# Inhaled corticosteroids and COVID-19 morbidity: Nationwide cohort study

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ABSTRACT

Background

Recent evidence suggest a beneficial effect of systemic corticosteroids for treatment of moderate-to-severe COVID-19. However, it is unknown if inhaled corticosteroid use is associated with reduced morbidity of the disease.

Methods

In a cohort of all hospitalized SARS-CoV-2 test-positive individuals in Denmark, we investigated the 30-day hazard ratio of mechanical ventilation or death among users of inhaled corticosteroids (ICS) compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists but not ICS (non-ICS inhaler), or no inhaled pharmaceutical use, by Cox regression adjusted for age, sex, and other confounders. In parallel, we investigated the association in a cohort of all influenza test-positive patients during 2010-2018.

Results

Among x,xxx SARS-CoV-2 test-positive patients, x,xxx underwent mechanical ventilation and xxx died within 30-days. ICS use was associated with a hazard ratio of x.xx (95% confidence interval [CI], x.xx to x.xx) for mechanical ventilation and x.xx (95% CI, x.xx to x.xx) for death compared to non-ICS inhaler use. Compared to no inhaled pharmaceuticals, the hazard ratio of mechanical ventilation or death was x.xx (95% CI, x.xx to x.xx) and x.xx (95% CI, x.xx to x.xx), respectively. Among influenza patients, the equivalent hazard ratios were x.xx (95% CI, x.xx to x.xx) and x.xx (95% CI, x.xx to x.xx) for mechanical ventilation, and x.xx (95% CI, x.xx to x.xx) and x.xx (95% CI, x.xx to x.xx) for death compared to non-ICS inhaler use and no inhaled pharmaceuticals, respectively.

Conclusions

Inhaled corticosteroid use was associated with increased/similar/decreased COVID-19 morbidity compared to no use, which was similar/different to influenza.

## BACKGROUND

Infection with the novel coronavirus SARS-CoV-2, the causative agent of the COVID-19 pandemic, does not have any specific prophylaxis and only limited treatment options (1–3). Studies report that SARS-CoV-2 infection often lead to severe airway inflammation(4) and the new, not yet peer reviewed, RECOVERY-trial suggests a large beneficial effect of the per oral corticosteroid dexamethasone in hospitalized COVID-19 patients requiring nasal oxygen or mechanical ventilation(3). Nevertheless, the role of inhaled corticosteroids in morbidity of COVID-19 is unknown. Adding to the uncertainty, pre-clinical studies suggests inhaled corticosteroids downregulate the SARS-CoV-2 receptors ACE2/TMPRSS2(5) and inhibit SARS-CoV-2 replication(6), while there is evidence of more severe disease in COPD patients(7,8).

Using the unique Danish nationwide registers on prescription drug use, laboratory confirmed infectious disease, and hospital admissions data, we here present a nationwide cohort study of inhaled corticosteroids and COVID-19 outcomes. To narrow in on the effect of inhaled corticosteroids on COVID-19 morbidity, we used influenza infection during the 2010-2018 influenza epidemics as a comparison.

## METHODS

### *Materials*

The Danish Civil Registration System (CRS) allows linkage of national health registers, in addition to providing demographic information on the Danish population. Information on PCR tests for SARS-CoV-2 and influenza infection is available through MiBA, the Danish Microbiology Database, which includes all microbiological test results in Denmark, starting from 2010. The Danish National Patient Register covers information on hospital admission, transfer to intensive care units (ICU), use of mechanical ventilation, and diagnostic codes to identify underlying comorbidities. The Register of Medicinal Product Statistics, which contains information on all filled prescriptions in Denmark, provides information on pharmaceutical exposures of interest. The Cause of Death Register includes information on all registered deaths in Denmark.

### *Study population*

All hospitalized individuals in Denmark with a positive SARS-CoV-2 PCR test up to xx Month 2020 were included in the COVID-19 cohort from date of testing. The COVID-19 cohort were followed up for mechanical ventilation or death within 30-days from test date. Individuals tested PCR positive for influenza type A or B during 2010-2018 were included in an equivalent influenza cohort from date of testing and followed up for mechanical ventilation or death within 30-days from test date. For sensitivity analyses, we included individuals

who were test-positive for SARS-CoV-2 while out-of-hospital, who were investigated for hospitalization or death within 30-days from test date in an independent cohort.

*Study variables*

Exposure groups were categorized as 1) individuals with inhaled corticosteroid (ICS) use, defined as one or more filled prescriptions of inhaled corticosteroids within the last six months, with or without simultaneous filled prescriptions for other inhaled pharmaceuticals (i.e. $\beta_2$-receptor agonist and/or muscarinic receptor antagonists), or use of combinatory inhalers (e.g. combined ICS and $\beta_2$-receptor agonist inhaler), 2) individuals with $\beta_2$-receptor agonist and/or muscarinic receptor antagonists use defined as one or more filled prescriptions within the last six months, but not ICS use, and 3) individuals without regular ICS, $\beta_2$-receptor agonist, or muscarinic receptor antagonist use. Information on other covariates of interest were defined by relevant pharmaceutical, demographic, and diagnostic codes (see Table 1 and Table S11).

*Outcomes*

Information on date of mechanical ventilation were acquired from the Danish National Patient Register using relevant diagnostic code (Table S11). Information on date of death was acquired from the Cause of death register.

*Statistical analysis*

Our main analysis was conducted among hospitalized test-positive individuals for influenza (in 2010-2018) and COVID-19 (in 2020), respectively. We followed participants for 30 days from the date of testing positive until either mechanical ventilation, death, or loss to follow-up from other causes. We used Cox proportional hazards regression to estimate the hazard ratios of death and mechanical ventilation comparing exposure groups. We estimated 30-day cumulative hazards according to exposure status taking competing risks into account using the Nelson-Aalen estimator. In the Cox models, we took potential confounders into account through direct propensity score adjustment. We considered the following covariates: Age, sex, atrial fibrillation, asthma, chronic pulmonary disease (incl. COPD), dementia, heart failure, hypertension, inflammatory bowel disease, malignancy, renal failure, Charlson Comordidity index score, $\geq 5$ asthma or COPD exacerbations within the latest five years, number of filled prescription within 90 days, per oral corticosteroid use. Covariate status was ascertained 6 months before study entry (before exposure ascertainment). Propensity scores was estimated using logistic regression of probability of exposure on the

above-mentioned covariates as main effects. We estimated separate propensity scores for each exposure group of interest.

To evaluate how robust our main outcome estimates are to unmeasured confounding, we conducted quantitative bias analysis in the form of E-value analysis(9). We calculated E-values for both the main outcome measures and the corresponding limits of the confidence intervals closest to the null.

RESULTS

See TABLES and FIGURES.

DISCUSSION

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TABLES

**Table 1.** Baseline demographic information on individuals in Denmark tested positive for influenza (type A og B) during the 2010-2018 influenza epidemics, and individuals tested positive for SARS-CoV-2 during the COVID-19 epidemic in 2020.

| | **Influenza epidemics (2010-2018)**<br>Influenza test-positive | **COVID-19 epidemic (2020)**<br>SARS-CoV-2 test-positive |
|---|---|---|
| *n* | | |
| Hospitalization rate | | |
| Age (median, IQR) | | |
| Female sex (%) | | |
| Comorbidities (%): | | |
| Atrial fibrillation | | |
| Asthma | | |
| Chronic pulmonary disease(incl. COPD) | | |
| Dementia | | |
| Heart failure | | |
| Hypertension | | |
| Inflammatory bowel disease | | |
| Malignancy | | |
| Renal failure | | |
| Charlson Comorbidity index score | | |
| ≥ 5 asthma or COPD exacerbations within the latest five years | | |
| Pharmaceuticals: | | |
| Number of filled prescription within 90 days (median, IQR) | | |
| Use of inhaled pharmaceuticals (%): | | |
| β2-agonists | | |
| Corticosteroids | | |
| Muscarinic receptor antagonists | | |
| Other | | |
| Combinations of the above | | |
| None | | |
| Use of per oral corticosteroids (%): | | |

| | | |
|---|---|---|
| Regular corticosteroids prescription | | |
| No regular prescription | | |

| **Table 2.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in hospitalized test-positive individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively. | | | | |
|---|---|---|---|---|
| | **30-day relative risk of mechanical ventilation** *hazard ratio (95% CI)* | | **30-day relative risk of death** *hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

FIGURES

**Figure 1.** Cumulative hazard of mechanical ventilation within 30 days, among inhaled corticosteroid (ICS) users, users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or individuals without inhaled pharmaceutical use, in hospitalized test-positive individuals for COVID-19 (year 2020*, Panel A*) or influenza (year 2010-2018*, Panel B*), respectively.

**Panel A**: COVID-19. Days (x-axis) and Nelson-Aalen Cumulative Hazard (y-axis).

**Panel B**: Influenza. Days (x-axis) and Nelson-Aalen Cumulative Hazard (y-axis).

**Figure 2.** Cumulative hazard of death within 30 days, among inhaled corticosteroid (ICS) users, users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or individuals without inhaled pharmaceutical use, in hospitalized test-positive individuals for COVID-19 (year 2020*, Panel A*) or influenza (year 2010-2018*, Panel B*), respectively.

**Panel A**: COVID-19. Days (x-axis) and Nelson-Aalen Cumulative Hazard (y-axis).

**Panel B**: Influenza. Days (x-axis) and Nelson-Aalen Cumulative Hazard (y-axis).

SUPPLEMENTARY TABLES

**Table S1.** Hazard ratio of hospitalization or death within 30 days, among inhaled corticosteroid (ICS) users compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive, non-hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively.

| | **30-day relative risk of hospitalization** *hazard ratio (95% CI)* | | **30-day relative risk of death** *hazard ratio (95% CI)* | |
|---|---|---|---|---|
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S2.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users, by corticosteroid type, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively. | | |
|---|---|---|
| | **30-day relative risk of mechanical ventilation or death** *hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | | |
| beclomethasone | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| budesonide | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| fluticasone | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| mometasone | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ciclesonide | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | | |
| beclomethasone | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| budesonide | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| | | |
|---|---|---|
| fluticasone | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| mometasone | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ciclesonide | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

**Table S3.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively, excluding all individuals with use of per oral corticosteroids (ATC code H02ABxx) within the last six months.

| | **30-day relative risk of mechanical ventilation or death** *hazard ratio (95% CI)* | |
|---|---|---|
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S4.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users, by corticosteroid type, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive, hospitalized individuals for COVID-19 during time windows with narrow (25 February-24 March, 2020), wide (25 March-21 April, 2020), and broad (April 22-Xxx xx, 2020) testing strategies. | | |
|---|---|---|
| | **30-day relative risk of mechanical ventilation or death**<br>*hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 time periods | | |
| 25 February-24 March, 2020 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 25 March-21 April, 2020 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| April 22-Xxx xx, 2020 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S5.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive, hospitalized individuals for influenza during different influenza epidemics. | | |
|---|---|---|
| | **30-day relative risk of mechanical ventilation or death** *hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during different influenza epidemics | | |
| 2010/2011 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2011/2012 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2012/2013 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2013/2014 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2014/2015 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2015/2016 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2016/2017 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| 2017/2018 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S6.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive, hospitalized individuals for influenza by influenza type. | | |
|---|---|---|
| | **30-day relative risk of mechanical ventilation or death**<br>*hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during influenza, by influenza type | | |
| Influenza type A | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| Influenza type B | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S7.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users, by persistency of ICS use, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive, hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively. | | |
|---|---|---|
| | **30-day relative risk of mechanical ventilation or death** *hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | | |
| Persistent ICS use* | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| Sporadic ICS use† | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | | |
| Persistent ICS use* | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| Sporadic ICS use† | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

*Persistent use defined as ≥1 filled prescription per six months within the latest 10 years prior to testing for influenza/COVID-19, excluding the latest six months.

†Sporadic use defined as one filled prescription per two-year period within the latest 10 years prior to testing for influenza/COVID-19, excluding the latest six months.

**Table S8.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users, by drug combination with other inhaled pharmaceuticals, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively.

| | **30-day relative risk of mechanical ventilation or death** *hazard ratio (95% CI)* | | |
|---|---|---|---|
| Exposure comparison | Inhaled β2-receptor agonist without ICS | Inhaled muscarinic receptor antagonist without ICS | Inhaled β2-receptor agonist and muscarinic receptor antagonist without ICS |
| ICS use during COVID-19 | | | |
| with β2-receptor agonist | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| with muscarinic receptor antagonists | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| with both | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | | | |
| with β2-receptor agonist | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| with muscarinic receptor antagonists | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| with both | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

**Table S9.** Hazard ratio of mechanical ventilation or death within 30 days, among inhaled corticosteroid (ICS) users, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively, excluding all individuals with use of per oral xanthines (ATC code R03DA) or leukotriene receptor antagonist (ATC code R03DC) within the last six months.

| | **30-day relative risk of mechanical ventilation or death** *hazard ratio (95% CI)* | |
|---|---|---|
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S10.** Hazard ratio of death within 30 days, among inhaled corticosteroid (ICS) users, compared with users of inhaled β2-receptor agonist and/or muscarinic receptor antagonists and not ICS, or no inhaled pharmaceuticals, in test-positive hospitalized individuals for COVID-19 (year 2020) or influenza (year 2010-2018), respectively, undergoing mechanical ventilation during hospitalization. | | |
|---|---|---|
| | **30-day relative risk of death**<br>*hazard ratio (95% CI)* | |
| Exposure comparison | Inhaled β2-receptor agonist and/or muscarinic receptor antagonist | No inhaled pharmaceuticals |
| ICS use during COVID-19 | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |
| ICS use during influenza | x.xx (x.xx-x.xx) | x.xx (x.xx-x.xx) |

| **Table S11.** Pharmaceutical, demographic, and diagnostic codes used for exposure, covariate, and outcome ascertainment. | | |
|---|---|---|
| | **Data source*** | **Codes used** |
| *Exposures* | | |
| Inhaled pharmaceuticals | | |
| **Corticosteroids:** | | |
| Corticosteroids alone | RMPS | ATC: R03BAxx |
| Corticosteroids in combination with β2-receptor agonists and/or muscarinic receptor antagonists | RMPS | ATC: R03AKxx, R03AL08, R03AL09 |
| Corticosteroids by subtype: | | |
| Beclomethasone | RMPS | ATC: R03BA01, R03AK08 |
| Budesonide | RMPS | ATC: R03BA02, R03AK97 |
| Fluticasone | RMPS | ATC: R03BA05, R03AK06, R03AK10, R03AK11 |
| Mometasone | RMPS | ATC: R03BA07 |
| Ciclesonide | RMPS | ATC: R03BA08 |
| | | |
| **Non-ICS inhalers:** | | |
| β2-receptor agonists | RMPS | ATC: R03ACxx |
| Muscarinic receptor antagonists | RMPS | ATC: R03BBxx |
| β2-receptor agonists combined with muscarinic receptor antagonists | RMPS | ATC: R03AL01, R03AL02, R03AL03, R03AL04, R03AL05, R03AL06, R03AL07 |
| | | |
| Per oral pharmaceuticals for asthma/COPD | | |
| Corticosteroids | RMPS | ATC: H02AB04, H02AB06, H02AB07 |
| Theophylline | RMPS | ATC: R03DA |
| Montelukast | RMPS | ATC: R03DC |
| *Covariates* | | |
| Age | CRS | CRS number |
| Sex | CRS | CRS number |
| Atrial fibrillation/flutter | DNPR | I48 |
| Asthma | DNPR | J45-J46 |
| Chronic pulmonary disease (incl. COPD) | DNPR | J40–J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3 |
| Dementia | DNPR | F00–F03, F05.1, G30 |
| Heart failure | DNPR | I50x, I11.0, I13.0, I13.2 |
| Hypertension | RMPS | Utilized validated approach by as validated by JB Olesen et al, BMJ 2011 defined by combination treatment with at least two of the following classes of antihypertensive drugs: α adrenergic blockers (C02A, C02B, C02C), non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, |

| | | |
|---|---|---|
| | | C09BA, C09DA, C09XA52), vasodilators (C02DB, C02DD, C02DG, C04, C05), β blockers (C07), calcium channel blockers (C07F, C08, C09BB, C09DB), and renin-angiotensin system inhibitors (C09). |
| Inflammatory bowel disease | DNPR | K50x, K51x |
| Malignancy | DNPR | C00–C75 |
| Renal failure | DNPR | I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61, N30.0 |
| Charlson Comorbidity index score | DNPR | Use of SDU OPEN method. |
| ≥ 5 asthma or COPD exacerbations within the latest five years | DNPR | J44.0, J44.1, J46 five times or more within the latest five years. |
| Number of filled prescription within 90 days | RMPS | Number filled prescriptions by ATC codes registered. |
| *Outcomes* | | |
| Mechanical ventilation | DNPR | BGDA0 |
| Death | CDR | Date noted in register |

*Data sources: Register of Medicinal Product Statistics (RPMS), Civil Registration System (CRS), Danish National Patient Register (DNPR), Cause of Death Register (CDR).