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Early View

Original article

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Dynamics in diagnoses and pharmacotherapy before and after diagnosing idiopathic pulmonary fibrosis

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Running title

Diagnoses and pharmacotherapy in IPF

Take home message

Among IPF patients, an increased drug use was observed for diagnoses with symptoms overlapping those of IPF. Particularly this was observed during the last six months before an IPF diagnosis. This emphasizes the need for an increased IPF awareness.

ABSTRACT

Background

Idiopathic pulmonary fibrosis (IPF) is a well-characterised interstitial lung disease (ILD). Typically, the IPF diagnosis is delayed due to non-specific symptoms, but can also be delayed due to treatment attempts on false indication, or due to treatment targeting common comorbidities. This observational study aimed to assess the dynamics in the medication and diagnosis patterns in the period before and after an IPF diagnosis.

Methods

We identified all Danish patients with IPF during 2002 to 2017. We evaluated new and ongoing drug treatments and incident diagnoses 36 months before, and twelve months after an IPF diagnosis by use of Danish nationwide registries. To aid interpretation, ten random controls were recruited for each case.

Results

A total of 650 IPF patients were identified (median age 73 years [IQR 65-78], 70.3% males). Prior to the IPF diagnosis, the most prevalent diagnoses were dyspnea and non-IPF ILDs. For drug use, IPF patients had higher initiation rates for antibiotics, oral corticosteroids and mucolytics. In terms of drug volume, IPF patients used more respiratory drugs, antibiotics, immunosuppressants, corticosteroids, proton pump inhibitors, benzodiazepines and opium alkaloids within the six months preceding their

IPF diagnosis, compared to the controls. Overall drug use decreased after an IPF diagnosis, mainly due to a reduced glucocorticoid and cardiovascular drug use.

Conclusion

Among IPF patients, an increased drug use was observed for diagnoses with symptoms overlapping those of IPF, particularly this was observed during the last six months before an IPF diagnosis. This emphasizes the need for an increased IPF awareness.

INTRODUCTION

Among the interstitial lung diseases (ILD), idiopathic pulmonary fibrosis (IPF) differs from all other ILD subtypes by its progressive pulmonary fibrosis and worse prognosis [1–3]. Except for two highly targeted antifibrotic drugs, pirfenidone and nintedanib, no pharmacological treatment has proven effective to IPF [2, 4, 5]. Usually the early symptoms of IPF progress over months to years with a diagnostic delay of up to 2-5 years [6–8], as IPF often is confused with more common diagnoses such as heart failure, gastroesophageal reflux, or chronic obstructive pulmonary disease (COPD) [2, 9]. Treatment attempts for conditions similar to IPF are an independent risk factor for a delayed IPF diagnosis [10]. Incorrect initial diagnoses and additional diagnostic tests uncovering other diseases may lead to an increased drug use among IPF patients.

When the IPF diagnosis is established at a specialist center, medication prescribed on a false indication should be discontinued [11]. On the other hand, IPF is associated with comorbidities such as arrhythmia, chronic heart failure, pulmonary hypertension, thromboembolic disease, lung cancer, obstructive sleep apnea, osteoporosis, infections

and reflux disease [12, 13]. Therefore, patients diagnosed with IPF might be continuously treated for their comorbidities [14]. No published study has systematically appraised the dynamics in medication and diagnostic profile in patients before and after an IPF diagnosis. In other types of diseases, a pharmacoepidemiological approach has successfully been used to assess such changes [15].

In this study, we aimed at assessing changes in the medication and diagnosis patterns in the period before and after an IPF diagnosis is established.

METHODS AND MATERIALS

Design

In this descriptive longitudinal study, we identified all incident cases of IPF in Denmark during the period 2002 - 2017. We used the Danish nationwide health and prescription registries to describe new drug treatments and diagnoses in the period leading up to and following the IPF diagnosis.

Data sources

Danish National Health Service provides universal tax-supported health care for all Danish residents, thereby allowing truly population-based register studies [16]. We retrieved data from three Danish nationwide administrative registers that cover close to 100% of the Danish population: Danish Civil Registration System [16], The Danish National Patient Register (DNPR) [17], and the Danish Register of Medicinal Product Statistics (RMPS) [18].

The Danish Civil Person Register contains data on vital status (date of birth and death) and migrations to and from Denmark [16].

The DNPR holds information for all contacts to Danish hospitals since 1977 [17]. From 1995, outpatient clinic diagnoses, and emergency department contacts are included in the DNPR. Diagnoses are recorded according to International Classification of Diseases (ICD), 8th revision from 1977 to 1993 and 10th revision since 1994. The Danish National Health Board has modified the ICD10, using minor extensions of the codes where appropriate. Importantly, IPF has its own extended Danish ICD10 code J84.1A.

RMPS holds information on all prescribed drugs dispensed from public pharmacies since 1995 [18]. Prescription records data include the Central Person Registry number, date of dispensing, the substance, brand name, and quantity. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) code and the quantity is expressed by the use of the defined daily dose (DDD) [17, 18].

Study population

We identified all incident cases of IPF (ICD-10 [DK]: J84.1A) in Denmark between January 1, 2002 and December 31, 2017. We excluded subjects who had less than three years available look-back period before their diagnosis. Ten control subjects were matched to each IPF case based on age and sex, as an aid when interpreting our findings for IPF. The controls were assigned an index date identical to the diagnosis date of their corresponding IPF case. The same exclusion criteria were applied to IPF cases and controls.

Description of drug use

Prescription drugs were categorized according to the fourth level of the ATC classification (e.g. A02BC, proton pump inhibitors) to achieve a suitable granularity of prescription data [19].

We analyzed drug use in two ways: In the first analysis we defined incident use of drugs as the first prescription fill for a drug in the six months before an IPF diagnosis. On-going drug use was defined as any occurrence of a prescription for a drug in the same period with continuously prescription refilling. Discontinuation of a drug was defined as not refilling a prescription within six months after the IPF diagnosis. We tabulated the proportion of incident, on-going and discontinuing users for the most used drug classes among cases. For each drug, the median and interquartile range (IQR) of time between first prescription and IPF diagnosis was determined.

In the second analysis, we charted the number of different predefined drugs filled in three-month intervals starting 36 months before the IPF diagnosis date and ending 12 months after. In this analysis, drugs were broadly categorized into six categories: 1) respiratory drugs (ATC: R03), 2) immunosuppressants (ATC: L04), 3) antibiotics (ATC: J01), 4) glucocorticoids (ATC: H02BA), 5) cardiovascular drugs (ATC: B01AA and C), or 6) others. In addition, we calculated the cumulative number of DDDs dispensed in each three-month interval, while using the same broad categories. IPF cases were assumed to have a high mortality after their diagnosis were received [2, 20]. Therefore, in the calculations for a given three-month interval, we included only the subjects who survived throughout the interval.

Description of discharge diagnoses

In-patient and out-patient secondary care diagnoses were obtained from the DNPR. Only the first occurrence of a given diagnosis for a patient was considered, and to ensure a reasonable granularity, ICD10 diagnosis codes were grouped according to the third digit. The occurrence of new diagnoses in the three years prior to an IPF diagnosis was described, and the median time from the first non-IPF diagnosis to the IPF diagnosis and IQR were calculated. Among the cases, we described the prevalent diagnoses and the disease categories included in the Charlson comorbidity index and certain preselected disease categories relevant to the current study aim [21]. This categorization is presented as table 1 in the supplementary data material. To facilitate interpretation, comorbid diagnoses were described for both cases and controls.

In 2011, the clinical guideline for IPF was updated and issued [22], and the first antifibrotic drug pirfenidone was introduced. To reflect a possible change in IPF management, we carried out all analyses separately for the period 2002-2011 and 2012-2017, as well as for the entire study period. The interval for description of drug use was also extended to include three years prior to the IPF diagnosis.

Statistics and ethics

Data were analyzed using the framework of the Danish Health Data Board, using Stata version 15.1. Anonymized individual-level data were available to researchers. For confidentiality reasons, reporting exact counts below 5 is not permitted. Categorical data are presented as numbers and prevalences. Continuous variables are presented as medians with interquartile ranges (IQR).

According to Danish law, approval from an ethics committee is not required for pure register-based studies [23].

RESULTS

We identified 743 eligible IPF cases. Of these, 93 cases were diagnosed prior to 2002 or had less than three years of enrolment in the database, leaving a total of 650 IPF patients and 6,500 population controls (figure 1). Among incident IPF patients, the median age was 73 years (IQR 65-78 years), and 70.3% (n=457) were males (table 1). Cardiovascular diseases occurred more prevalent among IPF patients compared to controls, but cancer (including lymphoma and leukemia) occurred with almost similar prevalence among IPF patients and controls.

Within the study period, 464 IPF cases died (71.4%) compared to 1,159 controls (17.8%). The median survival time among IPF cases was 29.1 months (IQR: 8.1-65.1 months) within the entire study period 2002-2017 compared to 6.4 years (IQR: 5.5-8.2 years) for controls. Sensitivity analyses stratified to period 2002-2010 and 2011-2017 appear in the in the supplementary data material.

Diagnoses prior to IPF

Among the pre-selected disease categories prior to IPF diagnosis, the most prevalent diagnoses were dyspnea, non-IPF idiopathic interstitial pneumonias (IIPs) and pneumonia (14.0%, 13.2%, and 8.6%, respectively). All of these had a prevalence below 1% in the control group. Among IPF patients, 4.3% (n=28) were given a COPD

diagnosis during the period prior to the IPF diagnosis, compared to 0.5% (n=31) among the population controls (table 2).

From first occurrence for any of one the pre-selected disease categories, the median time was 2.3 months (IQR 1.9-2.4 months). Pulmonary hypertension appeared with the shortest median time up to the IPF diagnosis (median 1.7 months, IQR 1.0-4.2 months) (table 2).

The most prevalent ICD-10 diagnosis prior to the IPF diagnosis was “other interstitial lung disease than IPF” (J84 excluding J84.1A) (45.8%, n=298), followed by dyspnea (14.3%, n=93), and respiratory failure (8.9%, n=58). Of the specific diagnoses, only atrial fibrillation and flutter and essential (primary) hypertension reached prevalence above 1% among controls (table 3).

Pre- and postdiagnosis - Use of prescription drugs

For several major drug classes, the IPF cases had a higher proportion of incident users within six months prior to IPF diagnosis compared to the controls. The largest absolute differences in new drug use proportions between IPF patients and controls was observed for combinations of penicillin and beta-lactamase inhibitors, systemic glucocorticoids, and mucolytics (9.7% vs. 1.2%, 8.6% vs. 0.8%, and 6.5% vs. 0.3%), respectively (table 4).

A detailed overview of discontinuation rates of drugs after an IPF diagnosis is also presented in table 4. Of note, only 21.6% of IPF patients discontinued systemic glucocorticoids compared to 32.4% of controls, and only 18.8% of IPF patients discontinued mucolytics compared to 45.7% of the controls. The opposite was observed

for drugs for inhalation therapy (ATC-codes R03BB and R03BA) where 30.2 and 50.0% IPF patients discontinued inhalation therapy vs. 9.3 and 19.0% among controls.

Among IPF patients, we observed a high volume consumed for respiratory drugs, antibiotics, immunosuppressants, in particular systemic glucocorticoids, and the category of other drugs (e.g. proton pump inhibitors, benzodiazepines, and opium alkaloids) during the 12 month period before the IPF diagnosis (figure 2). These trends were not observed among controls.

DISCUSSION

This 16-year nationwide longitudinal observational study aimed to investigate dynamics in diagnoses and use of pharmacotherapy up to and after an established IPF diagnosis. Surprisingly, we found that only to a limited extent IPF patients had been given diagnoses as COPD (4.3%) or heart failure (1.8%) before IPF. Given their low prevalence in the analyses, these diagnoses may not necessarily be incorrect, but actually represent true co-morbid conditions to IPF due to common shared risk factors, i.e. tobacco use. Instead, non-specific diagnoses were used in disease categories as dyspnea (14.0%), broadly defined ILDs (13.2%), and pneumonia (8.6%). We interpret this as an indication of, that before the IPF diagnosis is established, there is a high level of suspicion among secondary care physicians that the patient may have an ILD, which prompt referrals to IPF specialist centers with access to multidisciplinary discussions. This may explain the low median time from first occurring respiratory diagnosis to IPF diagnosis of 2.3 months (table 3). Though other studies have found cough and malaise as early symptoms associated with IPF [24, 25] these appeared rarely in our register-

based population with prevalences of 3.1% and 1.8%, respectively (table 3). These differences are very likely explained by methodological differences in the selection of IPF populations, but also that ICD-10 coding in Denmark primarily refers to diagnoses and more rarely symptoms. Thereby, more non-specific respiratory symptoms are not systematically coded.

For prescription drug use, we found almost the same general level of drug use among cases and controls 36 months prior to IPF diagnosis. For IPF patients the drug use built up slowly six months prior to the IPF diagnosis and levelled thereafter. This may be explained by treatment attempts for differential diagnoses to IPF, especially the increased use of immunosuppressants and systemic glucocorticoids [10]. Inhaled bronchodilation therapy is not recommended as part of pharmacological IPF treatment. Furthermore, since the 2011 guideline on IPF there has been a strong recommendation against monotherapy with systemic glucocorticoids [22]. Surprisingly, a substantial proportion of the inhaled respiratory drugs, including inhaled corticosteroids, as well as systemic glucocorticoids continued after the IPF diagnosis. This may be due to pulmonary specialists not dedicating enough attention to deprescribing, due to deprescribing intention which is not properly communicated to primary care, due to slow tapering of systemic corticosteroid therapy, due to bronchodilators being used as soothing drugs, or due to a genuine continued need for these drugs, e.g. systemic glucocorticoids for IPF exacerbations [2, 26]. From the register data available in this study, it is difficult to identify the exact causes.

There are only few previous studies describing dynamics in diagnoses and drug use before and after an IPF diagnosis. To some extent, our study findings concur with previous studies with regard to specific symptom presentation, and age- and gender distribution [9, 11-13]. Guenther et al. found dyspnea to be the most dominant symptom (90.1%) in an IPF patient cohort, a result that supports our findings, based on ICD10 codes, which are some of the predominant pre-IPF diagnoses [13]. On the other hand, some of our findings are atypical for this patient population in relation to previous IPF cohort observations. Comorbidity is frequent in IPF patients and has been reported to occur with a mean number of 2.68 comorbidities per patient [12], and the most prevalent comorbidity disease categories to be ischemic heart- and cardiovascular diseases [9, 12, 13]. However, these observations are not consistent with our findings, where selected cardiovascular diseases occurred only in less than 5% of the IPF patients, not including atrial flutter. This discrepancy may be attributable to the difference in use of data from nationwide administrative registers, and the use of registry data obtained from clinical IPF databases based on self-reported information [12, 13] and electronic medical records [10]. The same tendency also applies to IPF medication, exemplified by findings in a German study in which drugs related to heart failure/arrhythmia (30.6%) and cardiovascular disease (52.6%) dominated, and occurred with a higher proportion compared to our results [14]. This difference is likely due to analyses based on insurance claims data among ILD patients in which IPF patients were only a subset [13]. The observed overall median survival of 29 months from our cohort resembles findings from other studies [20, 27].

The first international consensus statement on IPF was published in 2000 [28], and followed up by evidence based clinical guidelines on diagnosis and management in

2011 [22], 2015 [29], and 2018 [2]. During this 18-year period, the knowledge and understanding of IPF has increased and the pharmacological management of IPF has changed markedly. In the 2000 statement, systemic glucocorticoids were regarded as the cornerstone treatment in IPF, either as monotherapy or in combination with immunosuppressants. In the 2011 guideline, neither systemic glucocorticoid monotherapy, azathioprine nor N-acetylcysteine were recommended, and a minority of IPF patients were expected to benefit from a combination of all three drugs or pirfenidone [22]. However, this three-drug combination proved to confer an increased risk of death and hospitalization [30] and was removed from the 2015 guideline [29] in which the antifibrotic drugs, i.e. pirfenidone and nintedanib, were recommended as first choice IPF treatments [4, 5]. The only drugs, mentioned in both the 2000 and 2011 guidelines, were systemic glucocorticoids and to some extent N-acetylcystein, a fact which partly may explain our observed findings regarding discontinuations for these drug groups. When splitting the observation periods into 2002-2010 and 2011-2017 we observed an ongoing systemic glucocorticoid use among 40% and 21.5% of the IPF cases, which is also previously observed (appendix table 6 and 7) [13]. The decrease in post- diagnosis use of systemic glucocorticoids occurred when guidelines were changed to incorporate antifibrotic treatment with pirfenidone and nintedanib [22, 28]. Despite the apparent reduction in systemic glucocorticoid use between the two periods, a substantial use persisted in the 2011-2017 period, which is difficult to explain. Among the possible explanations are systemic glucocorticoid treatments of exacerbations or palliative use in patients with terminal IPF.

The median time from first occurrence of all pre-selected disease categories was around 2.3 months. This period may indirectly reflect the time span from when the tentative

diagnosis was settled at referral hospitals to the decisive IPF diagnosis was made and coded at the tertiary ILD referral centers in concordance with other observations [6].

The main strength of this study is the population-based approach covering an entire nation during a 16-year observation period by linkage of data from three highly valid national registries. The linkage made it possible to perform an individual-based longitudinal study on diagnoses and drug use prior to and after an IPF diagnosis. As proxies for drug utilization, we used prescription data from DNPR which possess high data completeness and thereby minimize the risk of information bias. Another strength is the inclusion of a non-diseased control group, which provide a reference for co-prescribed medication, drug persistence, and the observed trends in diagnosing and prescribing on a given date. The main limitation of our study is that all IPF diagnoses (ICD10 code J84.1A) is retrieved from DNPR, as the validity of the IPF diagnosis code has not been formally evaluated as for other pulmonary diagnoses [31]. With updated IPF guidelines, it also became evident that referral to tertiary ILD centers with access to multidisciplinary discussions improved the diagnostic confidence concurrent with a reduced diagnostic latency and mortality [6, 32, 33]. By use of this guideline recommended multidisciplinary discussion approach from 2011 and onwards, we expect that the ICD10-codes registered during the observation period 2011-2017 actually represent true IPF diagnoses [34]. Finally, though the number of IPF cases are comparable to IPF cohorts in previous register-based IPF studies [9, 12–14], the small patient number, however, may limit the statistical precision.

The results from this study may indirectly support IPF to be underdiagnosed as a consequence of being mistaken for other respiratory diseases [6, 10]. We uncovered that an increasing drug use for especially systemic glucocorticoids, proton pump inhibitors, benzodiazepines, and opium alkaloids, and inhalation medication, could be an independent risk factor for IPF, but also for its diagnostic latency [6]. This latter issue could be revealed in future studies looking into which patients, general practitioners, and physicians at referral hospitals, who were exposed to an increased knowledge on IPF risk factors.

In summary, the analyses from this nationwide study indicate that, among IPF patients, an increased drug use for diagnoses with symptoms like IPF exists, especially six months prior to IPF diagnosis. The increased drug use probably reflects the evident latency in IPF diagnostics, it emphasizes the need for an improved knowledge sharing and it prompts an increased focus on patients being referred to a specialist IPF center.

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AUTHOR CONTRIBUTION

JRD and DPH developed the concept, and designed the study together with LCL, CBL, and JH. JH collected data. LCL and DPH performed statistical analyses. JRD, LCL, CBL, JH, and DPH helped with data interpretation, and provided input for and critical revision of the manuscript. All authors had full access to all data and statistical reports. JRD drafted the initial manuscript. All authors reviewed and edited drafts and approved the final version for submission. JRD is the guarantor.

CONFLICT OF INTERESTS

JRD reports grants, personal fees and non-financial support from Roche and Boehringer Ingelheim, outside the submitted work. LCL reports participation in research projects outside the submitted work funded by Menarini Pharmaceutical and LEO Pharma, with funds paid to the institution where he was employed. CBL, JH and DPH declare no conflicts of interest.

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TABLES

Table 1

Baseline characteristics including comorbid conditions among patients with a diagnosis of idiopathic pulmonary fibrosis and sex- and age-matched controls.

	IPF-cases	Controls
	N=650	N=6,500
Age (IQR)	73 (65-78)	73 (65-78)
Male (%)	457 (70.3%)	4,570 (70.3%)
Charlson Comorbidity Index*		
0	268 (41.2%)	3,428 (52.7%)
1	129 (19.8%)	1,053 (16.2%)
2	105 (16.2%)	1,015 (15.6%)
3+	148 (22.8%)	1,004 (15.4%)
Myocardial infarction	79 (12.2%)	505 (7.9%)
Heart failure	90 (13.8%)	370 (5.8%)
Peripheral vascular disease	69 (10.6%)	444 (7.0%)
Cerebrovascular disease	68 (10.5%)	755 (11.9%)
Dementia	11 (1.7%)	136 (2.1%)
Rheumatic disease	74 (11.4%)	246 (3.9%)
Ulcus	47 (7.2%)	353 (5.6%)
Liver disease (mild)	16 (2.5%)	76 (1.2%)
Diabetes (uncompl.)	82 (12.6%)	476 (7.5%)
Hemiplegia	0 (0.0%)	18 (0.3%)
Kidney disease	30 (4.6%)	211 (3.3%)
Diabetes (compl.)	39 (6.0%)	236 (3.7%)
Leukemia	5 (0.8%)	32 (0.5%)
Lymphoma	9 (1.4%)	62 (1.0%)
Cancer (localised)	106 (16.3%)	1,231 (19.4%)
Liver disease (severe)	6 (0.9%)	15 (0.2%)
Cancer (non-localised)	8 (1.2%)	75 (1.2%)
HIV and AIDS	0 (0.0%)	0 (0.0%)

*Categorised according to number of comorbidies

AIDS = acquired immune deficiency syndrome

HIV = human immunodeficiency virus

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 2

Frequency of ten pre-specified disease categories among patients diagnosed with idiopathic pulmonary fibrosis (IPF) and sex- and age-matched population controls.

	IPF-cases			Controls		
Disease category	N	(%)	First occurrence relative to IPF diagnosis, months median (IQR)	N	(%)	First occurrence relative to index date, months median (IQR)
Dyspnea	91	(14.0)	2.2 (0.9-3.7)	28	(0.4)	3.6 (2.7-4.4)
Non-IPF IIP	86	(13.2)	2.7 (1.0-4.3)	n < 10	n < 10	n < 10
Pneumonia	56	(8.6)	2.0 (0.8-3.8)	42	(0.6)	2.9 (1.5-4.1
COPD	28	(4.3)	1.9 (0.9-2.7)	31	(0.5)	2.8 (1.7-4.2)
Cough	19	(2.9)	2.8 (1.7-4.0)	n < 10	n < 10	n < 10
Pulmonary hypertension	17	(2.6)	1.7 (1.0-4.2)	n < 10	n < 10	n < 10
Osteoporosis	17	(2.6)	2.4 (1.6-4.1)	25	(0.4)	2.5 (1.4-4.5)
Heart failure	17	(2.6)	1.8 (0.5-3.9)	35	(0.5)	2.7 (1.0-3.8)
Cardiac valve disease	11	(1.7)	2.6 (2.2-3.2)	24	(0.4)	2.9 (1.6-4.1)
Diabetes	11	(1.7)	3.1 (1.9-4.3)	25	(0.4)	3.3 (2.2-4.6)

COPD = chronic obstructiove pulmonary disease

IIP = idiopathic interstial pneumonias

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 3

The most prevalent diagnoses among patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) established within 3 years prior to the IPF diagnosis, and a randomly assigned index date among controls.

Diagnosis	ICD-10	N (%)	First occurrence relative to IPF diagnosis, months median (IQR)	N (%)	First occurrence relative to index date, months median (IQR)
Other interstitial pulmonary diseases other than J84.1A	J84	298 (45.8)	2.3 (1.0-3.9)	n<10	n<10
Abnormalities of breathing	R06	93 (14.3)	2.2 (0.9-3.7)	32 (0.5)	3.6(2.2-4.4)
Respiratory failure, not elsewhere classified	J96	58 (8.9)	2.3 (0.9-4.5)	18 (0.3)	3.8(1.9-5.0)
Pneumonia, organism unspecified	J18	51 (7.8)	2.2 (0.9-4.1)	32 (0.5)	3.2(2.0-4.8)
Abnormal findings on diagnostic imaging of lung	R91	39 (6.0)	2.2 (1.1-4.0)	n<10	n<10
Atrial fibrillation and flutter	I48	37 (5.7)	1.9 (1.2-3.8)	69 (1.1)	3.1(1.7-4.8)
Other chronic obstructive pulmonary disease	J44	33 (5.1)	1.8 (0.5-3.0)	47 (0.7)	3.2(1.7-4.3)
Bacterial pneumonia, not elsewhere classified	J15	24 (3.7)	2.6 (1.2-3.9)	22 (0.3)	2.8(1.2-3.4)
Heart failure	I50	23 (3.5)	1.6 (0.5-4.7)	44 (0.7)	2.7(1.4-4.4)
Cough	R05	20 (3.1)	2.8 (1.8-3.9)	n<10	n<10
Other pulmonary heart diseases	I27	19 (2.9)	1.9 (1.0-4.2)	n<10	n<10
Chronic ischaemic heart disease	I25	18 (2.8)	2.2 (0.5-3.4)	46 (0.7)	3.0(1.8-4.2)
Osteoporosis without pathological fracture	M81	17 (2.6)	2.5 (1.6-4.1)	22 (0.3)	2.5(1.4-3.8)
Non-insulin-dependent diabetes mellitus	E11	16 (2.5)	3.1 (1.8-4.4)	46 (0.7)	3.3(1.9-4.6)
Nonrheumatic aortic valve disorders	I35	15 (2.3)	2.5 (2.1-3.2)	26 (0.4)	3.2(1.6-4.2)
Essential (primary) hypertension	I10	15 (2.3)	2.7 (0.5-4.0)	73 (1.1)	3.1(1.9-4.3)
Angina pectoris	I20	15 (2.3)	2.8 (2.3-4.7)	23 (0.4)	3.1(2.0-4.7)
Senile cataract	H25	14 (2.2)	3.9 (1.5-4.2)	61 (0.9)	2.9(1.3-4.4)
Other respiratory disorders	J98	13 (2.0)	1.7 (0.7-3.6)	n<10	n<10
Haemorrhage from respiratory passages	R04	13 (2.0)	2.6 (0.3-4.2)	11 (0.2)	3.2(2.1-4.0)
Complications and ill-defined descriptions of heart disease	I51	12 (1.8)	2.0 (0.0-4.6)	n<10	n<10
Malaise and fatigue	R53	12 (1.8)	2.3 (0.6-3.4)	22 (0.3)	2.2(1.1-3.2)
Malignant neoplasm of bronchus and lung	C34	10 (1.5)	2.9 (1.7-4.2)	18 (0.3)	2.3(0.8-4.6)

ICD10 = Corresponding International Classification of Diseases, 10th revision codes

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 4

Dynamics of the most prevalent drug classes used by newly diagnosed patients with idiopathic pulmonary fibrosis (IPF) and their matched controls.

		IPF-cases			Controls		
Drug class, name	ATC	New users before IPF*, n (%)	Ongoing users before IPF†, n (%)	Discontinued after IPF‡, n (%)	New users before index date*	Ongoing users before index date†, n (%)	Discontinued after index date‡, n (%)
Combinations of penicillin, incl. beta-lactamase inhibitors	J01CR	63 (9.7)	127 (19.5)	32/86 (37.2)	76 (1.2)	158 (2.4)	94/163 (63.1)
Glucocorticoids (systemic)	H02AB	56 (8.6)	223 (34.3)	33/153 (21.6)	50 (0.8)	277 (4.3)	85/262 (32.4)
Mucolytics	R05CB	42 (6.5)	105 (16.2)	15/80 (18.8)	17 (0.3)	36 (0.6)	n<10
Proton pump inhibitors	A02BC	38 (5.8)	242 (37.2)	18/193 (9.3)	102 (1.6)	1016 (15.6)	140/993 (14.1)
Selective beta-2-adrenoreceptor agonists	R03AC	36 (5.5)	124 (19.1)	40/97 (41.2)	35 (0.5)	341 (5.2)	75/334 (22.5)
Loop diuretics	C03CA	31 (4.8)	152 (23.4)	24/108 (22.2)	58 (0.9)	543 (8.4)	48/522 (9.2)
Potassium	A12BA	28 (4.3)	123 (18.9)	18/85 (21.2)	71 (1.1)	506 (7.8)	53/483 (11.0)
Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK	24 (3.7)	90 (13.8)	27/71 (38.0)	21 (0.3)	295 (4.5)	21/287 (7.3)
Macrolides	J01FA	23 (3.5)	122 (18.8)	56/92 (60.9)	39 (0.6)	216 (3.3)	147/208 (70.7)
Paracetamol	N02BE	23 (3.5)	193 (29.7)	21/144 (14.6)	155 (2.4)	1261 (19.4)	232/1219 (19.0)
Other immunosuppressants	L04AX	22 (3.4)	71 (10.9)	22/48 (45.8)	n<10	62 (1.0)	n<10
Fluoroquinolones	J01MA	21 (3.2)	45 (6.9)	16/27 (59.3)	48 (0.7)	98 (1.5)	n<10
Natural opium alkaloids	N02AA	20 (3.1)	49 (7.5)	n<10	64 (1.0)	196 (3.0)	57/187 (30.5)
Inhaled anticholinergics	R03BB	20 (3.1)	75 (11.5)	16/53 (30.2)	27 (0.4)	224 (3.4)	20/215 (9.3)
Penicillins with extended spectrum	J01CA	18 (2.8)	76 (11.7)	26/54 (48.1)	58 (0.9)	361 (5.6)	196/345 (56.8)
Osmotically acting laxatives	A06AD	17 (2.6)	23 (3.5)	n<10	43 (0.7)	143 (2.2)	40/123 (32.5)
Adrenergics in combination with anticholinergics	R03AL	16 (2.5)	34 (5.2)	n<10	22 (0.3)	68 (1.0)	14/59 (23.7)
Opium alkaloids and derivatives	R05DA	15 (2.3)	47 (7.2)	19/36 (52.8)	31 (0.5)	142 (2.2)	n<10
Bisphosphonates	M05BA	15 (2.3)	84 (12.9)	n<10	19 (0.3)	237 (3.6)	n<10
Other opioids	N02AX	14 (2.2)	71 (10.9)	18/54 (33.3)	75 (1.2)	422 (6.5)	153/409 (37.4)
Benzodiazepine related drugs	N05CF	14 (2.2)	73 (11.2)	13/51 (25.5)	36 (0.6)	386 (5.9)	76/375 (20.3)
Selective serotonin reuptake inhibitors	N06AB	13 (2.0)	59 (9.1)	n<10	22 (0.3)	388 (6.0)	46/376 (12.2)
Aldosterone antagonists	C03DA	13 (2.0)	38 (5.8)	n<10	15 (0.2)	157 (2.4)	n<10
Platelet aggregation inhibitors	B01AC	12 (1.8)	224 (34.5)	15/168 (8.9)	62 (1.0)	1714 (26.4)	79/1675 (4.7)
Propulsives	A03FA	12 (1.8)	24 (3.7)	n<10	18 (0.3)	57 (0.9)	30/50 (60.0)
Statins	C10AA	12 (1.8)	235 (36.2)	13/182 (7.1)	68 (1.0)	2018 (31.0)	87/1991 (4.4)
Contact laxatives	A06AB	11 (1.7)	12 (1.8)	n<10	38 (0.6)	83 (1.3)	26/74 (35.1)
Thiazides and potassium in combination	C03AB	11 (1.7)	71 (10.9)	13/54 (24.1)	36 (0.6)	765 (11.8)	85/756 (11.2)
Corticosteroids and antiinfectives in combination	S01CA	10 (1.5)	13 (2.0)	n<10	66 (1.0)	131 (2.0)	101/131 (77.1)
Organic nitrates	C01DA	10 (1.5)	48 (7.4)	10/31 (32.3)	25 (0.4)	192 (3.0)	49/185 (26.5)

Opium cough suppressants and expectorants	R05FA	10 (1.5)	28 (4.3)	16/22 (72.7)	23 (0.4)	84 (1.3)	61/84 (72.6)
Systemic triazole antifungals	J02AC	10 (1.5)	23 (3.5)	n<10	20 (0.3)	51 (0.8)	n<10
Vitamin K antagonists	B01AA	10 (1.5)	46 (7.1)	n<10	27 (0.4)	378 (5.8)	19/370 (5.1)
Imidazole and triazole derivatives	D01AC	10 (1.5)	36 (5.5)	23/29 (79.3)	60 (0.9)	228 (3.5)	129/218 (59.2)
Glucocorticoids (inhaled)	R03BA	10 (1.5)	31 (4.8)	13/26 (50.0)	16 (0.2)	158 (2.4)	30/158 (19.0)

*) New use is defined as first-ever occurrence of the drug class within six months before the index date / diagnosis date

†) Ongoing use is defined as any occurrence of the drug class within the six months before the index date / diagnosis date

‡) Discontinuation is defined by the absence of any prescriptions on the drug class after the index date / diagnosis date compared to ongoing use. The denominator represents ongoing users who also have a six-month follow-up after the IPF diagnosis meaning that the denominator varies according to each drug.

ATC = anatomical therapeutic chemical classification

IPF = idiopathic pulmonary fibrosis

FIGURE LEGENDS

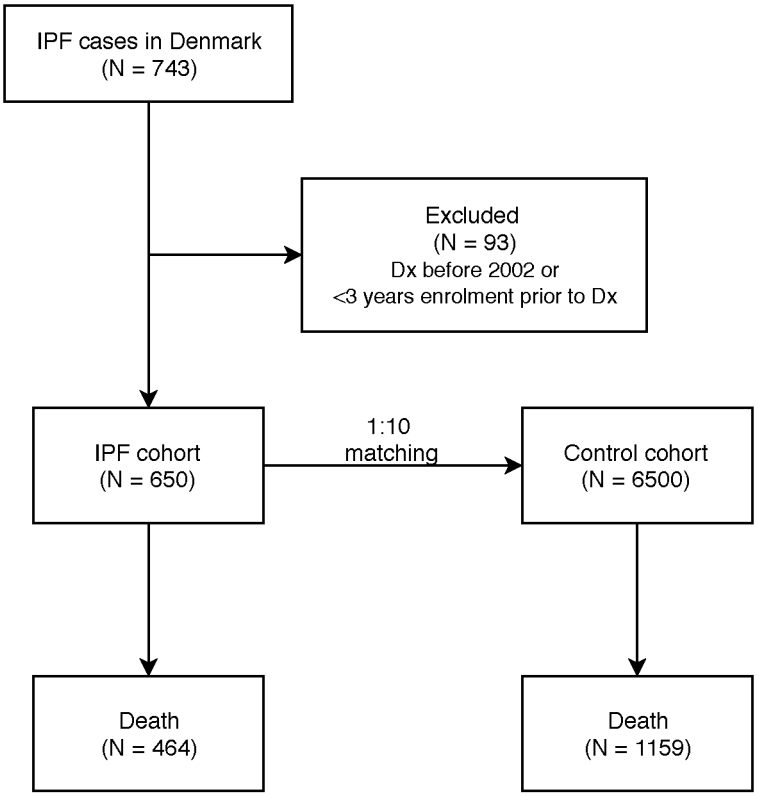
Figure 1

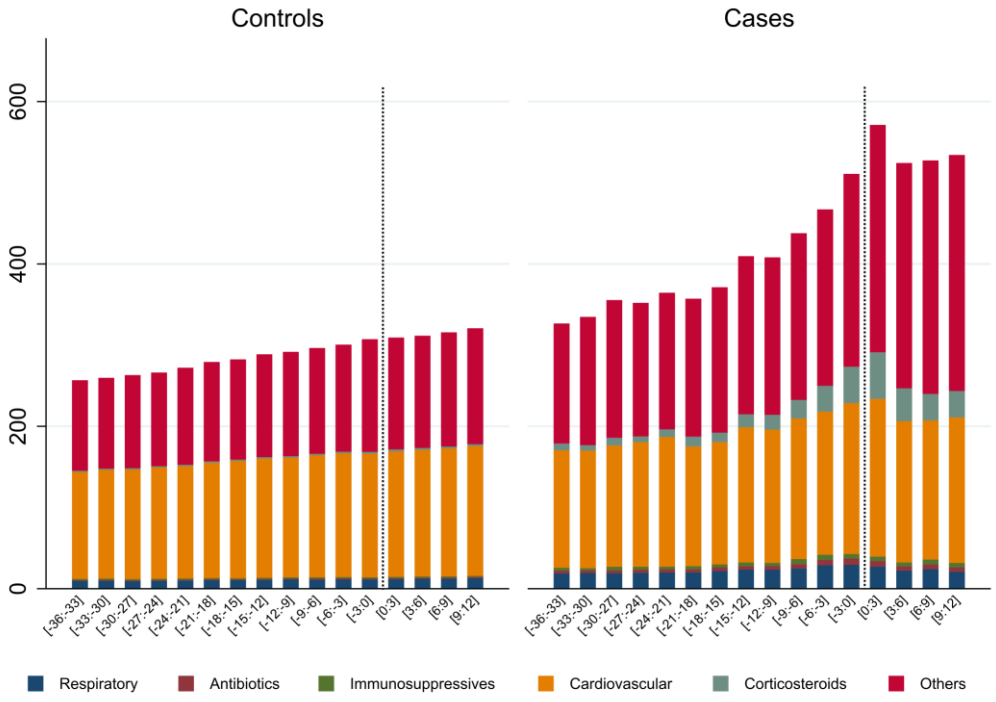
Study flow chart.

Dx = diagnosis, IPF = idiopathic pulmonary fibrosis.

Figure 2

Average number of defined daily doses used within three-month periods before and after the diagnosis date for cases with idiopathic pulmonary fibrosis and before and after the index date for their matched controls.


IPF cases in Denmark
(N = 743)
Excluded
(N = 93)
Dx before 2002 or
<3 years enrolment prior to Dx
IPF cohort
(N = 650)
1:10
matching
Control cohort
(N = 6500)
Death
(N = 464)
Death
(N = 1159)


Controls
Cases
600
400
200
0
[-36:-33]
[-33:-30]
[-30:-27]
[-27:-24]
[-24:-21]
[-21:-18]
[-18:-15]
[-15:-12]
[-12:-9]
[-9:-6]
[-6:-3]
[-3:0]
[0:3]
[3:6]
[6:9]
[9:12]
Respiratory
Antibiotics
Immunosuppressives
Cardiovascular
Corticosteroids
Others

SUPPLEMENTARY DATA

Table 1

ICD10 codes defining diseases

Disease	Corresponding International Classification of Diseases, 10th revision codes
Cardiovascular diseases	
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46; G81; G82
Mitral and/or aortic disease	I05-I06; I08; I34; I35
Pulmonary heart disease	I27
Thromboembolic disease	I26; I269; I801; I802; I803
Hypertension	I10-I15
Dementia	F00-F03; F051; G30
Pulmonary diseases	
Pneumonia	J12-J18; A481; A709
COPD	J40-J44 excluding J448B
Asthma	J448B; J45
Non-IPF-IIP	J841 excluding J841A
Bronchiectases	J47
Dyspnea	R060
Cough	R05
Other diseases	
Connective tissue disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	K221; K25-K28
Liver disease	B18; K700-K703; K709; K71; K73; K74; K760; B150; B160; B162; B190; K704; K72; K76.6; I85
Diabetes mellitus	E10-E12
Moderate/severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Any cancer excluding non-melanoma skin cancer and lung cancer	C00-C98
Lung cancer	C34
Osteoporosis	M80-M82
Thyroid disorders	E00; E03; E05; E01; E02; E04; E06; E07

ICD10 = Corresponding International Classification of Diseases, 10th revision codes

Table 2

Proportion of pre-specified categories among patients diagnosed with idiopathic pulmonary fibrosis and sex- and age-matched population controls stratified on year 2002-2010.

	IPF-cases		Controls	
Disease entity	N (%)	First occurrence relative to IPF diagnosis, months, median (IQR)	N	First occurrence relative to index date, months, median (IQR)
Pneumonia	14 (2.2)	1.8 (0.7-4.5)	n < 10	n < 10

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 3

Proportion of ten pre-specified categories among patients diagnosed with idiopathic pulmonary fibrosis and sex- and age-matched population controls stratified on year 2011-2017.

	IPF-cases		Controls	
Disease entity	N (%)	First occurrence relative to IPF diagnosis, months, median (IQR)	N (%)	First occurrence relative to index date, months, median (IQR)
Dyspnea	85 (13.1)	2.2 (0.9-3.8)	26.0 (0.4)	3.6 (2.5-4.4)
Non-IPF IIP	81 (12.5)	2.8 (1.1-4.3)	n<10	n<10
Pneumonia	42 (6.5)	2.0 (0.9-3.6)	40.0 (0.6)	2.9 (1.3-4.1)
COPD	19 (2.9)	1.7 (0.9-2.6)	28.0 (0.4)	2.7 (1.7-4.1)
Cough	16 (2.5)	3.0 (2.3-4.3)	n<10	n<10
Osteoporosis	13 (2.0)	2.5 (1.6-4.3)	21.0 (0.3)	2.5 (1.6-4.5)
Pulm. hypertension	12 (1.8)	2.2 (1.1-4.5)	n<10	n<10
Heart failure	12 (1.8)	3.4 (0.5-5.1)	26.0 (0.4)	2.7 (1.0-3.6)

COPD = chronic obstructiove pulmonary disease

IIP = idiopathic interstial pneumonias

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 4

Dominating diagnoses among patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) established within 3 years prior to the IPF diagnosis, and randomly assigned index date among controls during 2002-2010.

		IPF-cases		Controls	
Diagnosis	ICD-10	N (%)	First occurrence relative to IPF diagnosis, months, median (IQR)	N (%)	First occurrence relative to index date, months, median (IQR)
Other interstitial pulmonary diseases	J84	31 (4.8)	2.2 (0.9-3.5)	n<10	n<10
Pneumonia (organism unspecified)	J18	14 (2.2)	2.7 (1.4-4.9)	n<10	n<10
Other chronic obstructive pulmonary disease	J44	12 (1.8)	2.5 (0.8-3.3)	n<10	n<10
Respiratory failure (not elsewhere classified)	J96	11 (1.7)	1.6 (0.9-4.6)	n<10	n<10

ICD10 = Corresponding International Classification of Diseases, 10th revision codes

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 5

Dominating diagnoses among patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) established within 3 years prior to the IPF diagnosis, and randomly assigned index date among controls during 2011-2017.

		IPF-cases		Controls	
Diagnosis	ICD-10	N (%)	First occurrence relative to IPF diagnosis, months, median (IQR)	N	First occurrence relative to index date, months, median (IQR)
Other interstitial pulmonary diseases	J84	267 (41.1)	2.4 (1.0-4.0)	n<10	n<10
Abnormalities of breathing	R06	87 (13.4)	2.2 (0.8-3.8)	29 (0.4)	3.6 (2.3-4.4)
Respiratory failure, not elsewhere classified	J96	47 (7.2)	2.4 (0.9-4.5)	17 (0.3)	3.7 (1.9-4.3)
Pneumonia, organism unspecified	J18	37 (5.7)	2.0 (0.9-4.0)	29 (0.4)	3.1 (1.9-4.8)
Abnormal findings on diagnostic imaging of lung	R91	35 (5.4)	2.3 (1.1-4.6)	n<10	n<10
Atrial fibrillation and flutter	I48	33 (5.1)	2.1 (1.7-3.8)	55 (0.8)	3.1 (1.9-4.8)
Other chronic obstructive pulmonary disease	J44	21 (3.2)	1.1 (0.5-2.8)	42 (0.6)	3.1 (1.7-4.3)
Cough	R05	17 (2.6)	3.1 (2.6-4.0)	n<10	n<10
Bacterial pneumonia. not elsewhere classified	J15	17 (2.6)	3.1 (2.0-4.9)	21 (0.3)	2.8 (1.2-3.4)
Heart failure	I50	15 (2.3)	1.8 (0.6-4.7)	33 (0.5)	2.8 (1.2-4.2)
Angina pectoris	I20	15 (2.3)	2.8 (2.3-4.7)	19 (0.3)	3.1 (2.0-4.7)
Chronic ischaemic heart disease	I25	15 (2.3)	2.3 (0.5-4.4)	40 (0.6)	3.1 (1.6-4.2)
Essential (primary) hypertension	I10	14 (2.2)	2.9 (0.6-4.0)	65 (1.0)	3.2 (2.0-4.3)
Nonrheumatic aortic valve disorders	I35	13 (2.0)	2.5 (2.1-3.0)	24 (0.4)	3.3 (2.2-4.2)
Other pulmonary heart diseases	I27	13 (2.0)	1.9 (1.2-4.2)	n<10	n<10
Senile cataract	H25	13 (2.0)	3.9 (2.4-4.2)	57 (0.9)	2.9 (1.3-4.4)
Osteoporosis without pathological fracture	M81	12 (1.8)	2.8 (1.4-4.2)	17 (0.3)	2.5 (2.1-3.8)
Malaise and fatigue	R53	12 (1.8)	2.3 (0.6-3.4)	22 (0.3)	2.2 (1.1-3.2)
Other respiratory disorders	J98	11 (1.7)	1.7 (0.5-3.6)	n<10	n<10
Non-insulin-dependent diabetes mellitus	E11	10 (1.5)	3.0 (1.7-4.3)	40 (0.6)	3.5 (1.9-4.6)

ICD10 = Corresponding International Classification of Diseases, 10th revision codes

IPF = idiopathic pulmonary fibrosis

IQR = inter quartile range

Table 6

Dynamics of dominating drug classes used by newly diagnosed patients with idiopathic pulmonary fibrosis and their matched controls during 2002-2010.

		IPF-cases			Controls		
Drug class, name	ATC	New users before IPF, n (%)	Ongoing users before IPF, n (%)	Discontinued after IPF, n (%)	New users before index date, n (%)	Ongoing users before index date, n (%)	Discontinued after index date, n (%)
Potassium	A12BA	12 (11.4)	20 (19.0)	n < 10	n < 10	57 (5.4)	n < 10
Glucocorticoids (systemic)	H02AB	12 (11.4)	42 (40.0)	n < 10	10 (1.0)	38 (3.6)	17 (44.7)
Loop diuretics	C03CA	11 (10.5)	25 (23.8)	n < 10	n < 10	58 (5.5)	n < 10

ATC = Anatomical Therapeutic Chemical classification

Table 7

Dynamics of dominating drug classes used by newly diagnosed patients with idiopathic pulmonary fibrosis and their matched controls during 2011-2017.

		IPF-cases			Controls		
Drug class, name	ATC	New users before IPF*, n (%)	Ongoing users before IPF†, n (%)	Discontinued after IPF‡, n (%)	New users before index date*, n (%)	Ongoing users before index date†, n (%)	Discontinued after index date‡, n (%)
Combinations of penicillin, incl. beta-lactamase inhibitors	J01CR	55 (10.1)	117 (21.5)	32 (38.1)	71 (1.3)	152 (2.8)	91 (63.6)
Glucocorticoids	H02AB	44 (8.1)	181 (33.2)	32 (24.6)	40 (0.7)	239 (4.4)	69 (30.8)
Mucolytics	R05CB	34 (6.2)	80 (14.7)	12 (19.0)	14 (0.3)	30 (0.6)	13 (44.8)
Proton pump inhibitors	A02BC	31 (5.7)	216 (39.6)	16 (9.2)	90 (1.7)	922 (16.9)	124 (13.8)
Selective beta-2-adrenoreceptor agonists	R03AC	28 (5.1)	96 (17.6)	25 (32.9)	34 (0.6)	299 (5.5)	67 (22.9)
Sulfonamides, plain	C03CA	20 (3.7)	127 (23.3)	20 (20.6)	51 (0.9)	486 (8.9)	41 (8.8)
Anilides	N02BE	19 (3.5)	178 (32.7)	19 (13.8)	140 (2.6)	1164 (21.4)	208 (18.5)
Fluoroquinolones	J01MA	18 (3.3)	39 (7.2)	14 (58.3)	43 (0.8)	85 (1.6)	64 (78.0)
Macrolides	J01FA	18 (3.3)	94 (17.2)	44 (62.0)	28 (0.5)	171 (3.1)	117 (71.3)
Natural opium alkaloids	N02AA	17 (3.1)	44 (8.1)	n<10	54 (1.0)	172 (3.2)	49 (30.1)
Potassium	A12BA	16 (2.9)	103 (18.9)	14 (18.7)	64 (1.2)	449 (8.2)	47 (11.0)
Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK	16 (2.9)	71 (13.0)	22 (37.9)	16 (0.3)	269 (4.9)	19 (7.3)
Anticholinergics	R03BB	15 (2.8)	61 (11.2)	14 (31.1)	21 (0.4)	209 (3.8)	19 (9.5)
Opium alkaloids and derivatives	R05DA	15 (2.8)	44 (8.1)	18 (51.4)	26 (0.5)	122 (2.2)	52 (43.7)
Osmotically acting laxatives	A06AD	14 (2.6)	19 (3.5)	n<10	39 (0.7)	132 (2.4)	36 (32.1)
Bisphosphonates	M05BA	14 (2.6)	73 (13.4)	n<10	15 (0.3)	215 (3.9)	15 (7.0)
Adrenergics in combination with anticholinergics	R03AL	13 (2.4)	26 (4.8)	n<10	21 (0.4)	59 (1.1)	13 (26.0)
Other immunosuppressants	L04AX	13 (2.4)	49 (9.0)	19 (55.9)	n<10	56 (1.0)	n<10
Penicillins with extended spectrum	J01CA	12 (2.2)	56 (10.3)	20 (50.0)	43 (0.8)	318 (5.8)	163 (54.0)
Other opioids	N02AX	12 (2.2)	63 (11.6)	18 (36.0)	57 (1.0)	368 (6.8)	131 (36.9)
Selective serotonin reuptake inhibitors	N06AB	12 (2.2)	45 8.3)	n<10	19 (0.3)	323 (5.9)	35 (11.3)
Corticosteroids and antiinfectives in combination	S01CA	10 (1.8)	13 2.4)	n<10	61 (1.1)	116 (2.1)	89 (76.7)
Contact laxatives	A06AB	10 (1.8)	11 2.0)	n<10	36 (0.7)	74 (1.4)	25 (38.5)
HMG CoA reductase inhibitors	C10AA	10 (1.8)	210 38.5)	12 (7.3)	55 (1.0)	1802 (33.1)	80 (4.5)
Platelet aggregation inhibitors excl. heparin	B01AC	10 (1.8)	196 36.0)	13 (8.7)	48 (0.9)	1505 (27.6)	76 (5.2)

*) New use is defined as first-ever occurrence of the drug class within six months before the index date / diagnosis date

†) Ongoing use is defined as any occurrence of the drug class within the six months before the index date / diagnosis date

‡) Discontinuation is defined by the absence of any prescriptions on the drug class after the index date / diagnosis date compared to ongoing use

ATC = Anatomical Therapeutic Chemical classification