorical variables were calculated.

Sensitivity analyses

To assess the impact of variations in our baseline assumptions on modeled outcomes, we performed sensitivity testing on four variables. We varied: (1) the baseline distribution of GOLD airflow limitation stages, (2) the exacerbation rates, (3) the COPD population growth, and (4) the FEV1% of predicted cutoff required to consider patients for SITT therapy under the "Increased SITT" model and observed the impact on mortality, exacerbation counts and costs.

For the Baseline GOLD distribution, we either assumed that the Italian COPD population was 10% more or 10% less severe than the current assumption by shifting more/less patients to a higher or lower GOLD stage, respectively. In the scenario where we shifted severity up by 10%, we had a higher distribution of patients in higher GOLD stages than in the base model, and vice-versa for the 10% less severe scenario. Regarding Exacerbation

rates, we assumed that the Exacerbation rate was either 10% higher or lower than the Baseline assumption. For the COPD incidence, we assumed that the rate was either 1% higher or 1% lower than the base case assumption used. For the FEV1% of predicted cutoff, we modified the 65% cutoff to 80% in the "Increased SITT" model. This latter assumption is more aligned to the label of triple inhaled therapies and GOLD guidelines in 2024.

Table 1 Study population demographics, COPD severity and medication therapy by scenario

	Baseline	Across All 10 Years			
	Total Population	Total Population		Flagged Population	
		Status Quo	Increased SITT	Status Quo	Increased SITT
Total Years of Life	1.55 M	16.26 M	16.46 M	5.09 M	5.27 M
Average Age	74.3	75.1	75.1	76.7	76.8
Female, *n* (%)	668.4 K (43.1%)	6.97 M (40.2%)	7.04 M (40.2%)	2.21 M (41.2%)	2.28 M (41.2%)
Smoking Status Distribution					
Current, *n* (%)	1.02 M (66.0%)	9.66 M (55.8%)	9.74 M (55.6%)	2.82 M (52.6%)	2.89 M (52.3%)
Former, *n* (%)	455.9 K (29.4%)	6.97 M (40.2%)	7.07 M (40.4%)	2.33 M (43.4%)	2.41 M (43.6%)
Never, *n* (%)	71.4 K (4.6%)	683.7 K (3.9%)	689.6 K (3.9%)	218.4 K (4.1%)	225 K (4.1%)
FEV1% of Predicted Distribution					
GOLD 1: FEV1 > 80% predicted	227.3 K (14.7%)	3.79 M (21.9%)	3.8 M (21.7%)	693.8 K (12.9%)	700.4 K (12.7%)
GOLD 2: FEV1 ≥ 50% and < 80% predicted	695.8 K (44.9%)	8.81 M (50.9%)	8.86 M (50.6%)	2.09 M (39%)	2.13 M (38.5%)
GOLD 3: FEV1 ≥ 30% and < 50% predicted	427.9 K (27.6%)	3.07 M (17.7%)	3.12 M (17.8%)	1.51 M (28.1%)	1.56 M (28.3%)
GOLD 4: FEV1 < 30% predicted	199.1 K (12.8%)	1.66 M (9.6%)	1.72 M (9.8%)	1.07 M (20.0%)	1.14 M (20.5%)
Medication Distribution					
No Maintenance	109.1 K (7.0%)	979 K (5.7%)	979.3 K (5.6%)	0 (0%)	0 (0%)
LABA or LAMA	505.5 K (32.6%)	4.49 M (25.9%)	4.34 M (24.8%)	147 K (2.7%)	0 (0%)
ICS + LABA or ICS + LAMA	249.2 K (16.1%)	1.85 M (10.7%)	1.79 M (10.2%)	58.6 K (1.1%)	0 (0%)
LABA + LAMA	309 K (19.9%)	4.5 M (26.0%)	3.43 M (19.6%)	1.11 M (20.6%)	0 (0%)
MITT	318.4 K (20.5%)	1.87 M (10.8%)	0 (0.0%)	1.87 M (34.9%)	0 (0%)
SITT	58.8 K (3.8%)	3.63 M (20.9%)	6.97 M (39.8%)	2.18 M (40.6%)	5.53 M (100%)

total years of life represents the life years of contributed by all patients included in the model

FEV1 forced expiratory volume in 1 s, *LABA* long-acting beta 2- agonists, *LAMA* long-acting anticholinergics, *ICS* inhaled corticosteroids, *MITT* multiple inhaler triple therapy, *SITT* single inhaler triple therapy, *B* billions (1000 millions), *M* millions (1000 thousands), *K* thousands (10 hundreds)

Results

At baseline (or at year 0, prior to sampling), which is at the start of our model, the average age of COPD patients was 74.3 years old and 43.1%, or 668,400, were female. Regarding the severity of the airflow limitation at Baseline, GOLD Stage 1 represented 14.7% of patients (least severe), GOLD Stage 2 represented 44.9%, GOLD Stage 3 was 27.6%, and GOLD Stage 4 was 12.8% of patients (most severe). At Baseline, 7.0% received no maintenance COPD treatment, 32.6% received monotherapy (LABA or LAMA), 16.1% received either ICS + LABA or ICS + LAMA, 19.9% received LABA + LAMA, 20.5% received MITT, and 3.8% received SITT. Additional baseline characteristics are presented in Table 1 for the study population and over the 10 years of this model.

Figures 3 and 4 describe the annual medication transition from Baseline until year 10 under both the "Status Quo" and "Increased SITT" models. Notably, by the end of year 10, 28% of patient years are using SITT in the "Status Quo" model compared to 45% in the "Increased SITT" model, with much of that additional patient-year coming from those that would be treated with LABA + LAMA therapy or MITT in the "Status Quo" model.

For the flagged population (meeting criteria for SITT according to GOLD) the severe Exacerbation rate was reduced from 17.8% in the "Status Quo" model to 15.1% in the "Increased SITT" model, representing a 15.1% reduction in severe exacerbations. The flagged population's moderate Exacerbation rate was reduced from 48.9% in the "Status Quo" model to 41.2% in the "Increased SITT" model, representing a 15.7% reduction. In addition, the all-cause mortality rate was reduced from 6.8% in the "Status Quo" model to 5.8% in the "Increased SITT" model for the flagged population, resulting in a mortality rate reduction of 10.9% (Table 2).

The "Increased SITT" model would lead to 109,800 fewer severe Exacerbations over 10 years in the flagged population, for a 12.2% reduction. Additionally, moderate Exacerbations would be reduced by 351,700, for a 12.7% reduction. The reductions in severe and moderate exacerbations equate to medical related cost savings of €627.1 million and €18.5 million, respectively, resulting in a total savings of €645.6 million over the 10 years for the flagged population. The annual "Status Quo" costs and annual incremental costs avoided due to increased SITT use are shown in Fig. 5.

Under the "Increased SITT" model for the flagged population, the average number of years of life remaining was extended by 1.3 years for patients aged 46–55, by 1.2 years for patients aged 56–65, by 1.0 years for patients

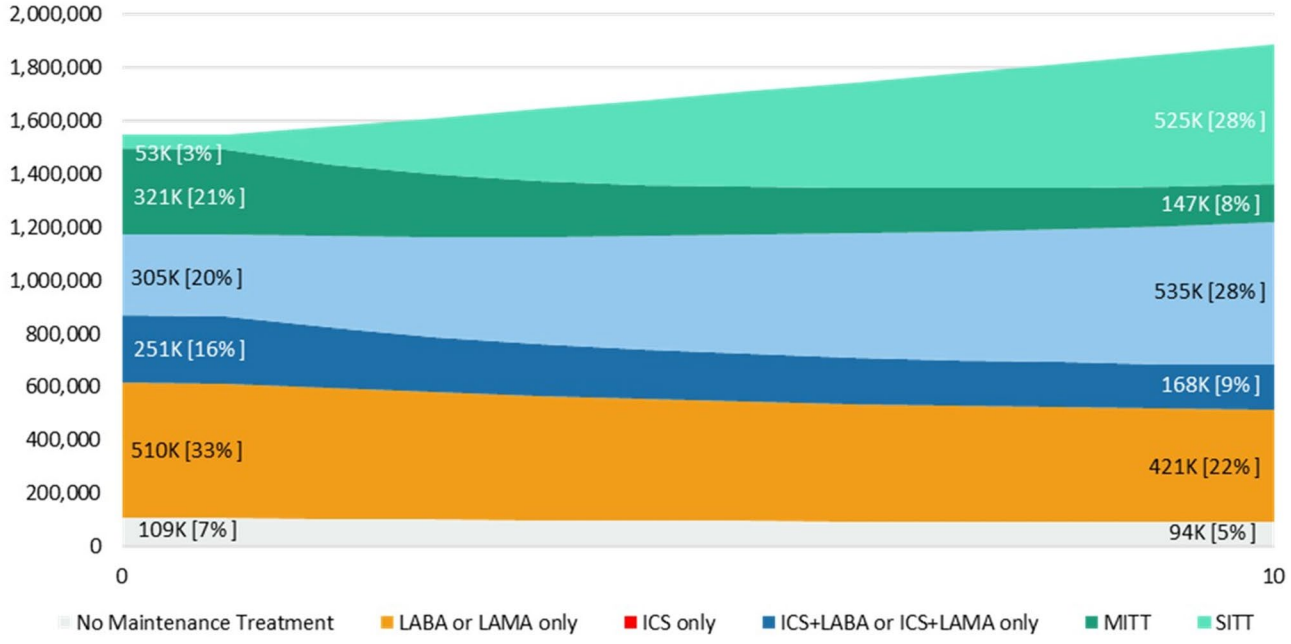

Fig. 3 "Status Quo" patient years by treatment – Over 10 years
LABA long-acting beta 2- agonists, *LAMA* long-acting anticholinergics, *ICS* inhaled corticosteroids, *MITT* multiple inhaler triple therapy, *SITT* single inhaler triple therapy, *K* thousands (10 hundreds)

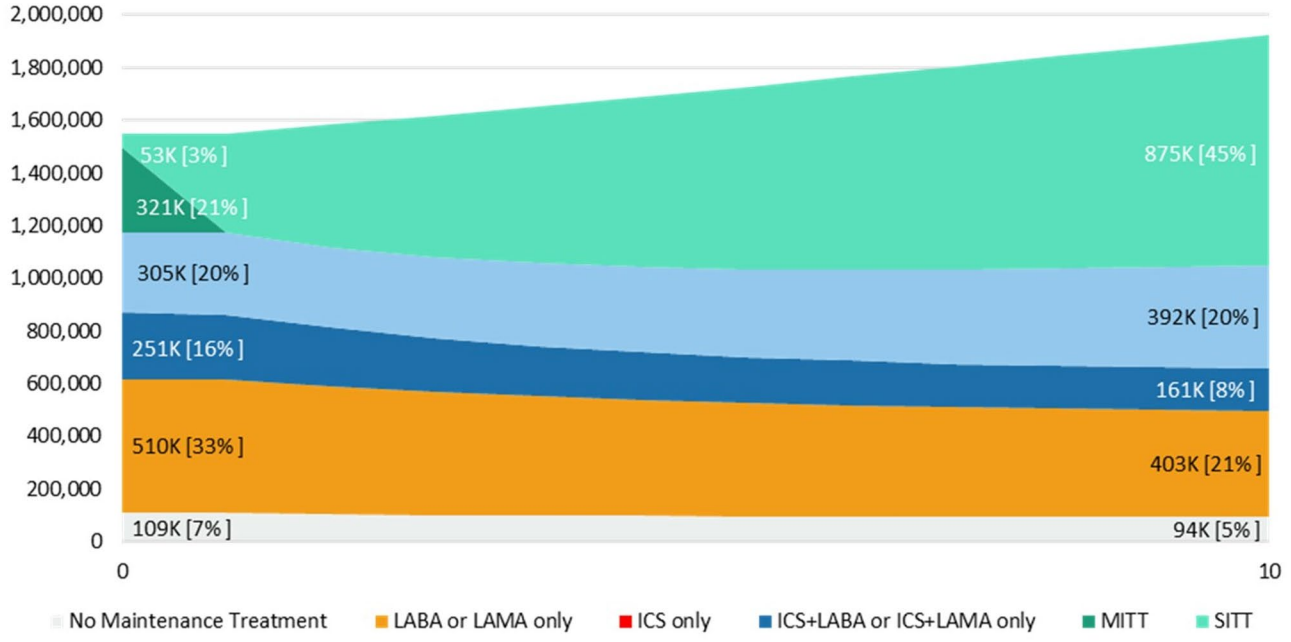

Fig. 4 "Increased SITT" patient years by treatment – Over 10 years
LABA long-acting beta 2- agonists, *LAMA* long-acting anticholinergics, *ICS* inhaled corticosteroids, *MITT* multiple inhaler triple therapy, *SITT* single inhaler triple therapy, *K* thousands (10 hundreds)

aged 66–75, by 0.8 years for patients aged 76–85, and by 0.4 years for patients over 86 (Fig. 6) with the most significant improvements are observed in the flagged population. The average remaining years of life for the total population are also shown in Fig. 6 The number needed to treat to extend the average patient life by 1 year was 20.6 for the total population and 5.9 for the flagged population over the modeled 10-years.

Sensitivity testing

Figure 7 shows the difference in "Status Quo" and "Increased SITT" results in the flagged population based

Table 2 Mortality, life years, and Exacerbation outcomes by population over 10 years

	Total Population				Flagged Population			
	Status Quo	Increased SITT	Absolute Difference	Percent Change	Status Quo	Increased SITT	Absolute Difference	Percent Change
Total Patient Years	16.26 M	16.46 M	200.38 K	1.2%	5.09 M	5.27 M	179.25 K	3.5%
Death counts	913.38 K	877.41 K	−35.97 K	−3.9%	355.92 K	317.03 K	−38.89 K	−10.9%
Clinical Outcomes								
Mortality rate (%)	5.5%	5.2%	−0.3%	−5.0%	6.8%	5.8%	−0.9%	−13.6%
Severe exacerbation counts	2.15 M	2.04 M	−103.21 K	−4.8%	903.67 K	793.87 K	−109.8 K	−12.2%
≥ 1 severe exacerbation rate (%)	13.2%	12.4%	−0.8%	−6.0%	17.8%	15.1%	−2.7%	−15.1%
Moderate exacerbation counts	7.57 M	7.23 M	−338.99 K	−4.5%	2.76 M	2.41 M	−351.65 K	−12.7%
≥ 1 moderate severe exacerbation rate (%)	42.6%	40.2%	−2.4%	−5.6%	48.9%	41.2%	−7.7%	−15.7%
Cost Outcomes								
Severe exacerbation cost, €	€ 12.3B	€ 11.71B	-€ 589.1 M	−4.8%	€ 5.21B	€ 4.58B	-€ 627.12 M	−12.0%
Moderate exacerbation cost, €	€ 400.55 M	€ 382.74 M	-€ 17.81 M	−4.4%	€ 146.43 M	€ 127.94 M	-€ 18.49 M	−12.6%

Each scenario was simulated separately, and therefore there may be slight variation in the outcomes for the non-Flagged population

B billions (1000 millions), *M* millions (1000 thousands), *K* thousands (10 hundreds), *SITT* single inhaler triple therapy

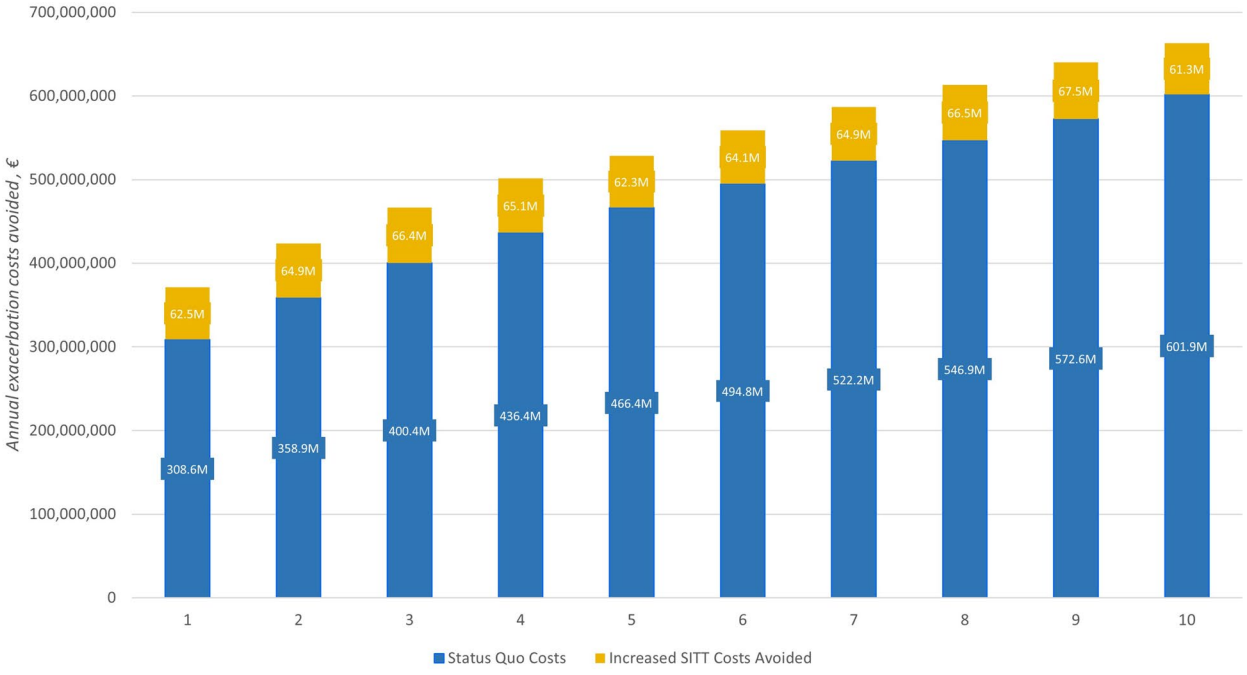

Fig. 5 Annual exacerbation costs (€) avoided under Increased SITT adoption over 10 years – Flagged Population
The blue bars represent the annual costs for the status quo population by year and the yellow bars represent the costs avoided for those that were in the increased SITT model. *SITT* single inhaler triple therapy, *M* millions (1000 thousands)

on the sensitivity testing as described in the methods above. Adjusting the FEV1% predicted threshold from 65 to 80% when considering SITT therapy had the largest impact on mortality and exacerbation rates. Adjusting the threshold would lead to more patient life years in the flagged population, thereby allowing for a higher reduction in death counts, and both severe and moderate exacerbations for the "Increased SITT" model compared to the "Status Quo" model. Additional details on the sensitivity testing are also provided in Supplemental Table 1.

Discussion

This study, together with the U.S. PROMETHEUS publication, demonstrates the potential benefits of increased SITT use in the Italian COPD population, based on our simulation model. By using real-word patient characteristics from published literature, we were able to closely approximate the characteristics of the Italian COPD population to understand the long-term benefits of increased SITT.

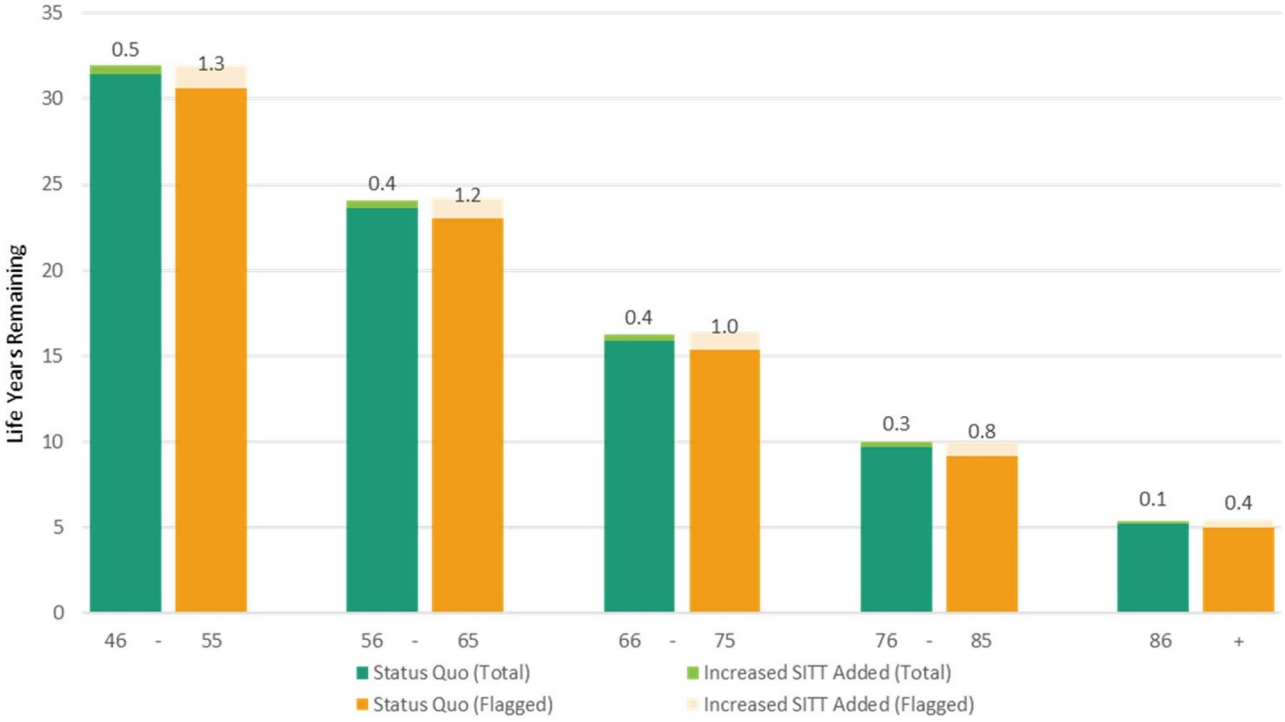

Fig. 6 Average years of life remaining and extended life-years per COPD patient, by age band – Over 10 years
SITT single inhaler triple therapy

We showed that the appropriate utilization of SITT could be beneficial to a larger group of COPD patients. Notably, existing literature points to the importance of Exacerbation avoidance, as they lead to a worsening of lung function as well as an increase in mortality. Additionally, Exacerbations are a large contributor to costs as they can lead to significantly higher rates of healthcare resource utilization. The results of our study show that more progressive SITT prescribing than currently observed over the 10-year study is projected to significantly decrease hospitalizations due to Exacerbations and produce substantial related medical cost savings. Overall, across all 10-years of the model, we found that increased SITT utilization would save €645.6 million in cost due to avoiding a total of 351,700 moderate and 109,800 severe exacerbations for the population that met GOLD guideline criteria for SITT prescribing (flagged population). We model that there would also be a reduction in the mortality rate by 13.6% for the flagged population from 6.8% in the "Status Quo" model to 5.9% in the "Increased SITT" model. In addition, our "Increased SITT" model resulted in an increase to the average life expectancy by 0.3 years for the total population and by 0.9 years for the flagged population. To extend the average patient's life by one year, the estimated number needed to treat is 20.6 for the total population and 5.9 for the flagged population. The results of our sensitivity testing also suggest that even with modifications to our assumptions, the overall direction of the results would remain unchanged. This reinforces the credibility of the assumptions used in this modeling. Our sensitivity testing also investigated the impact of changing the FEV1 threshold from 65% (as was used in ETHOS and the US PROMETHEUS work) to 80% as was studied in IMPACT. This allows us to understand the impact of a less-strict FEV1 threshold on patient outcomes. Changing the threshold would lead to an increase in patient life years within the flagged population, which in turn would enable a greater reduction in death counts, as well as in both severe and moderate exacerbations, for the "Increased SITT" model compared to the "Status Quo" model.

While randomized controlled trials, such as ETHOS and IMPACT, have shown the benefits of SITT utilization over dual therapies, this is the first study to model this impact on a large-scale Italian population.

The results of this modeling study could provide rationale for dedicated strategies to consider implementation of SITT among appropriate patients and to modify existing SITT prescribing practices in Italy. Consequently, a policy change in COPD management should be considered by decision makers to enhance COPD therapy adherence and optimize the utilization of SITT in eligible patients.

The study has limitations. A limitation of our study is the absence of detailed clinical and biological data, such as symptom severity and blood eosinophil count.

Fig. 7 Sensitivity testing: Differences in Status Quo and Increased SITT results from baseline under the sensitivity testing scenarios for the flagged population

FEV1 forced expiratory volume in 1 s, *SITT* single inhaler triple therapy, *K* thousands (10 hundreds)

Therefore, we modeled predicted FEV1 as a proxy of disease severity. We note that the lack of data on eosinophils could have led to a bias towards assuming all patients would respond to the addition of ICS, thereby potentially leading to an overestimation of the efficacy of triple therapy in our analysis. Annual COPD severity progression was modeled based on annual decline in FEV1, with additional declines for smokers. The FEV1% of predicted cutoff of 65% was selected to align with ETHOS and PROMETHEUS studies; however, the impact of alternative cutoffs was explored in a sensitivity analysis. Outcomes noted in clinical trials may not translate directly to the real-world population and therefore some results in our analysis may be overstated. The average age of our population was also higher than other studies of COPD patients, this older age is based on data that is epidemiological and sourced from large datasets representing the Italian population. However, the difference in age may understate benefits of increased SITT use in a younger population. In addition, we did not account for therapy de-escalation and only modeled one-directional movement in our analysis. Lastly, we did not factor the costs of specific maintenance medications into our model when describing the cost of exacerbations.

The direct costs of maintenance pharmacotherapy have not been included limiting the conclusiveness of the overall economic picture. However, given the high number of available formulations of ICS/LABA and LAMA and their combination in MITT, along with the variability in their costs and generic availability, as well as the limited data on market share reliable data on the direct costs of maintenance pharmacotherapy is difficult to obtain. Additionally, the availability of specific scientific evidence relevant to the Italian context was limited. Consequently, certain model parameters were derived from international studies. To mitigate this potential bias, we selected data from geographical regions with healthcare systems and patient populations that were considered reasonably comparable to the Italian context. Lastly, we did not attempt to model use of other oral or biologic agents for COPD. We assumed that any use would continue at current rates. The aim of this paper is not to predict the outcomes in COPD patients in Italy in the next 10 years, but to estimate the impact of a modification in prescribing patterns according to GOLD of available pharmaceuticals.

Conclusion

In conclusion, an increase in the use of SITT in Italian patients with COPD showed a potential for significant savings in direct healthcare costs, as it could lead to lower mortality rates and lower rates of both severe and moderate exacerbations.

Abbreviations

COPD	Chronic obstructive pulmonary disease
RCT	Randomized controlled trial
SITT	Single-inhaler triple therapy
MITT	Multi-inhaler triple therapy
LABA	Long-acting beta 2- agonists
LAMA	Long-acting anticholinergics
ICS	Inhaled corticosteroids
FEV_1	Forced exhalation volume in 1 s
ED	Emergency department
IP	Inpatient
OP	Outpatient
OCS	Oral corticosteroids
ABX	Antibiotics

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03358-8.

Supplementary Material 1.

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Authors' contributions

Pierachille Santus, Bianca Oresta, Davide Finocchiaro, Piergiuseppe De Rosa, John Bell, Melissa Caplen, Jennifer Carioto, Prachi Bhatt, Bruce Pyenson, Alberto Papi were all involved in the review of assumptions, the review of modeling results, and manuscript drafting or review.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Pierachille Santus and Alberto Papi have been remunerated for validating assumptions, sources, and interpreting results of the present work. Bianca Oresta, Davide Finocchiaro, Piergiuseppe De Rosa, and John Bell are employees of AstraZeneca and may hold stock and/or stock options in the company. Melissa Caplen, Jennifer Carioto, Prachi Bhatt, and Bruce Pyenson are employees of Milliman, which was contracted by AstraZeneca to conduct this study. The American Academy of Actuaries requires its members to identify their credentials in their work product. Bruce Pyenson, Jennifer Carioto, and Melissa Caplen are members of the American Academy of Actuaries and meet its relevant qualification requirements.

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