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Patient Characteristics, Healthcare Contacts and Drug Use in Polycythaemia Vera in Denmark

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ABSTRACT

Objective: Patients with polycythaemia vera (PV) may experience symptoms and cardiovascular complications before receiving a diagnosis. Understanding the associated patterns of healthcare and drug utilisation may help detect patients who need diagnostic workup. In this study, we described healthcare contacts and prescription drug use in patients with PV in Denmark before and after their diagnosis.

Methods: We conducted a descriptive study using national Danish registries, matching patients with PV diagnosed between 2012 and 2021 ($n = 1428$) to the background population on age and sex.

Results: Patients with PV had a median age of 70 years [61–77] with an equal distribution of men and women. The patients were comparable to the comparison group across most characteristics except for a history of cardiovascular disease. In the 3 months before and 6 months after diagnosis, patients with PV had an increased number of healthcare contacts and rate of new drugs. The drug rate returned to baseline after 6 months, while outpatient contacts remained increased.

Conclusions: Patients with PV experienced an increase in healthcare and drug utilisation around the time of diagnosis, but were comparable to the background population up to 3 months before, with no indicators allowing earlier detection of PV related to drug use or healthcare contacts.

1 | Introduction

Polycythaemia vera (PV) is a myeloproliferative neoplasm (MPN) that occurs due to a mutation in the Janus kinase 2 (*JAK2*) gene in the majority of cases [1–3]. PV is characterised by an overproduction of red blood cells, often accompanied by elevated counts of white blood cells and platelets. This overproduction leads to increased blood viscosity, increasing the risk of microvascular

symptoms and thrombotic events [4–7]. Microvascular symptoms encompass a range of symptoms, commonly headache, dizziness and visual disturbances. Additionally, patients often report fatigue, pruritus, headaches, impaired concentration and night sweats [8–10].

Patients with PV often exhibit symptoms before receiving a formal diagnosis, and this pre-diagnosis period may vary from

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months to years [11–13]. Some of these symptoms would logically prompt more frequent contact with the healthcare system and treatment attempts with prescription drugs.

Examining patterns in healthcare contacts and use of prescription drugs could provide a better understanding of the disease progression and symptom burden and potentially offer opportunities for earlier detection. Rapid diagnostic work-up is crucial to minimise the time patients are at increased risk of vascular complications, and early detection may have an important impact on the patient's prognosis [14]. To our knowledge, no studies describe the use of prescription drugs among patients with PV, and only limited studies have examined their use of healthcare resources [15–17].

We aimed to describe patients with PV in Denmark during the years leading up to and following their diagnosis by describing (i) patient characteristics, (ii) contacts to the healthcare system and (iii) use of prescription drugs.

2 | Methods

In this descriptive study, we examined the patterns of healthcare contacts and drug use among patients with PV in Denmark, compared to individuals from the general population without a PV diagnosis, matched on the diagnosis date, by birth year and sex.

2.1 | Data Collection

We used six data sources: The Danish National Patient Registry contains data on all hospital contacts since 1995 [18]. All patients have been recorded according to the World Health Organization's International Statistical Classification of Diseases, 10th revision (ICD-10), since 1994 [19].

The Danish National Chronic Myeloid Neoplasia Registry (DCMR) contains information on patients with MPNs diagnosed in Denmark since 2010. Healthcare professionals manually enter data from hospital files on patients diagnosed with various MPNs, including PV. DCMR contains molecular data, laboratory data, data on disease-specific symptoms, risk factors and initiated treatments specific to each patient [20].

The Danish National Prescription Registry contains data on all prescriptions redeemed at Danish pharmacies since 1995, including the date of prescription redemption and the quantity and type of medication based on the Anatomic Therapeutic Chemical (ATC) index [21, 22]. The register does not include data on over-the-counter sales, in-hospital drug use and drugs supplied directly from hospitals (e.g., chemotherapy and immunosuppressants) [21].

The Danish National Health Service Register contains data on activities of the various healthcare professionals: general practitioners (GPs), practicing medical specialists, physiotherapists, dentists, psychologists, chiropractors and chiropodists. Data from the registry is available from 1990 onwards [23].

The Danish Cancer Registry contains data on all incident cancer cases in Denmark since 1943 [24].

The Civil Registration System contains individual-level information on residents in Denmark since 1968, on demographics including age, sex, death and migration [25].

We linked these registries, using the unique personal identification number assigned to all Danes [26]. The linking took place at the Danish Health Data Authority. The healthcare system in Denmark is structured to promote equity and ensure cost-free access to GPs and hospitals, as well as provide subsidies for prescription drugs for all citizens. Thus, the data derived from the Danish registers offer a robust portrayal of drug use and healthcare contact within the national population [21, 27].

2.2 | Cohort Identification

The cohort was identified as individuals aged ≥ 18 years diagnosed with PV between January 1, 2012 and December 31, 2021. The index date was defined as the first date a patient was registered with a diagnosis of PV (ICD-10 code D45*) in the Danish National Patient Registry [18] (primary or secondary diagnosis).

We matched each patient with PV on birth year and sex to 10 individuals from the background population on the index date. Individuals from the background population were allowed to be matched to more than one patient with PV. Individuals who were later diagnosed with PV were included in the background population and thus available as controls up until their own index date.

Eligibility criteria for the study included diagnosis confirmation in DCMR, having resided in Denmark ≥ 10 years prior to the index date, and having no previous cancer diagnosis other than non-melanoma skin cancer (NMSC) and potential PV-related diagnoses.

Individuals in both the PV cohort and the comparison cohort were followed from the index date until death, cancer diagnosis (ignoring PV-related diagnoses or NMSC), emigration, PV diagnosis (the comparison cohort only), or end of follow-up (December 31, 2023), whichever came first.

All codes and definitions are available in Appendix A.

2.3 | Risk Group

Each patient with PV was categorized into a risk group based on age and thrombotic history. Low-risk classification was assigned to patients < 60 years of age with no history of thrombosis, while high-risk classification included those aged ≥ 60 years and/or with a history of thrombosis [28].

2.4 | Healthcare Contacts

Healthcare contacts were defined as any outpatient contact (including all interactions with hospital departments not requiring inpatient admission), inpatient contact, emergency contacts (emergency department or on-call doctor), or contacts with GPs, private practicing specialists (ophthalmologists, ear-nose-throat doctors or specialist physicians), or

therapists (physiotherapists, psychologists, chiropractors, or equine-assisted therapists). The specific registries and codes used to define each type of healthcare contact can be found in Appendix A.

2.5 | Study Drugs

We included all prescription drugs using the ATC index [22]. In some analyses, drug categorisation was conducted using the fourth level of the ATC code, corresponding to specific drug classes (e.g., M04AA urate synthesis inhibiting agents). In other analyses, we used the full ATC code for the specific drug (e.g., M04AA01 allopurinol).

2.6 | Incident User

We defined incident drug use as the first prescription filled at a pharmacy for each specific drug class, except antibiotics, in 5 years. A person was counted as an incident antibiotic user the first time a prescription for an antibiotic was filled in 30 days. A person was counted as an incident antibiotic user again if there were 30 or more days between prescription fills for antibiotics. The list of ATC codes used to define antibiotics can be found in Appendix A.

2.7 | Data Analysis

2.7.1 | Patient Characteristics

We described the baseline characteristics of the study population, including sex, age at index date, follow-up time, history of cardiovascular disease (CVD), diabetes, Charlson Comorbidity Index (CCI) and Nordic Multimorbidity Index (NMI) [29].

We characterised patients with PV using data from the DCMR, encompassing variables including risk score, previous thromboses, cardiovascular risk factors, smoking, obesity, clinical symptoms and laboratory parameters.

We described the five-year mortality of patients with PV and the comparison group using a Kaplan–Meier survival model. The analysis was repeated for patients with PV only, stratified by sex and risk group.

2.7.2 | Healthcare Contacts

Healthcare contacts were described in the 2 years leading up to and the 2 years after the index date in both the PV group and the comparison group. We described healthcare contacts both overall and separately for each type of healthcare contact as the number of contacts per person in three-month intervals.

2.7.3 | Drug Use

Incident non-antibiotic drug use was described in 2 years leading up to and 2 years following the index date in both the PV and the comparison group. The incidence rate of new drug use was

estimated as the number of new drug classes per 100 persons per month. The analysis was repeated for incident antibiotic use in 3-month intervals and for patients with PV only, stratified by sex and risk group. The specific drugs contributing the most to peaks in incident drug use before and after the index date were identified by calculating the incidence rate difference between patients with PV and the comparison group. The type of prescriber responsible for initiating the drugs contributing most to the peak was identified for both groups 2 years before and after the index date.

All analyses were performed using R version 4.3.3.

2.8 | Approvals and Ethics

The study was registered at the University of Southern Denmark (RIO no. 12.058). According to Danish law, studies based solely on register data do not require approval from an ethics review board [30].

3 | Results

We identified 2613 incident patients with PV and 25,781 individuals in the comparison group during the study period from January 1, 2012, to December 31, 2021. After applying the exclusion criteria, the study population consisted of 1428 patients with PV and 11,854 individuals in the comparison group. The full selection process and the number of individuals matched to each patient with PV can be found in Appendix A and Figure S1.

3.1 | Patient Characteristics

The median age at the index date was 70 years (interquartile range [IQR] 61–77 years) with an equal distribution of men and women (Table 1 and Figure S2). Patients with PV were comparable to the comparison group across most characteristics except for history of CVD (30% of patients with PV and 19% of the comparison group).

Most patients with PV (83%) were classified as high-risk at diagnosis, with the median age in the high-risk group being 72 years [IQR 66–79] and the median age in the low-risk group being 51 years [IQR 46–55] (Table 2). 70% of patients with PV had cardiovascular risk factors, and 30% had a history of a previous thrombosis. Smoking was reported in 24% of patients with PV, with a median of 30 pack-years (IQR 20–48). All median laboratory values were above normal ranges. At the time of diagnosis, the most prevalent patient-reported symptom was microvascular symptoms (33%).

Five years after the index date, 89% (95% CI: 88–90) of the comparison cohort were still alive, compared to 85% (95% CI: 83–87) in the PV cohort (Figure S3). When patients with PV were stratified by risk group, mortality was negligible in the low-risk group, with 99.6% (95% CI: 99–100) alive after 5 years, compared to 82% (95% CI: 80–85) in the high-risk group (Figure S4). There was no difference in survival between men and women (Figure S5).

TABLE 1 | Baseline characteristics of patients with polycythaemia vera (PV) and the comparison group on the index date.

	PV patients (n = 1428)	Comparison group (n = 11 854)
Sex, n (%)		
Men	703 (49)	5885 (50)
Women	725 (51)	5969 (50)
Age, median [IQR]	70 [61–77]	69 [60–76]
Age groups, n (%)		
18–40	36 (2.5)	293 (2.5)
41–60	320 (22)	2829 (24)
61–85	997 (70)	8163 (69)
≥ 85	75 (5.3)	569 (4.8)
Comorbidities, n (%)		
History of cardiovascular disease	422 (30)	2292 (19)
Diabetes	148 (10)	1228 (10)
Charlson Comorbidity Index, n (%)		
0–1	1224 (86)	10 340 (87)
2–3	166 (12)	1291 (11)
≥ 4	38 (2.7)	223 (1.9)
Nordic Multimorbidity Index, mean ± SD	11 (±11)	10 (±12)
Follow-up time, years, mean ± SD	5.5 (±3.0)	5.8 (±3.0)

Abbreviations: IQR = Interquartile range; SD = Standard deviation.

3.2 | Healthcare Contacts

The number of healthcare contacts remained relatively stable in the 2 years before the index date, ranging from a mean of 2.0 to 2.4 contacts per patient with PV every 3 months (Figure 1A). However, this number increased in the last 3 months before the index date and peaked at 6.2 healthcare contacts per person in the first 3 months after the index date. After the peak, the number of healthcare contacts per PV patient decreased to a range of 3.6 to 3.3 contacts every 3 months. The number of healthcare contacts in the comparison group remained stable, ranging from 2.1 to 2.5 contacts per person every 3 months throughout the period (Figure 1A and Figure S6).

In the years leading up to the index date, the mean number of healthcare contacts per patient with PV was primarily driven by GP visits, with an average of 1.3–1.4 contacts every 3 months (Figure 1B). Contacts with other healthcare services were each less than 0.52 per patient with PV every 3 months, until the last 3 months before the index date. In this period, the mean number of

TABLE 2 | Characteristics of patients with polycythaemia vera (PV) with data from the Danish National Chronic Myeloid Neoplasia Registry at the time of diagnosis.

	PV patients (n = 1428)
Risk score (%)	
Low risk	246 (17)
High risk	1182 (83)
Previous thrombosis (%)	422 (30)
Deep vein thrombosis	67 (4.7)
Pulmonary embolism	33 (2.3)
Myocardial infarction	86 (6.0)
Cerebral stroke	191 (13)
Transient ischemic attack	33 (2.3)
Splanchnic thromboses	23 (1.6)
Other thrombosis	51 (3.6)
Smoking (%)	338 (24)
Pack years, median [IQR]	30 [20, 48]
Laboratory data, median [IQR]	
EVF—Haematocrit (%)	53 [49, 58]
Haemoglobin (g/dL)	71 [65, 77]
Platelet count (10 ⁹ /L)	532 [367, 709]
Leukocytes (10 ⁹ /L)	11 [8.8, 14]
JAK2 positive allelic burden (%)	34 [18, 54]
Symptoms (%)	
Severe skin itching	192 (13)
Increased sweating	236 (17)
Microvascular Symptoms ^a	466 (33)
Splenomegaly	410 (29)
Obesity (BMI > 30) (%)	67 (4.7)
Cardiovascular risk factors ^b (%)	1002 (70)

Note: High risk = age ≥ 60 years or previous thromboembolic complications. Low risk = age < 60 years and no previous thromboembolic complications.

^aAt least one of the following: visual disturbances, dizziness, headache, erythromelalgia, necrosis.

^bAt least one of the following: Obesity, smoking, previous smoking, hypertension, diabetes, hypercholesterolemia, factor V Leiden.

outpatient contacts increased to 2.7 per patient, and the mean number of inpatient contacts increased from less than 0.10 to 0.38 contacts per patient. After the index date, outpatient contacts peaked at 4.0 per patient with PV during the first 3 months, then decreased to a stable range of 1.4–1.7 contacts every 3 months. Other healthcare contacts remained relatively stable after the index date.

3.3 | Drug Use

The incidence rate of new drugs per 100 patients with PV per month increased in the 3 months leading up to the index date

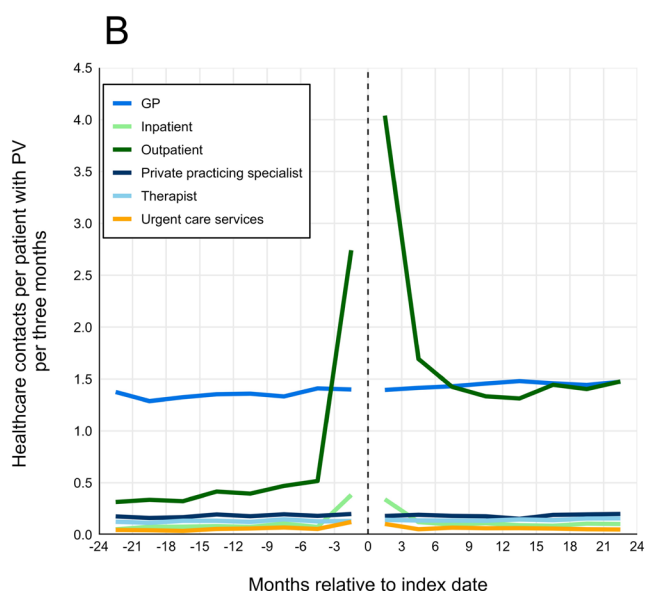
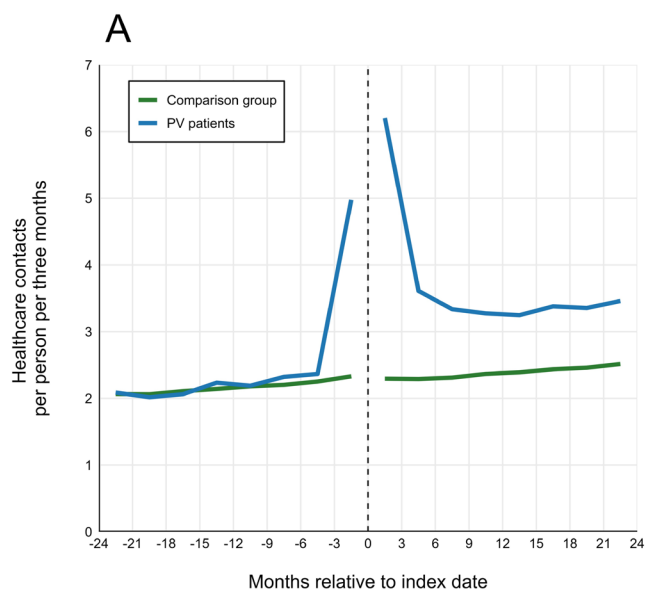


FIGURE 1 | The number of healthcare contacts per person per 3 months in the 2 years leading up to the index date and the 2 years following the index date. (A) The number of healthcare contacts per person for patients with polycythaemia vera (PV) and the comparison group. (B) The number of healthcare contacts per patient with PV for each type of healthcare contact. GP=general practitioner, emergency contacts=emergency department or on-call doctor, private practicing specialists=ophthalmologists, ear-nose-throat doctors, or specialist physicians, therapists=physiotherapists, psychologists, chiropractors, or equine-assisted therapists.

and the first 6 months after the index date, reaching a peak of 57 (95% CI: 53–61) new drug classes per 100 patients with PV in the first month after the index date (Figure 2). Before and after this increase, patients with PV used a mean of 8.5 (95% CI: 7.1–10) to 15 (95% CI: 13–17) new drug classes per 100 persons per month. The comparison group used a mean of 7.5 (95% CI: 7.0–8.0) to 9.8 (95% CI: 9.2–10) new drug classes per 100 persons per month throughout the period. The analysis was repeated for patients with PV stratified by risk group and sex, showing no significant

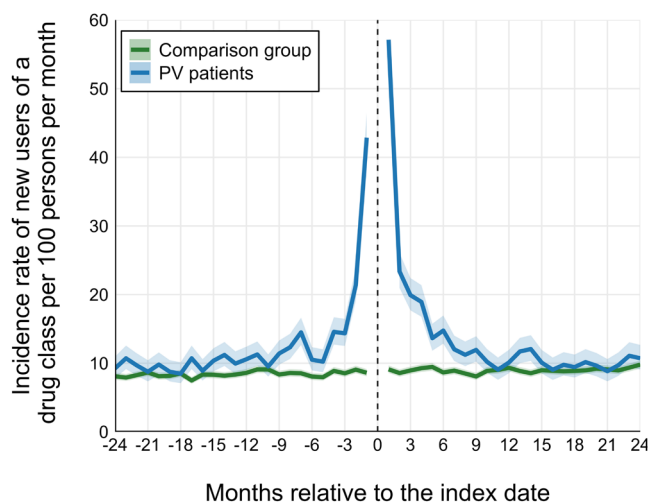


FIGURE 2 | The monthly incidence of new drug classes for both patients with polycythaemia vera (PV) and the comparison group during the 2 years preceding and following the index date, with 95% confidence intervals.

difference (Figures S7 and S8). Patients with PV generally had a higher incidence rate of antibiotics than the comparison group (Figure S9). The incidence rate for patients with PV increased from 16 (95% CI: 14–18) the year before the index date to 27 (95% CI: 25–30) new antibiotics per 100 persons in the 3 months leading up to the index date, with a slight decrease after the index date. The incidence rate in the comparison group remained stable at 16 (95% CI: 16–17) to 18 (95% CI: 17–18) new antibiotics per 100 persons per 3 months.

The primary drugs responsible for the peak in the 3 months leading up to diagnosis in patients with PV were acetylsalicylic acid, clopidogrel, amlodipine, losartan and atorvastatin, with an incidence rate difference compared to the comparison group of 13, 3.4, 2.6, 2.5 and 2.3 per 100 persons per month, respectively (Table 3).

The primary drugs responsible for the peak up to 6 months after diagnosis in patients with PV were acetylsalicylic acid, allopurinol, paracetamol, clopidogrel, and hydroxycarbamide, with an incidence rate difference compared to the comparison group of 27, 15, 4.5, 3.7 and 3.0 per 100 persons per month, respectively (Table 4). Both before and after the index date, drugs used to treat thromboses or prevent thrombotic events were frequently initiated.

GPs were generally responsible for prescribing most of the most frequently initiated drugs used before and after the index date, except for the last 2 months before and 3 months after the index date to patients with PV (Figure S10). In this period, haematologists and other hospital specialists initiated most of the drugs, with a peak in the first month after diagnosis (50% haematologists, 19% other hospital specialists, and 13% GPs). After the diagnosis, haematologists continued to prescribe 6.4%–26% of the most frequently initiated drugs to patients with PV, with GPs prescribing 42%–66% of the drugs. In the comparison group, GPs prescribed most of the frequently initiated drugs (60%–74%) (Figure S11).

TABLE 3 | The drugs initiated among patients with polycythaemia vera (PV) and the comparison group, the last 3 months before the index date, corresponding to the period of the highest incidence rate of new drugs before the index date. The table includes the 20 drugs with the highest incidence rate difference in patients with PV compared to the comparison group.

ATC code	Drug	PV group incident prescriptions per 100 persons per month	Comparison group incident prescriptions per 100 persons per month	Incidence rate difference
B01AC06	Acetylsalicylic acid	14	0.37	13
B01AC04	Clopidogrel	3.8	0.35	3.4
C08CA01	Amlodipine	3.2	0.54	2.6
C09CA01	Losartan	2.9	0.38	2.5
C10AA05	Atorvastatin	2.9	0.61	2.3
A02BC02	Pantoprazole	2.5	0.66	1.8
C07AB02	Metoprolol	1.8	0.24	1.5
N02BE01	Paracetamol	3.0	1.6	1.4
M04AA01	Allopurinol	1.5	0.08	1.4
C09AA02	Enalapril	1.5	0.24	1.2
A12BA01	Potassium chloride	1.6	0.39	1.2
C03AB01	Bendroflumethiazide and potassium	1.3	0.32	0.94
C10AA01	Simvastatin	1.2	0.31	0.88
C03CA01	Furosemide	1.2	0.31	0.88
N02AX02	Tramadol	1.5	0.75	0.72
C09DA01	Losartan and diuretics	0.84	0.13	0.70
B01AA03	Warfarin	0.77	0.067	0.70
C08CA13	Lercanidipine	0.84	0.14	0.70
B01AC24	Ticagrelor	0.70	0.042	0.66
C05BA01	Organo-heparinoid	0.70	0.059	0.64

Abbreviation: ATC = anatomic therapeutic chemical.

4 | Discussion

We observed an increase in both healthcare contacts and drug use among patients with PV compared to the background population within 3 months before and 6 months after the diagnosis date. The increase in drug use was primarily driven by drugs used to treat thromboses or prevent thrombotic events, particularly acetylsalicylic acid, while the rise in healthcare contacts was due to a higher frequency of outpatient contacts. Before and after this period, both the rate of drug initiation and healthcare contacts other than outpatient contacts were comparable between patients with PV and the background population.

The main strength of this study is the linking of the various high-quality national registries, providing close to complete data on healthcare contacts and prescription drug use, and thereby reducing the potential for selection bias. Another strength is the use of DCMR. In Denmark, patients with a suspected PV diagnosis are referred to a haematology department, where the diagnosis is confirmed by a haematologist and reported to DCMR, enhancing the diagnostic accuracy.

There are several limitations to consider. Despite being a nationwide study, PV is a rare condition, resulting in a limited number of patients, which may affect the power of the findings. Additionally, many drugs used by patients with PV to manage symptoms, such as antihistamines and paracetamol, are sold over the counter and thus not captured in the data. Similarly, most cytoreductive treatments are provided to patients free of charge directly through the hospital and therefore also not included, which will underestimate the use of new drugs for PV patients after diagnosis. Hydroxyurea can, in some cases, be dispensed through community pharmacies, which may explain its limited presence in Table 4. The data recorded in DCMR has not been validated, and not all patients are registered across all parameters, so the number of patients counted for each parameter may not reflect the true number. Additionally, symptom data for the general population is not available, so while one-third of PV patients report experiencing microvascular symptoms, similar symptoms could also occur in the general population. A study comparing symptom burden between patients with PV and the general population using a questionnaire found that patients with PV generally reported

TABLE 4 | The drugs initiated among patients with polycythaemia vera (PV) and the comparison group, the first 6 months after the index date, corresponding to the period of the highest incidence rate of new drugs after the index date. The table includes the 20 drugs with the highest incidence rate difference in patients with PV compared to the comparison group.

ATC code	Drug	PV group incident prescriptions per 100 persons per month	Comparison group incident prescriptions per 100 persons per month	Incidence rate difference
B01AC06	Acetylsalicylic acid	28	0.63	27
M04AA01	Allopurinol	15	0.16	15
N02BE01	Paracetamol	7.6	3.1	4.5
B01AC04	Clopidogrel	4.3	0.62	3.7
L01XX05	Hydroxyurea	3.0	0	3.0
C10AA01	Simvastatin	2.6	0.22	2.3
A02BC02	Pantoprazole	3.6	1.4	2.2
A06AD65	Macrogol, combinations	2.8	0.79	2.0
A12BA01	Potassium chloride	2.7	0.90	1.8
B01AA03	Warfarin	1.8	0.16	1.6
A03FA01	Metoclopramide	1.9	0.35	1.5
R06AE07	Cetirizine	1.8	0.34	1.5
N05CF01	Zopiclone	1.8	0.39	1.4
C03AB01	Bendroflumethiazide and potassium	1.9	0.65	1.2
N02AX02	Tramadol	2.5	1.3	1.2
C03CA01	Furosemide	2.0	0.87	1.2
H02AB06	Prednisolone	2.0	0.8	1.2
A02BC03	Lansoprazole	1.5	0.35	1.1
C10AA05	Atorvastatin	2.3	1.3	1.1
B01AF02	Apixaban	1.3	0.30	1.0

Abbreviation: ATC = anatomic therapeutic chemical.

a slightly higher symptom burden, particularly regarding fatigue [31].

The diagnosis date as recorded in the health registries carries some uncertainty, as the diagnosis may be suspected before it is officially confirmed [32]. The increased number of healthcare contacts before diagnosis is likely driven by patients undergoing diagnostic evaluations, leading to increased hospital visits. The increased drug use during the months just prior to diagnosis likely reflects the treatment initiation for PV before the formal PV diagnosis has been registered, which is also seen in the rising proportion of drugs initiated by haematologists.

The increase in healthcare contacts driven by more frequent outpatient visits might be caused by the initiation of therapy, consultations regarding adverse effects, adjustment of medication and the need for regular phlebotomies in the initial months after diagnosis [33].

Many of the most frequently initiated drugs, both before and after diagnosis, are closely linked to thrombosis prevention and

treatment. This could be due to a thrombotic event as the initial event that leads to the detection of the PV diagnosis. A study shows that the risk of thrombosis is highest in the first 3 months after diagnosis, possibly because the patients are not yet adequately treated or because of the heightened attention that is given to thrombosis risk immediately after diagnosis [7].

Drugs such as paracetamol, antihistamines and allopurinol also appear in the top 20 initiated drugs. Paracetamol and antihistamines are likely used to treat symptoms. The use of allopurinol might be increased because of the elevated risk of gout due to increased blood cell production, which results in elevated uric acid levels due to the high turnover of blood cells [34].

The earliest observable difference between patients with PV and the comparison group was the rate of new antibiotic prescriptions. Beginning 9 months before diagnosis, patients with PV had a higher rate of antibiotic prescriptions, which increased up to the diagnosis date and remained slightly elevated compared to the comparison group. This could be due to a higher risk of infection in individuals with PV compared to the general population, which

has been found in a Swedish study on the period after diagnosis [35]. Another explanation could be that patients with an infection undergo blood tests, leading to the detection of their PV diagnosis. The slightly elevated rate of antibiotic use among patients with PV post-diagnosis may be attributable to rare instances of cytoreductive drug overmedication, which can induce neutropenia and consequently heighten the risk of infections. Also, regional variations in Denmark exist in the administration of antibiotics to patients, with differences in whether antibiotics are dispensed directly by hospitals or prescribed for collection at a pharmacy, which might affect the recorded rate of antibiotics after the diagnosis.

In conclusion, we observed a peak in healthcare contacts and drug use among patients with PV around the time of diagnosis. The peaks were primarily driven by drugs used to treat thrombosis or prevent thrombotic events, particularly acetylsalicylic acid and outpatient contacts, accompanied by a moderate increase in inpatient contacts. Up to 3 to 6 months before diagnosis, the healthcare contacts and drug use among patients with PV were similar to those of the background population. After diagnosis, the rate of new drug use returned to that of the comparison group within 6 months, which might indicate that symptoms and complications related to the PV diagnosis are managed well after the first 6 months. While outpatient contacts remained higher than in the comparison group, all other healthcare contacts were comparable after the diagnosis. There is no indication in our data for earlier detection of PV, as patients with PV largely resemble the general population before diagnosis regarding healthcare contacts and drug use.

Author Contributions

K.M.L. was responsible for data acquisition, conducted the analyses and drafted the manuscript. A.P. conceived the original study idea and provided overall supervision, guiding the selection of appropriate methods, definitions and analytical strategies. M.B., C.L.A. and D.A.P. played a key role in shaping the study design to ensure clinical relevance, contributed to the methodological approach and provided critical perspectives that informed the interpretation of results and the final framing of the manuscript. All authors read and approved the final manuscript for submission.

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Ethics Statement

The study was registered at the University of Southern Denmark (RIO no. 12.058). According to Danish law, studies based solely on register data do not require approval from an ethics review board.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data were used under license from the Danish Health Data Authority. Individual-level data cannot be shared by the authors owing to Danish data protection regulations.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ejh70008-sup-0001-Supinfo.docx.

Appendix A

The ICD-10 codes are not included when excluding for prior cancer and defining the end of follow-up.

ICD-10 codes not included

C44*	Non-melanoma skin cancer
D46*	Myelodysplastic syndromes
D47*	Other neoplasms from lymphoid and haematopoietic tissue.

Abbreviation: ICD-10 = International Statistical Classification of Diseases, 10th revision.

The number of patients with PV matched to 4–10 persons from the comparison group after exclusion.

Number of matched persons in the comparison group

Number of PV patients	Number of matched persons in the comparison group
264	10
426	9
394	8
212	7
93	6
30	5
9	4

The ICD-10 codes and ATC codes are used to define diabetes.

ICD-10 codes for diabetes

ATC codes for diabetes

E10* (Type 1 diabetes mellitus)	A10*
E11* (Type 2 diabetes mellitus)	Excluding the following weight loss medication
E13* (Other diabetes)	A10BJ06 with drug-id:
E14* (Non-specified diabetes)	066923, 131 824, 178 249, 178 307, 187 574, 191 243, 191 797, 386 270, 394 103, 396 934, 409 687, 418 253, 468 849, 534 716 (wegovy)
	And A10BJ02 with drug-id:
	079356, 114 620, 131 577, 164 108, 395 175, 439 932, 461 535, 466 374, 575 140, 599 897 (Saxenda)

Abbreviations: ATC = anatomic therapeutic chemical; ICD-10 = International Statistical Classification of Diseases, 10th revision.

ATC codes are used to define antibiotics.

ATC code

Antibiotic group

J*	Agents against infectious diseases for systemic use
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ATC code	Antibiotic group
P01AB01	Antibiotic for protozoal and anaerobic bacterial infections
S01AA* and S01AE*	Antibiotics for ophthalmological use
S02AA* and S02AE*	Ear preparations containing antibiotics
D06A*	Antibiotics for dermatological use
G01AA*	Antibiotics for gynaecological use

Abbreviation: ATC = anatomic therapeutic chemical.

ICD-10 codes used to define cardiovascular disease (CVD).

CVD	ICD-10
Ischemic heart disease	I2 [0–5]
Atrial fibrillation	I48*
Stroke	I6 [0–4]
Heart failure	I (099A 1 (10 3 [02]) 50)

Abbreviations: CVD = cardiovascular disease; ICD-10 = International Statistical Classification of Diseases, 10th revision.

List of healthcare contacts and the registers used to define each health-care contact type.

Healthcare parameter	Register
Inpatient episodes	The Danish National Patient Registry
Outpatient contacts	The Danish National Patient Registry
Urgent care services (Emergency department and on-call doctor)	The Danish National Patient Registry Danish National Health Service Registry
GP contacts	Danish National Health Service Registry
Private practicing specialist	Danish National Health Service Registry
Therapist (physiotherapists, psychologists, chiropractors, or equine-assisted therapists)	Danish National Health Service Registry

Abbreviation: GP = general practitioner.