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**A DATA-DRIVEN PRIORITIZATION
ALGORITHM FOR MEDICATION REVIEW
IN OLDER ADULTS: FROM REAL-WORLD
EVIDENCE TO CLINICAL PRACTICE**

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Abstract

Inappropriate prescribing in older adults represents a growing challenge for healthcare systems worldwide, given the rising multimorbidity and polypharmacy in aging populations. Inappropriate pharmacological regimens not only increase the risk of adverse drug reactions and hospitalizations but also contribute to excessive healthcare costs and a decline in patient quality of life.

Given their unique clinical complexity and physiological vulnerability, older adults are particularly exposed to the risks associated with inappropriate medication use, making them a critical target for preventive strategies aimed at optimizing pharmacotherapy and reducing avoidable harm. Among these measures, periodic implementation of medication review is recommended. However, healthcare professionals- particularly general practitioners -are central to the management of chronic therapies, face increasing time constraints often hinder the systematic implementation of medication reviews. In this context, there is a pressing need for flexible, data-driven tools that can support clinicians in identifying patients most likely to benefit from medication review interventions, thereby optimizing the allocation of time and resources.

This thesis presents the development of a prioritization algorithm aimed at prioritizing older patients expected to gain the greatest benefit from medication review interventions, based on comprehensive real-world data. Conducted over a three-year doctoral research project, the work addresses a pressing public health concern- polypharmacy and inappropriate drug use among the elderly- and proposes a pragmatic, data-driven solution to enhance prescribing safety and optimize clinical resources in primary care.

After in depth literature review, six prescribing inappropriateness indicators (PIIs) were identified:

- Potentially inappropriate medications (PIMs);
- Potential drug–drug interactions (pDDIs);
- Fall-risk-increasing drugs (FRIDs);
- Therapeutic duplications (TDs);

- High anticholinergic cognitive burden (ACB);
- High sedative load (SL).

The identification of these indicators was based on established international criteria, adapted to the Italian drug market and validated through robust operational definitions.

The work was conducted using health care administrative databases from four Local Health Units in Lombardy (Italy), covering over 640,000 individuals aged 65 years or older between 2015 and 2018. Exposure to each PII was determined by operational definitions accounting for drug dispensation dates, ATC classification, Defined Daily Doses and co-prescribing windows. Individuals with first exposure between January 2015 and September 2018 were followed for 90 days to evaluate the risk of all-cause hospitalization, using a risk-set matching strategy with one control per exposed individual, matched on age and sex. Multivariable logistic regression models, adjusted for high-dimensional propensity scores, were used to estimate the odds ratios (ORs) of all-cause hospitalization associated with each PII.

All six PIIs were significantly associated with increased hospitalization risk. The highest risks were observed for FRIDs (OR 1.62, 95% CI: 1.51–1.73), PIMs (OR 1.55, 95% CI: 1.48–1.62), and TDs (OR 1.52, 95% CI: 1.46–1.58). SL score (OR 1.43, 95% CI: 1.31–1.56) and ACB score (OR 1.52, 95% CI: 1.43–1.61)

Established the baseline OR for each PII, we developed decision tree models for each indicator to identify high-risk patient profiles- i.e., combinations of demographic and clinical characteristics associated with significantly elevated hospitalization risk beyond that conferred by exposure alone. Each scenario was validated using conditional logistic regression in comparison with the overall risk of the indicators alone. Across multiple bootstrap samples, 59 distinct high-risk scenarios were identified: 14 for SL, 14 for TDs, 11 for FRIDs, 10 for pDDIs, 7 for PIMs, and 4 for ACB. These scenarios characterize subgroups of patients who should be rapidly prioritized for clinical attention, as they are at particularly high risk of hospitalization.

To estimate the real-world impact of using the algorithm, we applied the scenarios to a cohort of 501,785 older adults in the first half of 2018. A total of 55.3% (n=270,487) of individuals had at least one PII. Among these, 11.2% matched at least one high-risk

scenario, representing 20.2% of those with inappropriate exposure. SL score and PIMs exhibited lower prioritization efficiency (4.5% and 3.5% respectively). Conversely, pDDIs and TDs flagged over one-third of exposed individuals as high-risk. By considering prioritizing all individuals with at least three indicators, as well as those with one or two indicators who fell into the highest-risk scenarios, a total of 49–52 patients per physician would be selected.

This work presents a novel and pragmatic framework to support prioritization in medication review processes. By leveraging routinely collected administrative data, the proposed algorithm enables targeted identification of older adults at heightened risk for adverse drug events. The model's integration of individual-level risk profiles and cumulative burden metrics offers a powerful and scalable tool for supporting deprescribing strategies in real-world clinical practice, particularly within constrained primary care settings. This work lays the foundation for future prospective validation studies and the potential integration of the algorithm into digital clinical decision support systems.

Riassunto

La prescrizione inappropriata negli adulti anziani rappresenta una sfida crescente per i sistemi sanitari di tutto il mondo, dato l'aumento della multimorbilità e della politerapia nella popolazione che invecchia. Regimi farmacologici inappropriati non solo aumentano il rischio di reazioni avverse da farmaci e di ospedalizzazioni, ma contribuiscono anche a costi sanitari eccessivi e a un declino della qualità della vita del paziente.

Data la loro peculiare complessità clinica e vulnerabilità fisiologica, gli anziani sono particolarmente esposti ai rischi associati all'uso inappropriato di farmaci, rendendoli un target critico per strategie preventive volte a ottimizzare la farmacoterapia e a ridurre i danni evitabili. Tra queste misure, è raccomandata l'implementazione periodica della revisione della terapia farmacologica. Tuttavia, i professionisti sanitari - in particolare i medici di medicina generale - pur essendo centrali nella gestione delle terapie croniche, affrontano crescenti vincoli di tempo che spesso ostacolano l'implementazione sistematica di tali revisioni. In questo contesto, vi è un'urgente necessità di strumenti flessibili e basati sui dati che possano supportare i clinici nell'identificare i pazienti che possono beneficiare maggiormente di interventi di revisione della terapia, ottimizzando così l'allocazione di tempo e risorse.

Questa tesi presenta lo sviluppo di un algoritmo finalizzato a prioritizzare i pazienti anziani che dovrebbero ottenere il maggior beneficio da interventi di revisione della terapia, basandosi su dati completi del mondo reale. Svolto nell'arco di un progetto di ricerca di dottorato triennale, il lavoro affronta un problema urgente di sanità pubblica - la politerapia e l'uso inappropriato di farmaci tra gli anziani - e propone una soluzione pragmatica e basata sui dati per migliorare la sicurezza prescrittiva e ottimizzare le risorse cliniche nell'assistenza primaria.

A seguito di un'approfondita revisione della letteratura, sono stati identificati sei indicatori di inappropriatezza prescrittiva (PII):

- Farmaci potenzialmente inappropriati (PIMs)
- Potenziali interazioni farmaco-farmaco (pDDIs)
- Farmaci che aumentano il rischio di caduta (FRIDs)

- Duplicazioni terapeutiche (TDs)
- Elevato carico cognitivo anticolinergico (ACB)
- Elevato carico sedativo (SL)

L'identificazione di questi indicatori si è basata su criteri internazionali consolidati, adattati al mercato farmaceutico italiano e validati attraverso robuste definizioni operative.

Il lavoro è stato condotto utilizzando i database amministrativi sanitari di quattro Unità Sanitarie Locali in Lombardia (Italia), coprendo oltre 640.000 individui di età pari o superiore a 65 anni tra il 2015 e il 2018. L'esposizione a ciascun PII è stata determinata tramite definizioni operative che tenevano conto delle date di dispensazione dei farmaci, della classificazione ATC, delle Dosi Definite Giornaliere e delle finestre di co-prescrizione. Gli individui con una prima esposizione tra gennaio 2015 e settembre 2018 sono stati seguiti per 90 giorni per valutare il rischio di ospedalizzazione per tutte le cause, utilizzando una strategia di appaiamento per set di rischio con un controllo per ogni individuo esposto, abbinato per età e sesso. Sono stati usati modelli di regressione logistica multivariata, aggiustati per *high dimension propensity score*, per stimare gli *odds ratio* (OR) di ospedalizzazione per tutte le cause associati a ciascun PII.

Tutti e sei i PII sono risultati significativamente associati a un aumento del rischio di ospedalizzazione. I rischi più elevati sono stati osservati per i FRIDs (OR 1,62; IC 95%: 1,51–1,73), i PIMs (OR 1,55; IC 95%: 1,48–1,62) e le TDs (OR 1,52; IC 95%: 1,46–1,58). Anche il punteggio SL (OR 1,43; IC 95%: 1,31–1,56) e il punteggio ACB (OR 1,52; IC 95%: 1,43–1,61) hanno mostrato un'associazione significativa.

Una volta stabilito l'OR di base per ciascun PII, abbiamo sviluppato modelli ad albero decisionale per ogni indicatore al fine di identificare profili di pazienti ad alto rischio, ovvero combinazioni di caratteristiche demografiche e cliniche associate a un rischio di ospedalizzazione significativamente più elevato rispetto a quello conferito dalla sola esposizione. Ogni scenario è stato validato utilizzando la regressione logistica condizionale in confronto al rischio complessivo dei singoli indicatori. Attraverso campioni bootstrap multipli, sono stati identificati 59 scenari distinti ad alto rischio:

14 per SL, 14 per TDs, 11 per FRIDs, 10 per pDDIs, 7 per PIMs e 4 per ACB. Questi scenari caratterizzano sottogruppi di pazienti che dovrebbero essere rapidamente prioritizzati per l'attenzione clinica, poiché presentano un rischio di ospedalizzazione particolarmente elevato.

Per stimare l'impatto dell'algoritmo nel mondo reale, abbiamo applicato gli scenari a una coorte di 501.785 anziani nel primo semestre del 2018. Il 55,3% (n=270.487) degli individui presentava almeno un PII. Tra questi, l'11,2% corrispondeva ad almeno uno scenario ad alto rischio, rappresentando il 20,2% di coloro con un'esposizione inappropriata. I punteggi SL e i PIMs hanno mostrato una minore efficienza di prioritizzazione (rispettivamente 4,5% e 3,5%). Al contrario, le pDDIs e le TDs hanno identificato come ad alto rischio oltre un terzo degli individui esposti. Considerando di prioritizzare tutti gli individui con almeno tre indicatori, così come quelli con uno o due indicatori che rientravano negli scenari a più alto rischio, verrebbero selezionati un totale di 48–50 pazienti per medico.

Questo lavoro presenta un *framework* innovativo e pragmatico a supporto della prioritizzazione nei processi di revisione della terapia farmacologica. Sfruttando dati amministrativi raccolti routinariamente, l'algoritmo proposto consente l'identificazione mirata di anziani a maggior rischio di eventi avversi da farmaci. L'integrazione nel modello di profili di rischio a livello individuale e di metriche di carico cumulativo offre uno strumento potente e scalabile per supportare le strategie di deprescrizione nella pratica clinica reale, in particolare in contesti di assistenza primaria con risorse limitate. Questo lavoro pone le basi per futuri studi di validazione prospettica e per la potenziale integrazione dell'algoritmo nei sistemi digitali di supporto decisionale clinico.

List of abbreviations

ACB	Anticholinergic Cognitive Burden
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical (classification)
BG	Bergamo
DDD	Defined Daily Dose
FRID	Fall-Risk-Increasing Drug
GP	General Practitioner
LC	Lecco
LHU	Local Health Unit
MB	Monza Brianza
MN	Mantova
NHS	National Health Service
pDDI	Potential Drug–Drug Interaction
PII	Prescribing Inappropriateness Indicator
PIM	Potentially Inappropriate Medication
QoL	Quality of Life
SL	Sedative Load
TD	Therapeutic Duplication
WHO	World Health Organization

CHAPTER 1

Aging and medications use

1.1 The older population

The aging of the global population has been a well-known and widely discussed phenomenon for several years, although this trend may vary depending on the socioeconomic situation of the country in question, as well as fluctuating data sources due to sociopolitical changes. It is the result of all those processes encompassing healthcare, medicine, economic, and social factors, and it is one of the four global demographic "megatrends" alongside population growth, international migration, and urbanization. The social and economic changes associated with population aging are fundamental to the 17 Sustainable Development Goals (SDGs), reported in **Figure 1**, included in the 2030 Agenda for Sustainable Development. Population aging trends are particularly relevant to eradicating poverty (SDG 1), ensuring healthy lives and promoting well-being for all and at all ages (SDG 3), achieving gender equality (SDG 5), promoting full and productive employment and decent work for all (SDG 8), reducing inequalities within and among countries (SDG 10), and making cities and human settlements inclusive, safe, resilient, and sustainable (SDG 11). Beside socioeconomic and sociopolitical factors, also the decline in fertility and the increase in longevity have led to a rise in the percentage of elderly individuals within the population ^{1 2}.



Figure 1- The 17 world Sustainable Development Goals (SDGs)

The division into chronological age groups is adopted as a proxy for the economic dependency of the elderly population, recognizing the diversity among individuals in terms of economic activity and functional capacity, considering the diversity in levels

of economic activity during various traditional working phases, tracking changes in economic dependency, and relying on the most widely available comprehensive global data. The most common measure is the old-age dependency ratio, which equals the number of people aged 65 and over divided by the number of people aged between 20 (or 18) and 64. The division into chronological age groups provides a replicable and simple way to measure and track various population indicators, even though there are differences considering the entire globe scenarios. **Figure 2** illustrates the global number of elderly people in 2019, showing that individuals aged 65 and over amounted to 703 million, with a prediction of 1.5 billion people aged 65 and over by 2050 but their distribution is not and will not be equally distributed worldwide ³.

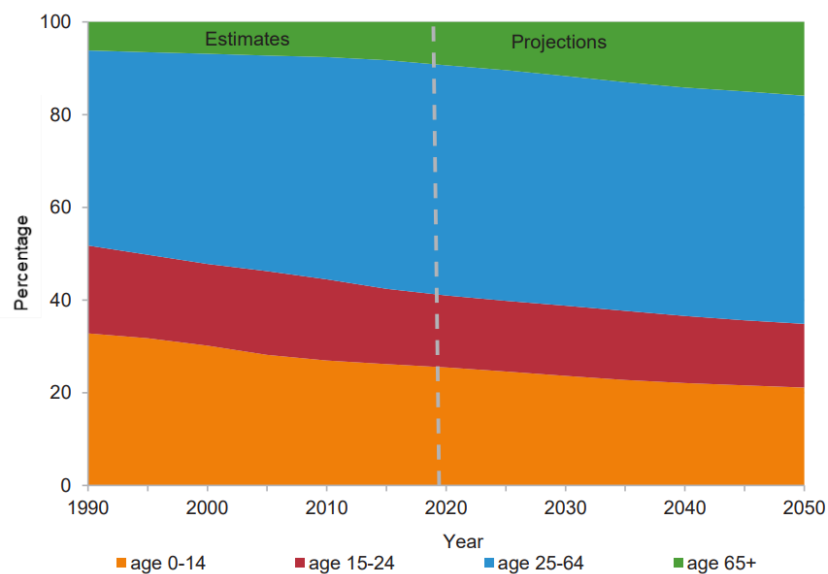


Figure 2- Global population percentage for age group from 1990 to 2050

Life expectancy at older ages increased by 7.7 years (12%) from the period 1990–1995 to 2015–2020. In North America and Europe, in 2019, the ratio of elderly individuals to those of working age was 30 to 100, and it is projected to reach 49 to 100 by 2050 ². Italy is experiencing one of the most pronounced aging trends in Europe, largely because of the Baby Boom, occurred in Italy between 1963 and 1965 (**Figure 3**). These generations, born during this period of high fertility, are now reaching their early 60-65s remaining a part of the under-65 age group. This demographic shift implies that, over the next decades, these individuals will enter the over 65 age group and older individuals will move into the over-80 category (**Figure 4**).

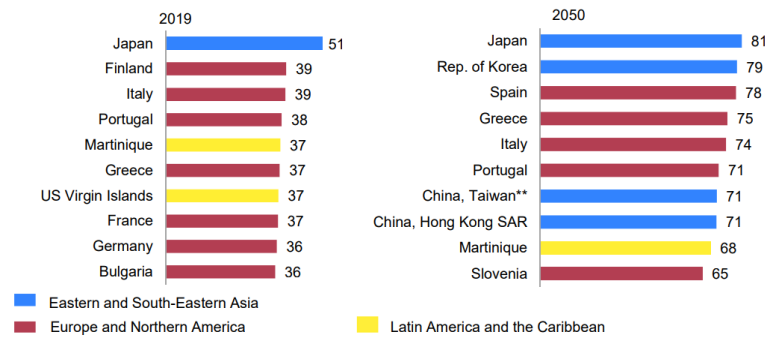


Figure 3- The ten countries or regions (excluding Australia and New Zealand) with the highest elderly-to-working-age ratio (65+/20-64) (2019 on the left, 2050 on the right) ⁴

In 2019, 2022 and 2023, there were over 14 million people aged 65 and older in Italy, representing 24% of the resident population ^{5 6 7}. In addition to this demographic boom, it is important to consider all the scientific advancements of the last century up to the present day, particularly in the fields of healthcare and pharmacology, as well as the approach to treating diseases by eradicating symptoms rather than addressing the root cause of the illness itself. This has resulted in many elderly individuals appearing to be in good health, despite dealing with multiple overlapping conditions with under control symptoms, contributing to an increase in average life expectancy. The result is that many older can live relatively healthy lives despite their conditions ⁸.

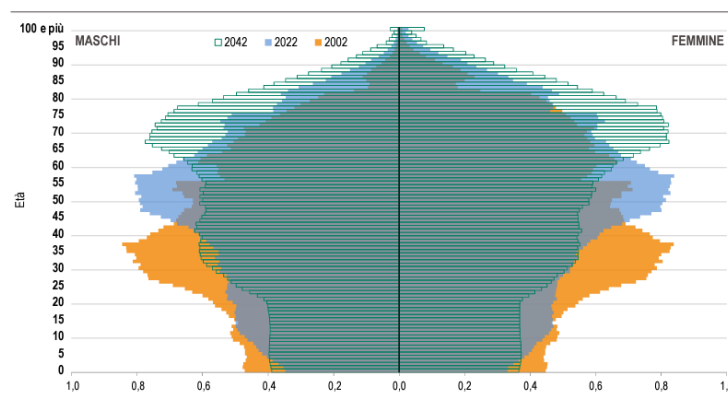


Figure 4- Age pyramid as on January 1st in the years 2002, 2022, and 2042 ⁵

1.2 Ageing

While chronological age is directly measurable, it does not always reflect the biological aging process that can be defined as the combination of several factors, such

as oxidative stress, telomere shortening, cellular senescence, DNA damage, mitochondrial dysfunction, and immunosenescence. These factors are not equally pronounced in every individual and lead to varying levels of aging, such as accelerated aging when multiple factors are differently present in an individual. The outcomes include pulmonary, metabolic, musculoskeletal, neurological, cardiovascular diseases, and cancer (**Figure 5**), which may appear individually or simultaneously in a single individual, leading to comorbidity conditions ⁹.

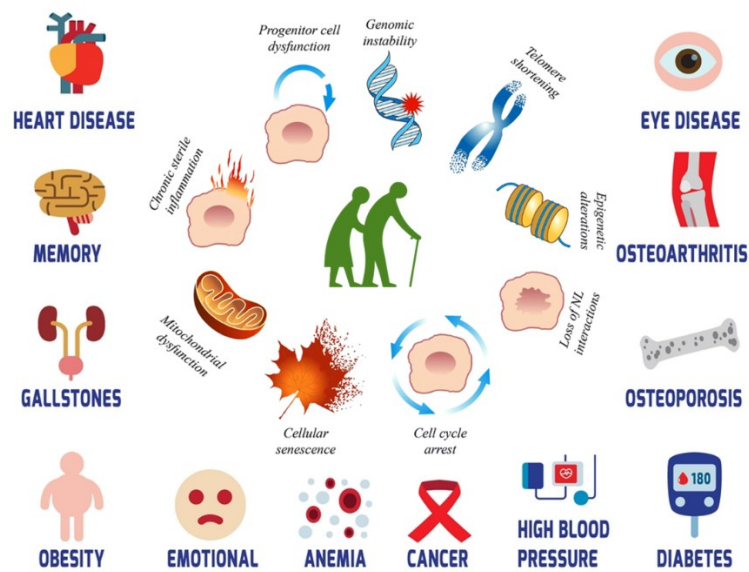


Figure 5- Age related molecular changes and possible outcomes

Looking at **Figure 6**, we can appreciate a clear relationship between chronological aging and the progressive increase in the number of comorbidities. This trend reflects the natural accumulation of chronic conditions over time, which is a hallmark of aging process: as chronological age increases, so does the number of concomitant disorders, leading to greater functional decline and dependency. Despite younger adults represents a consistent proportion of individuals, in the over 65 population multimorbidity becomes the norm rather than the exception. With advancing age, the complexity of care increases significantly, and the accumulation of morbidities contributes to frailty and vulnerability.

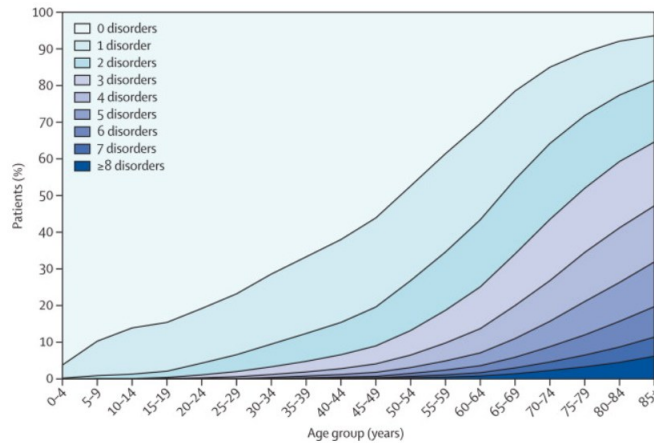


Figure 6- Age groups and percentage of patients in relation to the number of comorbidities ⁹

The aging process induces profound physiological modifications that alter the body's response to medications ¹⁰. These changes, which affect both pharmacokinetics (the effect of the body on a drug) and pharmacodynamics (the effect of a drug on the body), are fundamental to understand the increased vulnerability of older adults to adverse drug events. From a pharmacokinetic perspective, all phases of a drug through the body are impacted. Although gastrointestinal absorption is the least affected phase, changes such as delayed gastric emptying or increased pH can still alter the kinetics of certain drugs. More clinically relevant are the alterations in distribution, which are driven by shifts in body composition: with age, there is a decrease in lean body mass and total body water, and a relative increase in fat mass. Consequently, lipophilic drugs (such as diazepam) have a larger volume of distribution and a prolonged half-life, leading to an increased risk of accumulation and extended sedation. Conversely, hydrophilic drugs (like digoxin) are distributed in a smaller volume, reaching higher plasma concentrations for a given dose. Hepatic metabolism undergoes a significant decline, primarily due to reductions in liver mass and blood flow. This particularly affects drugs with high first-pass metabolism, whose bioavailability can increase substantially, and the activity of cytochrome P450 enzymes (especially CYP3A), although this reduction is more influenced by factors such as frailty and sarcopenia than by chronological age alone. In contrast, Phase II metabolic pathways (such as glucuronidation) remain relatively preserved, making drugs that follow this route (e.g., lorazepam, oxazepam) a generally safer choice in older adults.

Finally, the most clinically significant pharmacokinetic change is the reduction in renal elimination. The glomerular filtration rate (GFR) progressively declines with age, by approximately 7–8 mL/min per decade after age 30. This decline, coupled with reduced tubular secretion, impairs the clearance of numerous drugs and their active metabolites, drastically increasing the risk of toxicity and accumulation. The management of renally cleared drugs (such as many antibiotics, DOACs, or digoxin) therefore requires careful assessment of renal function and, frequently, dose adjustment.

These pharmacokinetic alterations, combined with an increased sensitivity of drug receptors (pharmacodynamics), explain why medication use in older adults demands a cautious and personalized clinical approach that extends beyond simple disease-based guidelines.

As illustrated in **Figure 7**, frailty is a multifactorial condition influenced by several interrelated domains, including physical health, social context, functional ability, and adherence to therapy.

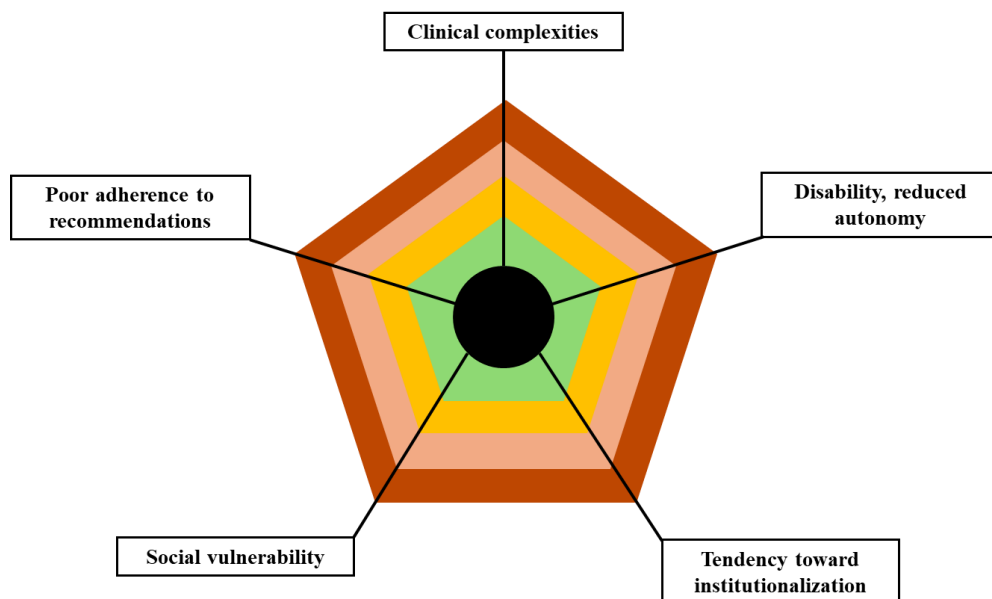


Figure 7- Multidimensional conceptualization of frailty

1.2.1 Frailty and social vulnerability

Frailty is a geriatric syndrome characterized by diminished physiological reserves, reduced homeostatic capacity, and heightened vulnerability to external stressors. Beyond this, frailty is also profoundly influenced by social determinants. Older adults who experience social isolation, low socioeconomic status, or limited access to supportive networks often exhibit worse health outcomes and greater clinical instability. Studies have shown that socially vulnerable individuals are more likely to present with both physical frailty and mental health deterioration, particularly depression and anxiety, which further compound their medical risks. A systematic review and meta-analysis involving over 40 studies found that socially isolated older adults had a 1.5-fold increased risk of becoming frail and were more likely to experience functional decline and mortality ¹¹. Data from community-dwelling older populations suggest meeting criteria for social frailty ¹². These findings reinforce the concept that social vulnerability is not merely a contextual background but an active determinant of health decline in older age.

1.2.2 Disability, reduced autonomy, and risk of adverse outcomes

Frailty often leads to progressive functional decline and disability with impairment in daily activities. Older adults may struggle with basic activities of daily living, such as bathing, dressing, and mobility. This decline is not only a marker of advanced frailty but also a predictor of adverse outcomes. studies have demonstrated that frailty significantly increases the risk of loss of autonomy and subsequent admission to long-term care facilities¹³. In addition, frail older adults face a higher likelihood of hospitalization. Their diminished physiological capacity makes them more susceptible to acute illnesses, complications from chronic diseases, and slower recovery times. Hospital admissions among frail patients are associated with longer stays, increased risk of adverse events such as delirium and functional decline, and higher mortality rates ^{14 15}.

1.2.3 Therapeutic adherence and frailty

Frailty also affects patients' ability to manage and adhere to prescribed treatment regimens. Factors that contribute to poor adherence in older population included polypharmacy, cognitive impairment, depressive symptoms, and absence of caregiver support. Polypharmacy, which is common among frail elders due to multiple chronic conditions, increases the complexity of medication management and the risk of drug interactions and side effects. Cognitive impairments, including mild cognitive decline or dementia, further reduce patients' capacity to follow complex dosing schedules or recognize the importance of adherence. Additionally, depressive symptoms often present in frail individuals can diminish motivation and energy to maintain consistent medication regimens. The absence of reliable caregiver support exacerbates these difficulties, leaving many frail older adults without the assistance needed to manage their treatments properly. Frail older adults with high medication burden are more likely to experience functional decline and emergency admissions compared to their robust counterpart ^{16 17}.

1.3 Medications in the older population

The growing clinical complexity must be considered in the context of population aging, which is reshaping healthcare systems and their sustainability: as life expectancy increases, chronic diseases accumulate, and the healthcare demand generated by older adults becomes more complex and continuous. This shift poses a growing burden on primary care, hospital services, long-term care, and pharmaceutical management.

1.3.1 Polypharmacotherapy

The presence of a chronic disease usually implies the use of an on-purpose therapy. When more chronic disease occurs, a more therapies are added, and so on, potentially leading to an n number of diseases for an n number of pharmacological therapies and several treatment regimens: this is known as *polypharmacotherapy* ¹⁸. This term

combines the definitions of *polytherapy* (simultaneous use of multiple prescribed medications) and *polypharmacy* (use of multiple medications that are not necessary for the therapeutic purpose, including those not formally prescribed) ¹⁹.

Figure 8 illustrates the complexity of managing patients with multimorbidity, where multiple coexisting conditions often leading to the use of multiple treatments. Clinical decisions are frequently guided by disease-specific guidelines that are typically based on evidence excluding patients with multiple chronic conditions. As a result, the applicability of such guidelines to real-world multimorbid populations is limited. Achieving balance between the need to manage multiple coexisting conditions and the imperative to modulate the pharmacological burden, avoid drug interactions, and minimize adverse effects, while preserving the patient's quality of life, is critical in optimizing care for individuals with complex health needs.

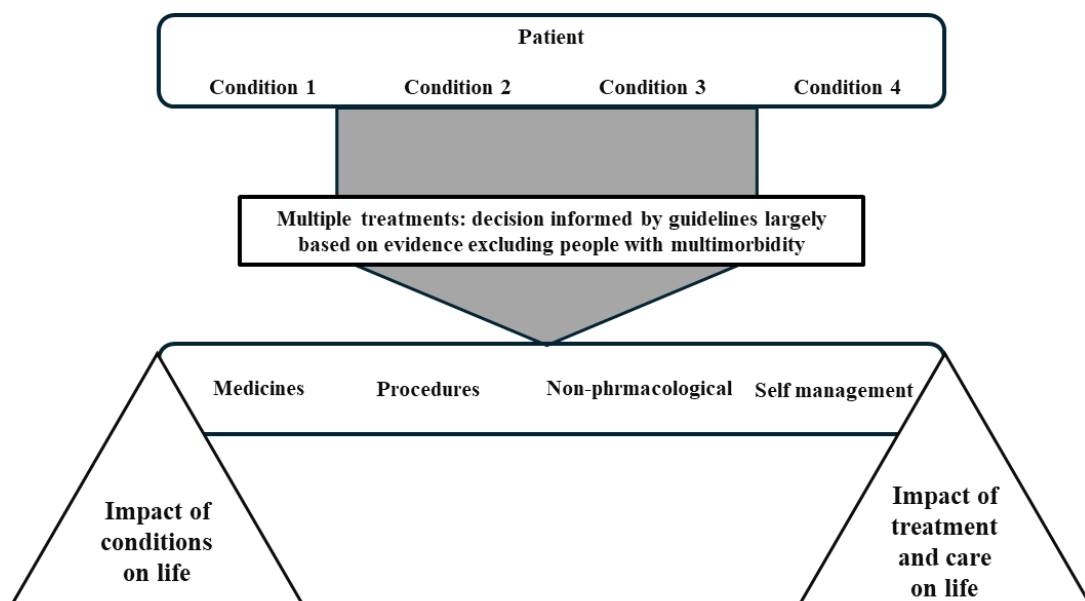


Figure 8- *Single condition focused model vs multimorbidity*

Polypharmacy is a complex phenomenon with significant implications in clinical practice. **Figure 9** illustrates a cognitive cycle that highlights the main factors involved in polypharmacy, presented as a focal point around which critical elements such as under- and over-prescription, inappropriate medication use, adverse effects (which can, in turn, trigger the prescribing cascade), poor adherence to therapy, and increased healthcare costs. This cycle is further influenced by external factors like the patient's

comorbidity conditions, which often necessitate the use of multiple medications, and secondary prevention regimens.

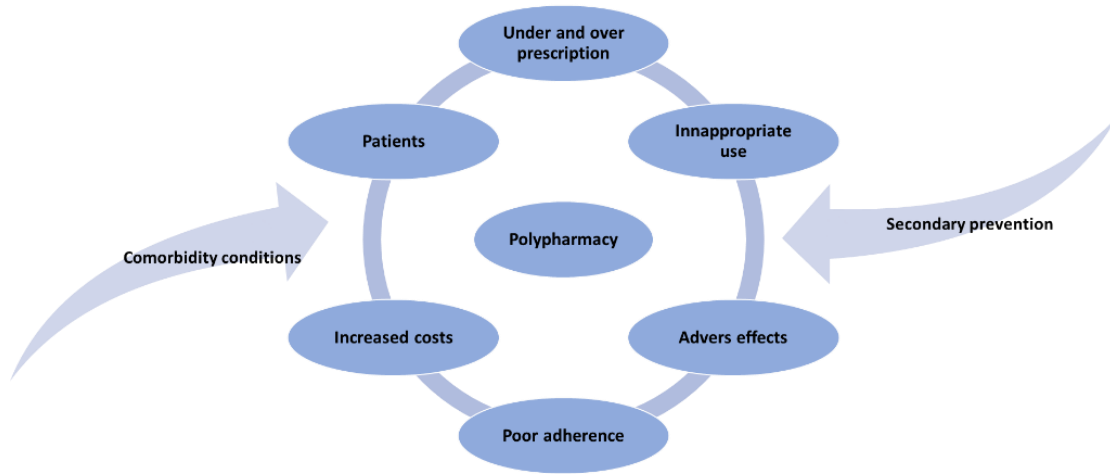


Figure 9- Factors Involved in Polypharmacy

As the complexity of therapeutic regimens increases with age- often due to multimorbidity and polypharmacy- so does the challenge of maintaining the risk benefit balance of therapies. This complexity directly impacts medication adherence, which refers to the extent to which a patient acts in accordance with the agreed-upon recommendations from a healthcare provider. Older adults with lower levels of autonomy, particularly in cognitive and functional domains, are less likely to effectively manage their medication schedules and follow medical recommendations, thereby demonstrating lower rates of adherence.

1.3.2 Adverse drug reactions

Aging leads to altered homeostasis of the body, which, along with polytherapy, increases the number of adverse drug reactions (ADRs).

In Italy, individuals over 65 account for 25% of all ADRs, and among these, 50% have led to hospitalization. Moreover, an evaluation of the severity level showed that 37% of suspected ADR reports in patients aged ≥ 65 years were serious, compared to 30% in the general population. Furthermore, 27% of reports recorded for older patients

indicated that they required more hospitalization or long-term care, compared to 21% for the general population, with a relevant impact on National Health Service costs (**Figure 10**)²⁰. This phenomenon highlights a significant clinical challenge in the management of the older population which vulnerability can be attributed to multimorbidity, polypharmacy, and physio-pathological changes. These factors are key in altering the pharmacokinetics and pharmacodynamics of drugs, thereby increasing the risk of ADRs and impacting the overall risk-benefit balance of medication.

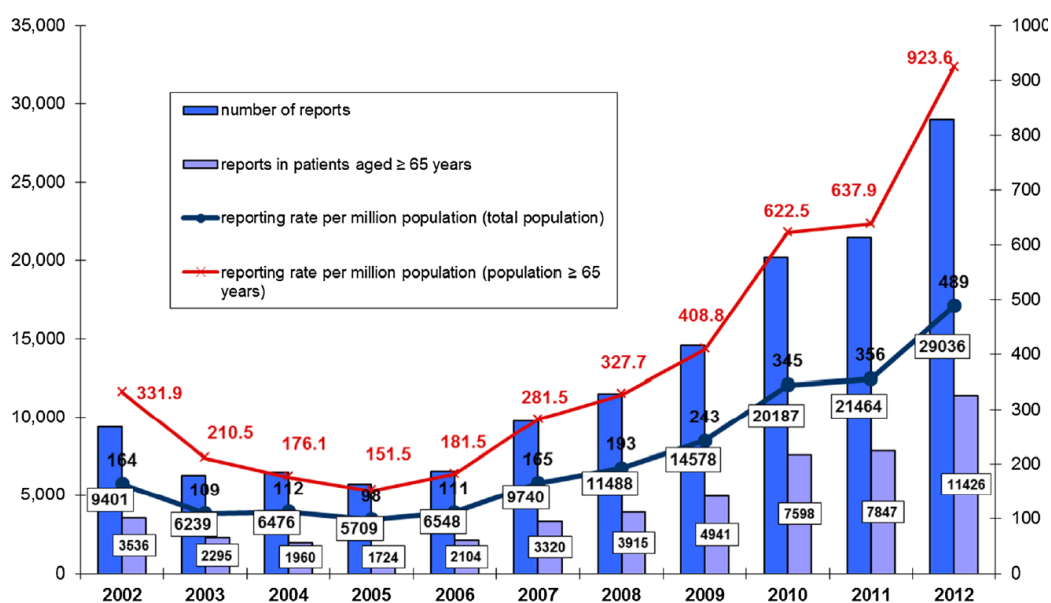


Figure 10- Total number of reports, including those from patients >65 years, for suspected adverse reactions from 2001 to 2012²⁰

1.3.3 Appropriateness and inappropriateness

To ensure an appropriate risk-benefit balance, patients should receive pharmacological therapies suited to their clinical needs, in doses that meet their individual requirements, for an appropriate duration, and at the lowest cost to themselves and their community²¹. Appropriate prescribing means that therapies must be supported by the best available evidence, have a clear purpose, be optimized, and involve the patient's agreement, as well as their commitment, understanding personal needs, values, and preferences. An appropriate therapy must be goal-oriented, regularly reviewed, and

adjusted when necessary, and should always involve the patient's informed agreement and active participation. In this framework, appropriateness goes beyond simply choosing the "right" drug- it reflects a dynamic, patient-centred process aimed at maximizing therapeutic benefit while minimizing harm. On the other hand, inappropriate prescribing refers to any deviation from the ideal of appropriate prescribing. It can include prescribing medications that are unnecessary, potentially harmful, or no longer supported by current clinical evidence. Inappropriate therapies may also involve incorrect dosages, excessive treatment duration, the omission of necessary medications- particularly in vulnerable populations such as the older population. To guide clinicians, the appropriate prescribing process can be conceptualized as a flow which includes identifying the correct indication, selecting the most suitable pharmacological option, evaluating risks and benefits, considering patient preferences, and periodically reassessing the therapy. Any disruption or failure at one or more stages of this process results in inappropriate prescribing. Older adults represent a particularly high-risk group for inappropriate prescribing. Factors such as multimorbidity, age-related physiological changes, and a reduced ability or willingness to adhere to complex regimens complicate therapeutic decisions. Polypharmacy can increase the risk of ADRs, drug-drug interactions, poor adherence, and increased healthcare costs. Moreover, both overprescribing and underprescribing are common, leading to inefficiencies and preventable harm. The outcomes of inappropriate prescribing vary depending on the context and severity. In some instances, it may not cause any immediate clinical effects, but in more serious cases, it can lead to significant consequences, such as the worsening of the patient's condition, the need for additional diagnostic tests, increased hospital admissions, and even higher mortality rates, particularly among older adults or those with multiple co-existing health conditions that may affect their physiological function²². Beyond these medical impacts, inappropriate prescribing can also negatively affect the patient's quality of life, causing unnecessary discomfort, and strain the relationship between the clinician and the patient. Moreover, the misuse of medications can place a financial burden on both the patient and the healthcare system, driving up costs and contributing to the wastage of valuable healthcare resources. This, in turn, may limit access to other critical treatments or increase overall healthcare costs²³.

Inappropriate prescribing reflects a systemic issue that extends beyond individual clinical encounters. It may be deep-rooted in fragmented healthcare, lack of coordination among healthcare providers, poor or lacking clinical guidelines, or limited time for shared decision-making. These challenges are particularly pronounced in certain older patients who often require input from multiple specialists and long-term therapeutic management. Addressing inappropriate prescribing, therefore, demands not only improved clinical judgment, but also broader organizational and policy-level interventions aimed at optimizing medication use, enhancing communication across care settings, and empowering patients in their treatments.

1.3.4 Medication review

When a therapy is not appropriate- due to lack of efficacy, safety concerns, or evolving patient needs- it should be revised through process known as *Medication Review* (MR): a structured and systematic critical assessment of a patient's medication regimen, including prescribed drugs, over-the-counter (OTC) products and complementary therapies. The aim is to optimizing therapeutic outcomes, minimizing medication-related problems and the number of medications, reducing unnecessary healthcare costs and wastes ²⁴. MR assesses the appropriateness, effectiveness, safety, and adherence of each treatment, and it should be typically carried out in collaboration with patient and relevant healthcare professionals, such as general practitioners, pharmacists, and specialists. Through MR, clinicians can adjust dosages, discontinue unnecessary drugs, and ensure that the medication regimen aligns with current clinical guidelines and the patient's evolving health status, ensuring the risk-benefit balance. A key component of this process is deprescribing, defined as the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes ²⁵. Deprescribing is not simply about stopping drugs but rather ensuring that every medication prescribed continues to meet the patient's current therapeutic needs in light of evolving clinical evidence and individual health status. In the Italian healthcare system, the responsibility of medication review falls to GPs, given their longitudinal relationship with patients and comprehensive knowledge of their medical history. While GPs are central to

deprescribing practices within the framework of the Italian National Health System (NHS), they face several challenges in translating this responsibility into routine clinical action. One of the main barriers reported by Italian GPs is the need to modify prescriptions initiated by other clinicians, particularly specialists ²⁶. This reflects a broader issue of care fragmentation and limited interdisciplinary communication. Indeed, older patients are usually managed by multiple providers across different care settings, making it difficult for the GP to confidently adjust or discontinue medications without full knowledge of the entire therapeutic rationale. Additional obstacles include time constraints, insufficient training in deprescribing methodologies, and the lack of formalized, easily applicable guidelines. Many GPs also report difficulty accessing complete clinical information, which impairs their ability to assess the full appropriateness of a patient's drug regimen ²⁶. Although pharmacists could provide meaningful support in this process, the role of clinical pharmacy in Italy is still evolving and varies significantly across regions. Moreover, structured collaboration between GPs and pharmacists remains limited in practice even if wanted by GPs ²⁶. Despite these challenges, GPs are uniquely positioned to lead medication optimization efforts, thanks to their holistic understanding of the patient's medical history, comorbidities, and social context. Strengthening their role in deprescribing will require system-level interventions, including standardized tools, targeted training, and improved communication pathways between all healthcare professionals involved in the prescribing process.

1.4 The Italian Healthcare system

The Italian NHS, established in 1978, is a publicly funded system rooted in the principles of universality, equity, and accessibility. Built upon the Beveridge model, it aims to provide comprehensive, free-of-charge healthcare to all citizens, funded through national taxation ^{27,28}. The system is organized into three levels: national (Central Government), regional (Regional Governments), and local (Local Health Units, LHUs) ²⁹. This decentralization allows regions to have significant autonomy in organizing and delivering health services, even if they must still adhere to national guidelines and guarantee a set of essential health services, known as the *Livelli*

Essenziali di Assistenza (LEA), to all citizens. The central government's role is primarily regulatory, setting the essential care levels, while regional governments and Local Health Units (LHUs) are responsible for the daily provision of services. This decentralized structure grants regions the ability to tailor their health systems to local needs. The NHS operates as a network of institutions, including the Ministry of Health, regional health agencies, and local health units, along with private providers. These institutions are tasked with delivering a full range of services, from primary care to specialized treatments. Funding for the NHS is determined yearly by the national government, with allocations distributed to the regions based on population needs, often using an age-adjusted capitation method. Regions then distribute these fundings to their LHUs, which provide or contract services to ensure that health care needs include prevention, treatment of chronic diseases, and emergency care. The integration of services is intended to ensure continuity of care, particularly for those requiring both health and social care support ²⁹. In Italy, prescribing is primarily managed by GPs, who act as the main point of contact for patients and control access to specialist care. Pharmacists in Italy play a limited role, focusing predominantly on dispensing medications and offering general advice to patients, rather than being actively involved in clinical decision-making. Collaboration between GPs and other healthcare professionals in the prescribing process is generally less structured, and while electronic health records (EHRs) are increasingly being adopted, they are not yet fully integrated across all levels of care. GPs are self-employed professionals contracted with the NHS, acting as the first point of contact for citizens within the healthcare system. They are responsible for overall patient care, chronic disease management, prevention, and referrals to specialists or hospital services when necessary. The GP is crucial for continuity of care, territorial health management, and reducing unnecessary hospital visits, especially in the context of an aging population and increasing chronic conditions. In contrast to other European systems, the role of GPs in Italy reflects their integration into a tax-funded, regionally governed healthcare structure. While many European countries rely on GPs as gatekeepers to specialized and hospital care, Italy places a strong emphasis on GPs for comprehensive care, including chronic disease management resulting in GPs often under pressure due to higher patient loads reflecting the challenges of the NHS's decentralization.

CHAPTER 2

Aim of the project

In Italy, there is currently no officially designated professional responsible for systematically conducting medication reviews in older adults. GPs are arguably in the best position to carry out this task, given their ongoing relationship with patients and access to comprehensive clinical information. However, in practice, GPs often lack both the time, and the specific training required to perform thorough medication reviews. In Italy, a GP is responsible for approximately 1,500 patients, of whom at least 365 (around 24%) are aged 65 or older ³⁰, and it is difficult for a single GP to conduct an in-depth review for all older patients under his/her care. This situation highlights the need for tools that enable prioritization and selection of higher-risk patients, thereby optimizing available clinical resources. Although some real-world studies have focused on identifying patients at risk of inappropriate prescribing, there is still no practical, operational tool available in the Italian healthcare setting to help GPs routinely and effectively determine which older patients would benefit from a more detailed therapeutic assessment. What is currently missing is tools that allow GPs to focus their limited time and attention on patients at highest risk of inappropriate prescribing and related drug-related complications, a tool specifically designed to support the assessment of over 65 patients, tailored to the organizational features of the NHS, and based on the administrative health data available. These tools often struggle to provide meaningful prioritization, especially in real-world settings where multiple factors must be weighed.

In this context, our project introduces a structured, data-driven model to support the pharmacological management of older adults in primary care. Central to this approach is the development of a prioritization algorithm that leverages real-world data from regional healthcare databases to stratify patients based on their risk of inappropriate prescribing and drug-related complications. This risk-based stratification enables more efficient allocation of clinical resources by directing medication reviews to those most likely to benefit. Acknowledging the complexity of managing multimorbidity and polypharmacy in aging populations, the model is intended to support- not replace- clinical judgment, with healthcare providers and general practitioners remaining at the core of the decision-making process.

Specifically, this project pursued the following goals:

- *Identification of inappropriateness criteria*: we identified explicit indicators of potentially inappropriate prescribing specifically tailored and applicable to Italian healthcare administrative data and with clinical meaning to the population aged 65 and older. The aim was to capture at-risk patients beyond the standard drug lists. Particular attention was paid to selecting indicators that both reflect a meaningful clinical impact in older adults and are reliably traceable within Italian administrative datasets.
- *Risk assessment associated with each indicator*: for each selected indicator of inappropriate prescribing, we estimated the all-cause hospitalization risk, to quantify the clinical impact of each selected indicator. This analysis enabled us to demonstrate and quantify the association between the indicators and the risk of all-cause hospitalization.
- *Development of a prioritization algorithm*: based on the results obtained, we quantify we selected scenario at higher risk prioritizing those with the greatest potential for harm. We developed an algorithm capable of stratifying older patients according to their risk profile, with the goal of facilitating the identification of individuals who would benefit most from a targeted medication review. For each indicator, we sought to define specific patient-level conditions or prescribing contexts associated with an even higher risk than that conferred by the indicator alone.

Figure 11 illustrates the core steps of the project, each corresponding to a specific objective pursued throughout the study.

These stages reflect the progression from identifying clinically relevant indicators of inappropriateness, to quantifying their associated risks, and finally, to the development of a data-driven prioritization algorithm. The figure provides a structured overview of the methodological framework used to guide the project and achieve its goals.

The final algorithm was designed to be simple, interpretable, and compatible with the structure of Italian administrative healthcare data. It was conceived as a practical tool

to support- rather than replace- clinical judgment, aiming to enable informed and sustainable therapeutic decisions in the pharmacological management of older adults.

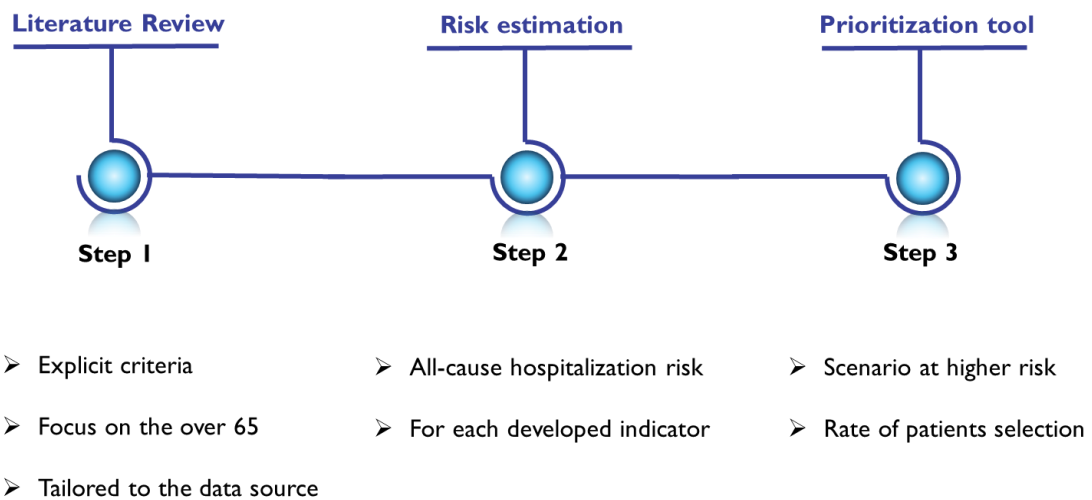


Figure 11- *Main steps of the project*

In summary, this project addresses a gap in managing pharmacotherapy for older adults by introducing a pragmatic, evidence-based approach to prioritize medication reviews. It aims to support healthcare professionals in delivering safer, more effective, and patient-centred care in the face of growing multimorbidity and polypharmacy challenges inherent in aging populations.

CHAPTER 3

Selection and management of inappropriate prescribing criteria

The process of evaluating the appropriateness of a pharmacological therapy is complex and to develop the core of our prioritization algorithm, it was therefore essential to first establish a robust framework of explicit criteria, carefully selected from the existing literature and adapted to the specific context of the Italian healthcare system. The following sections will detail this process, beginning with an overview of the methods used to evaluate medication prescriptions. We will then describe the systematic selection of the explicit indicators used in this thesis and the final development of the operational definitions necessary to apply these criteria to real-world administrative data.

3.1 Evaluation of medication prescriptions

Drug prescribing is a pivotal step in the healthcare process and one of the most impactful actions in patient care. Given its importance, it is essential that prescribing practices can be evaluated; however, the complexity of the process makes it challenging to define effective indicators. The pathway from clinical diagnosis to the selection of an appropriate pharmacological treatment is multifaceted, involving clinical, administrative, and ethical dimensions. Within this intricate context, the concept of appropriateness becomes central- not only as a standard of good clinical practice but also as a key criterion for assessing the quality and efficiency of healthcare delivery. To provide a more comprehensive framework for understanding the medication use process, Bell et al.³¹ proposed a model encompassing five distinct domains: prescribing, transmission, dispensing, administration, and monitoring (**Figure 12**). Each domain includes variables and measurable outcomes, both in terms of appropriate use and inappropriate use, especially in the context of polypharmacy or high-risk patient populations.

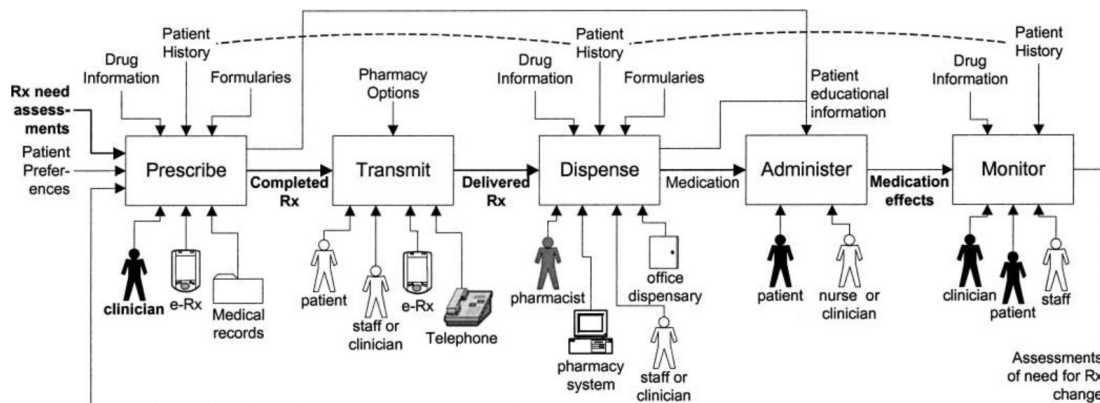


Figure 12- *The functional model of medication management proposed by Bell and colleagues*

Due to the complexity of the prescribing process, it is not always easy to determine whether a prescription is truly appropriate. For this reason, measuring prescribing appropriateness becomes essential not only to evaluate individual clinical decisions, but also to monitor overall healthcare performance, identify gaps in practice, and guide improvement efforts. To achieve this, it is necessary to develop and adopt clear, measurable indicators that can objectively assess whether a prescription aligns with best practices and therapeutic goals. Without such indicators, the concept of appropriateness risks remaining too abstract, limiting its utility in quality assurance, benchmarking, and health policy planning.

3.2 Indicators of appropriate prescribing

According to the Organisation for Economic Co-operation and Development (OECD), a quality indicator in prescribing is defined as: "A systematically developed statement that helps assess the degree to which medical treatment is appropriate, effective, and efficient". These indicators serve both as guides for the clinician and as tools for health systems to promote rational, safe, and cost-effective drug use. They also help in identifying areas of underuse, overuse, or misuse of pharmacological treatments. These indicators are fundamental tools for evaluating prescriptive behaviour, for identifying potentially inappropriate prescriptions (PIMs), and for implementing improvement actions. would have the following key characteristic ³²:

- valid, and reliable;

- highly or optimally specific and sensitive;
- based on agreed definitions;
- described exhaustively and exclusively;
- able to discriminate well;
- be related to clearly identifiable events for the user;
- suitable for comparisons; and (vii) evidence-based.

The need to measure appropriateness is increasingly evident in public health and is supported by a growing number of indicators developed internationally. These are used not only in clinical evaluation at the individual level but also in system-wide assessments, research studies, and policymaking. Appropriateness indicators are usually grouped into three main categories:

- structural: relate to the healthcare setting and organizational capacity;
- process: evaluate whether the actions performed are consistent with evidence-based recommendations;
- outcome: focus on the consequences of care in terms of patient health (death, disease, discomfort, disability, dissatisfaction).

Indicators can also be classified along another axis:

- drug-oriented indicators, which evaluate use based on the molecule or class of drugs ³³;
- disease-oriented indicators, which evaluate pharmacological appropriateness for specific clinical conditions;
- patient-oriented indicators, which consider patient characteristics and personalized needs ^{34 35}.

While the first two types are easier to apply- especially in administrative datasets- the patient-oriented indicators, though more difficult to assess, provide a higher level of clinical relevance and better support the principles of personalized medicine. These require access to clinical records, lab data, and context-specific information (such as functional status or frailty indexes), and are often more labor-intensive but more accurate in predicting inappropriate prescribing risks. The development of standardized, valid, and reproducible indicators for identifying PIMs is therefore

essential for improving therapeutic appropriateness and patient safety especially in older adults.

Finally, based on the topic evaluated, the main types of appropriateness indicators include:

- Prescribing indicators, which describe variability in clinicians' prescribing patterns under different clinical or pathological conditions, often expressed as the prevalence of affected patients;
- Consumption indicators, which assess variability in medication use by volume (e.g., Defined Daily Dose per 1,000 inhabitants/day) or cost (e.g., per capita pharmaceutical spending). These indicators are used to evaluate deviations from average values at different administrative levels (national, regional, local);
- Adherence indicators, which evaluate how well prescribing practices align with predefined therapeutic standards. These include adherence to ongoing drug use (e.g., chronic therapy continuation) and adherence to appropriate indications (e.g., drugs prescribed only when evidence-based indications are met).

The selection of indicators to assess prescribing appropriateness should be guided by several key criteria. First, indicators must be evidence-based, reflecting current clinical guidelines and best practices supported by robust scientific data. They should also be clinically relevant, meaning they capture aspects of prescribing that have a real impact on patient outcomes. In addition, indicators need to be measurable and reproducible, relying on data that are readily available and consistently recorded in clinical practice, such as electronic health records or prescription databases. Feasibility is another essential consideration: indicators should not impose excessive burden on healthcare providers or systems. Lastly, good indicators must be sensitive to change, allowing them to detect improvements (or deterioration) over time and in response to targeted interventions. The selection of indicators should also be grounded both on clinical and economic considerations. Clinically, indicators are functional to the improvement of health outcomes by guiding prescribing practices in line with therapeutic recommendations. Economically, they help reduce the overall costs associated with

patient care, beyond the price of the medication itself. Indeed, appropriate prescribing reduces the likelihood of requiring additional healthcare services- such as diagnostic procedures, treatment of adverse drug reactions, or hospitalizations- and increases the chances of achieving the therapeutic purpose.

Indicators play a central role in programs designed to improve healthcare performance and can be seen as essential tools in balancing pharmaceutical expenditure and clinical results. Several tools have been developed to assess prescription quality, broadly categorized as implicit tools (based on expert judgment and clinical context), explicit tools (based on predefined drug- or disease-specific criteria), or hybrid approaches combining both methods. Implicit indicators rely on the evaluation of prescribing appropriateness by a trained reviewer using clinical judgment in the context of the patient's full medical profile. This approach can be guided by structured tools, such as the MAI (Medication Appropriateness Index) and the PAI (Prescribing Appropriateness Index). MAI^{36 37} evaluates ten criteria: indication, efficacy, dosage, correct directions, practical indications, drug-drug interactions, drug-disease interactions, duplication, duration, and cost (**Figure 13**).

A weighted score is generated, which serves as a measure of prescribing appropriateness. Moreover, questions 1, 2, and 8 (indication, efficacy, and duplication) can be used to identify unnecessary polypharmacy and high rates of inappropriateness. It is not possible to evaluate misuse or underutilization of prescribed therapy. Additionally, it should be noted that application requires ten minutes per medication. Another example of implicit criteria is the AOU (Assessment of Underutilization of Medication, AOU), a structured tool used to evaluate whether patients are missing clinically indicated medications. It is commonly applied in the context of older adults or patients with multiple chronic conditions, where appropriate pharmacological therapy is crucial. The AOU involves a case-by-case review by a trained clinician who assesses whether any evidence-based treatments are lacking based on the patient's diagnoses, clinical status, and guidelines. Unlike tools that identify inappropriate prescriptions, the AOU focuses specifically on potential omissions, aiming to improve the completeness and quality of pharmacotherapy. Implicit tools are more flexible and patient-centered, allowing for a nuanced understanding of prescribing decisions. Their

main limitation, however, is that they are time-consuming, resource-intensive, and less reproducible, as they depend on the evaluator's expertise and interpretation.

To assess the appropriateness of the drug, please answer the following questions and circle the applicable rating:

1. Is there an indication for the drug?	A _____ B _____ C _____ Indicated Not Indicated
2. Is the medication effective for the condition?	A _____ B _____ C _____ Effective Ineffective
3. Is the dosage correct?	A _____ B _____ C + or C - Correct Incorrect
4. Are the directions correct?	A _____ B _____ C _____ Correct Incorrect
5. Are the directions practical?	A _____ B _____ C _____ Z Practical Impractical
6. Are there clinically significant drug-drug interactions?	A _____ B _____ C _____ Insignificant Significant
7. Are there clinically significant drug-disease/condition interactions?	A _____ B _____ C _____ Insignificant Significant
8. Is there unnecessary duplication with other drug(s)?	A _____ B _____ C _____ Necessary Unnecessary
9. Is the duration of therapy acceptable?	A _____ B _____ C _____ Acceptable Not acceptable
10. Is this drug the least expensive alternative compared to others of equal utility?	A _____ B _____ C _____ Least expensive Most expensive

Figure 13- *Medication Appropriateness Index, questions*

On the other hand, *explicit* criteria are measures based on predefined standards, generally drug- or disease-oriented, not patient-oriented. These can be applied even in the absence of clinical judgment and/or knowledge of the patient's clinical characteristics and do not take into account the factors that define the quality of healthcare³⁸. As a result, they are more easily standardized, straightforward to apply, and reproducible when used by different evaluators. Explicit criteria are presented as tables and lists, usually divided into categories such as medications to avoid in elderly patients, drug combinations that may cause drug-drug interactions, medications contraindicated in the presence of certain diseases, and possibly dosage recommendations, therapeutic alternatives, and also a weighted quality score of the recommendation based on the robustness of the source and evidence can be provided. However, these criteria do not consider comorbidities, previous ineffective therapeutic approaches, or the patient themselves (autonomy, willing, etc.). They also need to be regularly updated and adapted for each country. Each country has different healthcare

guidelines, even among European Union member states. Consider, for example, the differences in drugs available between European Union and United States; this makes international comparisons of prescription patterns extremely challenging.

Conceptually, explicit criteria are based on the Delphi method developed by the Rand Corporation ³⁹. This is a predictive method based on the comparison of expert opinions (rational and not aiming for consensus) on a new topic or one without an easily predictable solution. It was developed during the Cold War by Rand Corporation experts to assess the level of consensus among participants when confronted with uncertain issues. During the 1960s and 1970s, the Delphi Method was shown to offer significant advantages over traditional group discussions (such as conferences, brainstorming, and other interactive group processes) in situations where it was essential to compare the opinions of all involved experts. The Delphi Method is a decision-making process divided into an exploratory phase, an analytical phase, and a decision-making phase, which combines common knowledge to better address or resolve situations of uncertainty (**Figure 14**). The name "Delphi" humorously refers to the Oracle of Delphi, consulted for insights about the future, highlighting the importance of the question posed and the interpretation of the response. In numerous medical issues, there is often a need to solve problems characterized by uncertainty, whether related to the nature of the problem itself or to the interventions to be adopted

⁴⁰.

The use of explicit indicators has grown steadily over recent decades, in response to the growing complexity of pharmacotherapy and the need to ensure high-quality, safe, and cost-effective prescribing practices ⁴¹. Among the most widely adopted are the Beers Criteria ⁴², first developed in the United States and now regularly updated by the American Geriatrics Society. These criteria offer a comprehensive list of drugs that should generally be avoided in older adults due to an unfavourable risk-benefit profile, with recommendations based on specific comorbidities, drug-disease interactions, and dosage thresholds. Another valuable tool is the STOPP/START criteria ⁴³, which go beyond the identification of inappropriate medications by also including potentially beneficial therapies that are commonly under-prescribed. This dual approach addresses both overuse and underuse of pharmacotherapy, helping to better align

prescribing with the principles of comprehensive, patient-centred care. The criteria are especially suitable for use in geriatric settings and have been integrated into several European research and clinical initiatives. Similarly, the EU(7)-PIM list ⁴⁴ was developed to offer a harmonized European perspective on PIMs, taking into account regional prescribing habits and available formulations.

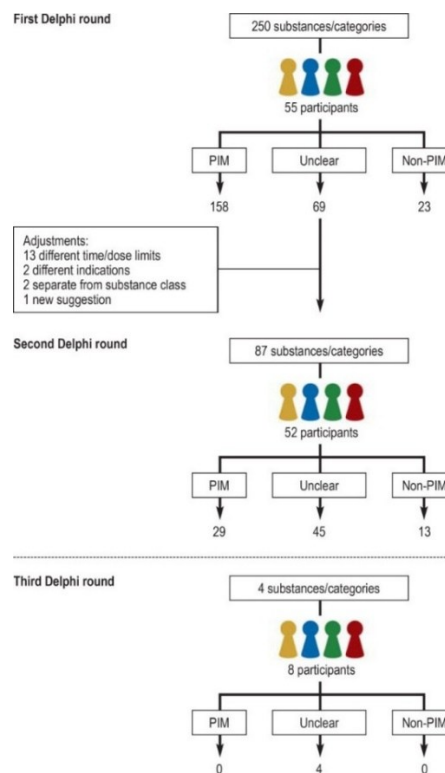


Figure 14- *Flows of Delphi methods*

Other examples of explicit indicators include disease-specific lists, such as those focusing on cardiovascular disease, diabetes, or mental health conditions, as well as polypharmacy thresholds (e.g., use of more than five or ten drugs concurrently) used to flag patients at higher risk of drug-related problems. These indicators are especially helpful in large-scale health service monitoring, research databases, and prescription audits, allowing for the identification of patterns and potential areas of intervention.

The key strength of explicit indicators lies in their reproducibility and scalability. Because they are based on predefined rules, they can be easily automated and applied in various settings, including retrospective analyses of electronic health records, claims databases, and administrative registries. This makes them extremely useful in epidemiological surveillance, health policy evaluation, and quality improvement

initiatives. Their objectivity also supports benchmarking and comparison across different regions, institutions, or time periods. However, explicit indicators also have limitations. Their rigidity can lead to oversimplification, as they often fail to account for the clinical complexity and individual needs of patients. For instance, a medication deemed inappropriate by explicit criteria may still be the best choice in a specific clinical scenario when weighed against alternatives. In addition, these indicators may become outdated if not regularly revised to reflect emerging evidence, new drugs on the market, or evolving clinical guidelines.

Despite their differences, explicit and implicit indicators are not mutually exclusive. Explicit tools can serve as an initial screening method to flag potential problems in large datasets, which can then be further assessed using implicit criteria in clinical settings. The choice between these methods should be guided by the specific objectives of the evaluation- whether for research, policy, education, or direct patient care- and by the availability of resources and clinical data. **Table 1** illustrates the key differences between explicit and implicit indicators across several important aspects.

Table 1- *Comparison Between Explicit and Implicit Prescribing Indicators*

Aspect	Explicit Indicators	Implicit Indicators
Definition	Predefined criteria based on guidelines or consensus	Case-by-case evaluation based on clinical judgment
Examples	Beers Criteria, STOPP/START, EU(7)-PIM	MAI (Medication Appropriateness Index), AOU (Assessment of Underutilization)
Application	Automated or semi-automated; suitable for large datasets	Manual; requires trained reviewer
Context sensitivity	Low- applies broadly	High- considers patient-specific factors
Reproducibility	High	Variable; depends on reviewer
Time and resources required	Low to moderate	High
Strengths	Objective, standardized, scalable	Nuanced, individualized
Limitations	May overlook context or exceptions	Less consistent, time-consuming
Best used for	Population-level monitoring, audits, quality metrics	In-depth clinical review, individualized care planning

3.3 Selection of explicit indicators

The first step in developing a prioritization algorithm involved a thorough and systematic literature search aimed at identifying existing explicit indicators of prescribing appropriateness. The focus was placed on tools and criteria developed for older adults and chronic patients, particularly those validated in international studies or used in large-scale healthcare monitoring systems. Sources included peer-reviewed publications, clinical guidelines, consensus statements, and pharmacological tools such as the Beers Criteria, STOPP/START, EU(7)-PIM list, and other disease-specific or drug-specific frameworks.

Once a comprehensive list of indicators was compiled, a critical selection process was undertaken to assess their applicability within the context of Italian administrative healthcare databases. This involved evaluating each indicator for feasibility of measurement based on the types of information typically available in these data sources, such as prescription records, diagnostic codes, and demographic data. Indicators that required clinical parameters not routinely captured in administrative datasets (e.g., laboratory values, blood pressure readings, or clinical notes) were excluded or flagged as not directly implementable.

Another essential phase consisted in the adaptation of selected indicators to reflect the pharmaceutical landscape and regulatory conditions in Italy. Many international criteria include drugs that are either unavailable, rarely prescribed, or not reimbursed within the Italian NHS. Therefore, a detailed review of the Italian formulary was conducted to ensure that all indicators referenced medications currently marketed and accessible in Italy. Where necessary, equivalent drugs available on the Italian market were substituted, and drug names were standardized according to the national classification system (Anatomical Therapeutic Chemical codes, ATC codes).

This iterative process resulted in a curated and context-specific set of explicit indicators that are both evidence-based and pragmatically suited for use in Italian administrative data. These indicators served as the foundation for the algorithm's logic, enabling the identification and prioritization of potentially inappropriate prescribing patterns across different levels of risk and clinical relevance.

3.3.1 Definition of a comprehensive list of Potentially Inappropriate Medications

The definition of PIMs encompasses drugs which should not be prescribed for the older population because the risk of adverse events outweighs the clinical benefit ^{45,46}. The development of an explicit indicator of PIMs in the older population started from published lists.

Beers Criteria (United States)

The criteria are named after Mark Howard Beers (April 28, 1954 – February 28, 2009), an American geriatrician who, in 1988, discovered that the concomitant use of antidepressants, antipsychotics, and sedatives was associated with symptoms of confusion and tremors in 850 nursing home residents in the Boston area ⁴⁷. In 1991, he compiled a list of medications (the Beers Criteria) that may be harmful to older adults, which has been updated in 1997, 2003, 2012, 2015, 2019, and 2023 ⁴⁸. The Beers Criteria are based on the Delphi method and are presented as six tables:

- Table 1: Designations of quality of evidence and strength of recommendations;
- Table 2: 2023 American Geriatrics Society Beers Criteria® for potentially inappropriate medication use in older adults;
- Table 3: 2023 American Geriatrics Society Beers Criteria® for potentially inappropriate medication use in older adults due to drug–disease or drug–syndrome interactions that may exacerbate the disease or syndrome;
- Table 4: 2023 American Geriatrics Society Beers Criteria® for potentially inappropriate medications: drugs to be used with caution in older adults;
- Table 5: 2023 American Geriatrics Society Beers Criteria® for potentially clinically important drug–drug interactions that should be avoided in older adults;
- Table 6: 2023 American Geriatrics Society Beers Criteria® for medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults.

The Beers Criteria were created and are updated based on the medications available in the United States; therefore, they may not be fully applicable in other countries where

medications not available in the U.S. are marketed, and vice versa. For this reason, many Countries developed their own criteria, but they are all based on Beers criteria.

PRISCUS list (Germany)

Published in 2010, the PRISCUS list is a German list of potentially inappropriate medications that older adults should avoid or that require particular attention (Holt et al., 2010). The approach for creating the PRISCUS list initially involved a qualitative analysis of PIM lists for older adults from other countries such as the USA, Canada, and France, with an evaluation of the applicability of those lists to the German pharmaceutical market in terms of drug availability and prescription frequency. After this first phase, literature evidence was sought on recommended medications and common problems in older adults with evidence of Adverse Drug Events (ADEs), and ADRs. This led to a third phase where 131 drugs from 24 pharmacological classes were selected. The modified Delphi method was used in the fourth and final phase: experts in geriatrics, clinical pharmacology, general medicine, internal medicine, pain therapy, neurology, psychiatry, and pharmacy assigned scores to each drug and proposed clinical monitoring parameters, dosage adjustments, alternatives, and comorbidities that might influence the risk of ADEs. Statistically, medications were selected for a second step, evaluated using the same procedure as the first step but with separate dosage and indication categories according to expert recommendations. The PRISCUS criteria were updated in 2023 (PRISCUS 2.0), which not only evaluated medications marketed in Germany but also in Austria (Austria PIM list). The update used a three-round Delphi method, where 25 experts participated in the first round, 52 in the second, and 8 in the third, for a total of 59 people who participated in at least one round, representing a wide range of medical specialties, including general medicine, geriatrics, clinical pharmacology, psychiatry, internal medicine, palliative care, hospital pharmacy, and cardiology. A total of 187 substances were evaluated as PIMs, and 36 were identified as non-PIMs, with 49 substances classified as "ambiguous" that could potentially be PIMs. Additionally, PRISCUS 2.0 includes possible pharmacological alternatives, monitoring information, comorbidities, and concomitant therapies to avoid, as well as the reasons and classifications for each type of PIM, along with a list of medications no longer marketed in Germany ⁴⁹.

McLeod criteria (Canada)

These criteria place greater emphasis on drug-drug and drug-disease interactions for prescribing inappropriateness in older adults. They were developed in 1997 based on the Beers Criteria model, excluding drugs not available on the Canadian market and those lacking sufficient evidence to justify their associated risks ⁵⁰. Preliminary lists of drug-drug and drug-disease interactions were created and then reviewed by experts, incorporating additional interactions found in the literature. Under the guidance of a geriatrician, inappropriate practices and further drug-disease interactions were also included. Ultimately, all medications included were reviewed using a modified Delphi method, leading to the creation of lists that gather inappropriate prescribing practices for the treatment of cardiovascular diseases in the elderly (according to 32 national experts), inappropriate prescribing practices of psychotropic drugs in the elderly, inappropriate prescribing practices of NSAIDs and other analgesics in the elderly, and inappropriate prescribing practices of various medications in the elderly. The McLeod criteria are based on the Beers criteria and literature, and in 2004, they were used alongside recent Beers criteria to develop the Rancourt criteria ⁵¹.

Laroche list (France)

Initially, in 1997, a list (PIM list) was derived from the Beers Criteria in France and elaborated in 2001 by nine French experts (five geriatricians, four pharmacologists). The list excluded drugs not available in France, drugs that require dosing information, and drugs that should not be prescribed to older adults except for specific indications. It included the concomitant use of two or more non-steroidal anti-inflammatory drugs (NSAIDs), the concomitant use of two or more psychotropic drugs from the same pharmacological class, and the use of any drug with anticholinergic properties, in addition to those already included in the Beers lists. There was no formal consensus method, and some criteria were excluded. Additionally, the consequences of marketing (e.g., withdrawal of drugs from the market) since 2001 were not considered. The French criteria, developed in 2007, not only used a two-round Delphi method but also introduced pharmacological alternatives. The initial phase involved a review of the Beers lists from 1991, 1997, and 2003, Canadian criteria, the 2001 French list, and other French guidelines. This led to the creation of a preliminary questionnaire (first

round) submitted to 15 experts, including five pharmacologists, one pharmacoepidemiologist, five geriatricians, two pharmacists, and two general practitioners with geriatrics qualifications. After analyzing the responses, a second questionnaire was submitted to the experts (second round), based on a synthesis of the first round. The process concluded with a final analysis and the publication of the lists. The questionnaires, based on a scoring system, not only covered medications or pharmacological classes generally to be avoided in older adults but also those to avoid in specific medical conditions. Experts were invited to suggest therapeutic alternatives and to add other criteria. Based on all these responses, a second questionnaire was generated, which also proposed pharmacological alternatives for certain criteria, indicated the reasons for inappropriateness, and resulted in the final list where experts also indicated the age at which the list could be applied^{52 25}.

Maio criteria (Italy)

The Maio Criteria were developed in 2007 through a collaboration between the Azienda Unità Sanitaria Locale (AUSL) of Parma and Thomas Jefferson University (Philadelphia). Nine experts (Group for the Appropriateness of Prescribing, GAP) participated, including three general practitioners (specialized in respiratory medicine, clinical cardiology, and geriatric care), a geriatrician, a hospital pharmacist, two psychiatrists, a cardiologist, and a director of long-term care facilities. The Delphi method was applied with three interactive cycles. Based on the 2002 Beers Criteria, a literature review, and alignment with the Italian pharmaceutical market, 23 inappropriate medications were identified in three categories:

- 17 medications always to avoid in older adults;
- 3 rarely appropriate medications;
- 3 medications to use only for specific indications.

Starting in 2011, the Maio Criteria were updated every three years. The 2020 revision introduced a fourth category: medications not covered by the National Health System to avoid^{53 54}.

Austrian criteria

The list published in 2012 was based on a two-round modified Delphi method. Before the Delphi method's first application, 14 Austrian experts active in hospital sectors or geriatric consulting were recruited, including a general practitioner, a neurology specialist, three internal medicine specialists, a psychiatrist, and two hospital pharmacists. Each criterion was scored, evaluated, and assessed for the implementation of the second round of the Delphi method, followed by a final analysis and evaluation of the results. To establish these criteria, a qualitative analysis of international lists from the United States, Canada, France, and Germany was conducted, along with a literature review tailored to age and adverse drug events. Adaptations to the Austrian pharmaceutical market resulted in a reduction from 131 drugs to 102, divided into 19 groups (according to local and national prescribing criteria). These criteria assess inappropriateness in older adults, suggest alternative medications, provide guidance on monitoring and dose adjustments, and consider drug-drug and drug-disease interactions, supplemented with comments based on individual observations ⁵⁵.

EU(7)-PIM list

These criteria were developed to create a European list of potentially inappropriate medications (PIMs) for older adults, aiming to facilitate comparative analyses of prescribing patterns across Europe in clinical practice. The preliminary list was based on German, American, Canadian, and French criteria, with input from 30 geriatric experts from Estonia, Finland, France, the Netherlands, Spain, and Sweden. The roles were divided as follows:

- 8 experts expanded the list by suggesting additional medications;
- two-round Delphi method: 27 experts evaluated the appropriateness, suggesting dose adjustments and therapeutic alternatives;
- 12 experts completed a final survey to address issues requiring further consensus.

A total of 282 drug classes across 34 therapeutic groups were identified as potentially inappropriate for older adults or restricted to specific doses or durations of use. The

PIM list also includes recommendations for dosage adjustments and therapeutic alternatives ⁴⁴.

ERD-list

The ERD-list (EDU.RE.DRUG list) is an explicit tool developed within the framework of the EDU.RE.DRUG study, a pragmatic, multicenter, controlled trial conducted in Italy ^{30 56}. The list was created through the adaptation and integration of three internationally recognized criteria for identifying potentially inappropriate medications (PIMs): the Beers Criteria (USA), the STOPP&START criteria (Ireland), and the EU(7)-PIM list (Europe). Unlike the original criteria, however, the ERD-list was specifically limited to drugs available and reimbursable under the Italian National Health Service (SSN), to ensure applicability within the context of national healthcare administrative databases. The list focuses solely on medications to always avoid in older adults, excluding those to be avoided only under specific clinical conditions (e.g., drug-disease interactions or drugs to be used with caution), as such information is typically not retrievable from administrative Italian data. As such, the ERD-list constitutes a standardized, reproducible tool that is easily applicable at the national level for monitoring inappropriate prescribing in the older population.

All these lists and other described in the systematic review of Motter et al. ⁴⁸ were reviewed, and explicit criteria were selected from Beers criteria ⁴², French Criteria ⁵², NORGE (Norway) ⁵⁷, Austrian Criteria (Austria) ⁵⁵, Castillo-Paramo (Spain) ⁵⁸, Clyne (Ireland) ²⁴, Czech National Criteria (Czech Republic) ⁵⁹, FORTA (Germany, Austria e Switzerland) ⁶⁰, Galan-Retamal (Spain) ⁶¹, GheOP3S (EU) ⁶² at the last version available, and the ERD-list (EDU.RE.DRUG list; ⁶³) developed based on the 2015 updated Beers ⁶⁴, the STOPP&START criteria ⁶⁵ and the EU-(7)-PIM list ⁴⁴. The criteria were systematically integrated to create a comprehensive set of potentially inappropriate medications. Moreover, only medications classified as reimbursable under class A (outpatient) by the Italian Medicines Agency (Agenzia, Italiana del Farmaco, AIFA) were included. This restriction allowed us to focus on drugs that are traceable within the NHS and relevant to real-world prescribing practices in Italy. The final list of potentially inappropriate medications adopted in this study (**Appendix 1**) included 189 drugs and 19 drug classes.

3.3.2 Potential Drug-Drug Interactions (pDDIs)

In the context of pharmacological management, DDIs represent an independent and substantial source of risk. DDIs occur when one drug's effect is altered by another drug⁶⁶. The concurrent use of two or more medications can lead to altered pharmacokinetics or pharmacodynamics, potentially resulting in ADEs, therapeutic failure, or increased toxicity. Previous studies have estimated that DDIs account for 10.3% of (ADEs) in the U.S. general population (2000–2002)⁶⁷ and 4.8% of hospital admissions among older adults worldwide (1990–2006)⁶⁸. The number of potential DDIs and associated ADEs is expected to increase as more patients with multimorbidity require polypharmacy⁶⁹. Older adults are particularly vulnerable to DDIs due to polypharmacy, which is often an outcome of managing multiple chronic conditions and thus therapies. Physiological changes associated with aging- including decreased renal and hepatic function, altered drug absorption, and changes in body composition- can further modulate the severity and clinical impact of these interactions. Additionally, age-related impairments in homeostatic mechanisms make older patients less able to compensate for pharmacological imbalances. Also, morbidity and multimorbidity can enhance the outcomes of DDIs.

DDIs may be classified into two major categories: *pharmacokinetic interactions*, which involve changes in the absorption, distribution, metabolism, or excretion (ADME) of a drug, and *pharmacodynamic interactions*, where the effect of one drug is modified by another at its site of action or through synergistic or antagonistic mechanisms. The severity and clinical relevance of a DDI can vary based on patient-specific factors such as comorbidities, frailty status, and concomitant therapies, on the other hand, not all clinically significant DDIs cause harm or require therapy modification particularly when the interacting effects may offset each other⁷⁰.

Potential pDDI were evaluated based on pDDI list elaborated by the MediRisk software, developed by Medilog group, based on INXBASE by Medbase, a Finnish company formed by experts in pharmacotherapy, which produces medical decision support databases to safeguard effective and safe use of drugs. INXBASE is a drug–drug interaction database containing short and concise evidence-based information concerning consequences of and recommendations for more than 20,000 drug

interactions (Inxbase; <https://www.medbase.fi/en/professionals/inxbase/>). Interactions were classified by clinical significance (ranging from minor ‘A’ to contraindicated ‘D’) and by the level of documentation (from 0 = in vitro evidence to 4= evidence from randomized clinical trials, systematic reviews, or meta-analyses). Only interactions with major clinical significance level (C), excluding those with the lowest documentation level (0), and contraindicated (D) were considered ⁷¹. The pDDI list is detailed in **Appendix 2**.

3.3.3 Fall Risk-Increasing Drugs (FRIDs)

Falls are among the leading causes of morbidity, hospitalization, and reduced functional independence in older adults, with a significant impact on both individual health outcomes and healthcare systems. Falls are often multifactorial, involving physiological changes related to aging, comorbidities, and environmental factors. However, medication use plays a significant and modifiable role. Fall risk-increasing drugs (FRIDs) are a category of medications that have been associated with a higher risk of falls, particularly in older adults. They are not inherently inappropriate but require careful consideration in patients at increased risk of falling, especially when prescribed in combination or at higher doses.

The mechanisms by which FRIDs increase fall risk can be broadly divided into two main categories: central nervous system (CNS) effects and cardiovascular effects, particularly orthostatic hypotension (**Table 2**) ⁷². CNS-active drugs include classes such as benzodiazepines, antipsychotics, antidepressants (especially tricyclics and Selective Serotonin Reuptake Inhibitors, SSRIs), opioids, and certain antiepileptics. These medications can cause sedation, dizziness, confusion, impaired motor coordination, and delayed reaction times. All of these effects compromise balance and awareness, increasing the likelihood of falls. For example, benzodiazepines can lead to excessive drowsiness and impaired cognition, particularly in frail elderly patients, making them particularly hazardous when fall risk is already elevated. In older adults, even low doses of these drugs can result in sedation, delayed reaction times, and confusion- all of which significantly increase fall risk. Importantly, these effects may

persist longer than expected due to altered drug metabolism and increased sensitivity to CNS-active compounds. On the other hand, drugs that affect cardiovascular regulation can increase fall risk through mechanisms related to hypotension or bradycardia. These include antihypertensives (such as alpha-blockers and centrally acting agents), diuretics, nitrates, and other vasodilators. Orthostatic hypotension- a sudden drop in blood pressure upon standing- is a key factor leading to syncope or dizziness, which in turn can cause falls. This condition is characterized by a significant drop in blood pressure upon standing, leading to dizziness, unsteadiness, or even transient loss of consciousness. Older patients, especially those with impaired autonomic function or pre-existing frailty, may be unable to compensate for these hemodynamic shifts, making them especially susceptible. Diuretics, particularly loop and thiazide diuretics, are also implicated due to their potential to cause dehydration, electrolyte disturbances, and volume depletion, all of which can lead to muscle weakness, cramps, and hypotension.

Table 2- *Fall risk-increasing drugs (FRIDs) and drugs that may cause or worsen orthostatism (ODs) according to the list from the Swedish National Board of Health and Welfare (NBHW) ⁷²*

Drugs that may increase the risk of falls
Opioids
Antipsychotics
Anxiolytics
Hypnotics and sedatives
Antidepressants
Drugs that may cause orthostatic hypotension
Vasodilators used in cardiac diseases (nitrates)
Antihypertensives
Diuretics
Beta-blockers
Calcium channel blockers
Agents acting on the renin-angiotensin system
Alpha-adrenoreceptor antagonists (used in BPH)
Dopaminergic agents (anti-Parkinson drugs)

It is also important to recognize that the cumulative burden of multiple FRIDs can have a synergistic effect on fall risk. The presence of three or more FRIDs has been shown in several studies to markedly increase the likelihood of falling, especially when combined with existing balance or mobility problems.

The selection of drugs to be included in our project for assessing fracture risk was strongly influenced by the limitations in evaluating the appropriateness of antihypertensive medications. These drugs are known to be associated with an increased risk of fractures when administered at doses higher than those required for adequate blood pressure control; however, such dosing appropriateness cannot be reliably assessed using administrative data. For this reason, the final list was restricted to psychotropic medications, associated with fracture risk primarily through CNS mechanisms (**Appendix 3**).

3.3.4 Therapeutic duplicates (TDs)

Therapeutic duplication refers to the concurrent use of two or more medications from the same pharmacological class or with overlapping therapeutic effects, without a clear clinical rationale. One recommendation included in some explicit criteria is to avoid any duplicate drug class prescription and optimize monotherapy within a single drug class before considering a new agent. Duplicate drug class prescription TDs puts the patient at increased risk of adverse drug reactions with no additional therapeutic benefits, and the risk of receiving duplicate therapy increases as patients receive more drugs from multiple healthcare institutions ⁷³. Therefore, the older subjects are at increased risk of TDs due to altered pharmacokinetics and pharmacodynamics associated with aging, which heighten the risks associated with unnecessary drug exposure. Moreover, hospitalization and drugs prescribed by internists and geriatricians are both factors associated with a small but definite increase in overall therapeutic duplicates in elderly patients admitted to internal medicine and geriatric wards, indeed almost 90% of patients discharged with at least one therapeutic still remain with duplicate within 3-month follow-up ⁷⁴. In many cases, duplications result from poor communication between multiple specialists, prescribers and GPs, lack of

shared medical records, or the continuation of outdated prescriptions during care transitions.

Unlike other indicators that rely on predefined lists of inappropriate medications or combinations, TD is often identified in the literature through ATC classification-based approaches. Specifically, studies detect duplication when two or more active substances belonging to the same ATC third or fourth level are prescribed concurrently, without a documented clinical justification^{74 75}.

3.3.5 Anticholinergic Burden score (ACB score)

Acetylcholine (ACh) is a key neurochemical involved in a wide variety of brain functions and other organs, such as the transmission of nerve impulses both in the CNS and in the peripheral nervous system, particularly at the neuromuscular junction and within the parasympathetic branch of the autonomic nervous system (**Figure 15**).

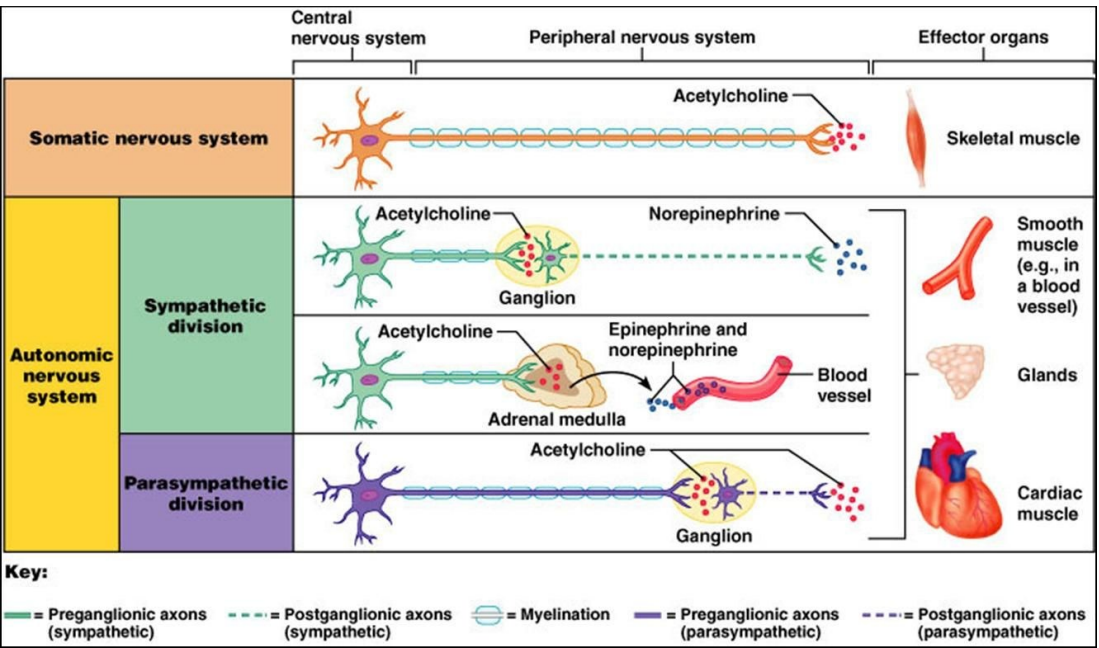


Figure 15- Somatic and autonomic nervous system

Its primary functions include the modulation of memory and learning (especially in the hippocampus and cortex), the regulation of muscle tone (at the neuromuscular endplate), the control of visceral activity (such as salivation, gastrointestinal motility, and heart rate), and the maintenance of attention and wakefulness (involving the

prefrontal cortex and the reticular activating system). At the receptor level, ACh exerts its effects through two main receptor families: muscarinic receptors (M1–M5), primarily responsible for post-ganglionic parasympathetic activity, and nicotinic receptors (Nm and Nn), which are involved in neuromuscular transmission and ganglionic synapses ⁷⁶.

Aging is associated with a progressive decline in the efficiency of the cholinergic system. This deterioration is attributed to reduced activity of choline acetyl transferase (the enzyme responsible for ACh synthesis), decreased sensitivity and density of central muscarinic receptors, and structural degeneration in cholinergic cortical regions. These neurochemical and anatomical changes have significant functional consequences: impaired cholinergic neurotransmission in brain areas critical for cognition contributes to executive dysfunction, increases the risk of mild cognitive impairment (MCI), and facilitates progression to neurodegenerative diseases such as Alzheimer's disease. Furthermore, the declining integrity of the cholinergic system increases susceptibility to acute cognitive disturbances, such as delirium, particularly in the presence of common triggers like infections, dehydration, or pharmacological agents ^{77,78}.

Many drugs used in clinical practice exert anticholinergic effects, either intentionally (as part of their mechanism of action) or as an unintended side effect. Notable examples include first-generation antihistamines (e.g., diphenhydramine), tricyclic antidepressants (e.g., amitriptyline), antipsychotics (e.g., chlorpromazine), antimuscarinics for urinary incontinence (e.g., oxybutynin), antiparkinsonian agents (e.g., benztropine), and muscle relaxants such as baclofen.

In older adults, these drugs are frequently prescribed for a range of conditions, including urinary incontinence, insomnia and agitation, chronic pain or depression, Parkinsonism or tremor, and gastrointestinal disorders. However, the use of anticholinergic medications in the older population is particularly problematic due to the brain's increased vulnerability to cholinergic inhibition in later life. Several physiological factors underline this sensitivity. First, the age-related decline in cholinergic tone means that even minor pharmacological antagonism can result in disproportionately severe effects. Second, pharmacokinetic changes associated with

aging- particularly reduced hepatic and renal clearance- prolong drug half-life and systemic exposure. Third, increased permeability of the blood–brain barrier facilitates drug entry into the CNS. Finally, diminished cognitive reserve limits the brain’s ability to compensate for neurochemical insults, making older adults more prone to confusion, sedation, delirium, and cognitive decline.

Collectively, these changes contribute to an increased anticholinergic burden, a clinically relevant concept in geriatric medicine that reflects cumulative exposure to anticholinergic agents. Elevated anticholinergic burden has been consistently associated with adverse outcomes in older adults, including accelerated cognitive deterioration, increased risk of dementia, higher incidence of delirium, and reduced overall quality of life (**Figure 16**).

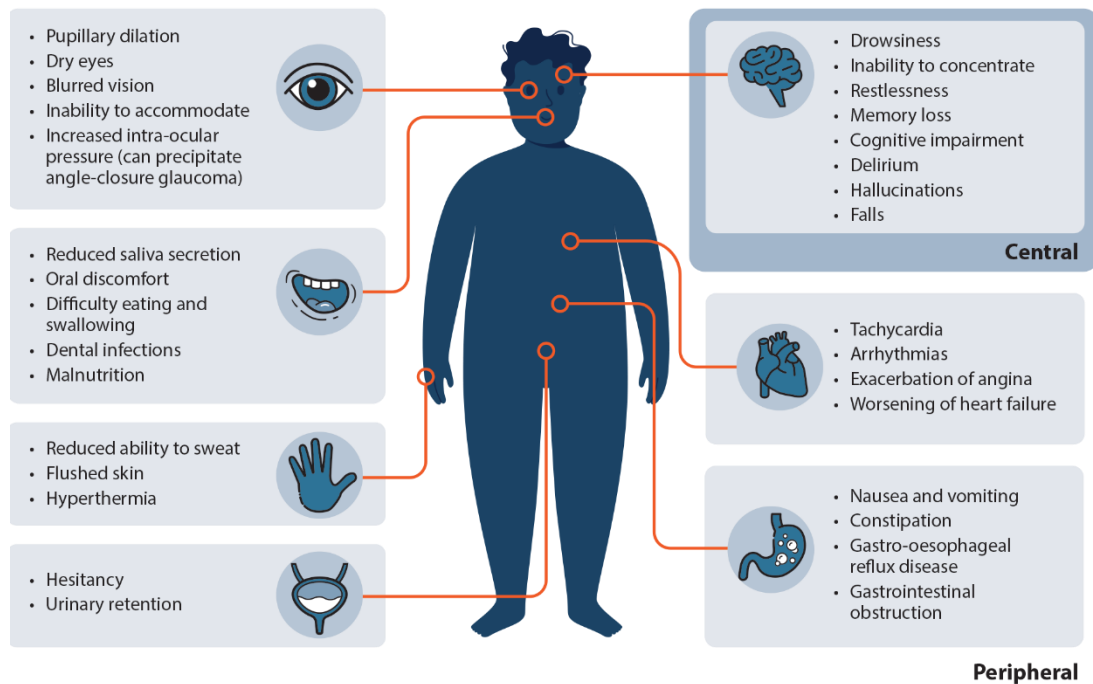


Figure 16- Overview of adverse anticholinergic effects.

ACB refers to the cumulative effect of anticholinergic activity caused by various medications taken either simultaneously or overtime. While each medication individually may have a relatively modest anticholinergic effect, the combined effect of multiple anticholinergic drugs can be extremely harmful, especially in elderly patients. This phenomenon is known as the cumulative effect of ACB.

Clinical studies and epidemiological research have shown that the accumulation of anticholinergic drugs in the bodies of older adults is strongly associated with an increased risk of dementia and other cognitive impairments. Even a moderate dose of anticholinergic medications, when taken regularly or in combination with other similar agents, can seriously impair brain function. Furthermore, the risk of adverse effects becomes proportional to the intensity and duration of exposure to anticholinergic drugs, emphasizing the importance of careful and ongoing evaluation of their use in elderly patients ^{79,80}.

The cumulative effect is not limited to the CNS but can also manifest physical symptoms such as urinary retention, constipation, and dry mouth. The inadequacy of anticholinergic treatment can thus significantly impair the patient's quality of life, increasing dependence on other forms of assistance and contributing to the deterioration of their autonomy.

The ACB concept has been explored through various scales, with 11 distinct ACB scales identified in the literature, including the ACB scale ⁸¹, modified ACB (mACB) ⁸¹, ADS ⁸², ARS ⁸³, Anticholinergic Loading Scale (ALS/ACL) ⁸⁴, Anticholinergic Burden Classification (ABC) ⁸⁵, AAS ⁸⁶, KABS ⁸⁷, German ACB ⁸⁸, Brazilian AAS ⁸⁹, and Anticholinergic Effect on Cognition (AEC) ⁹⁰. They all aim to measure the cumulative impact of anticholinergic drugs in older adults, their structure, methodology, and coverage vary substantially and together include over 800 unique drugs. These scales differ in the number of medications they consider, the sources of their potency ratings (ranging from expert consensus to receptor-binding assays), and whether or not they account for dosage and pharmacokinetics.

A pragmatic approach may involve cross-referencing multiple scales, particularly when evaluating polypharmacy in frail older adults. Al Rihani et al. developed a comprehensive ACB table through a structured review of the literature combined with expert consensus ⁹¹. Initially, researchers conducted a systematic search of published pharmacologic data to identify drugs with known or suspected anticholinergic activity. These drugs were then categorized according to the strength of evidence supporting their anticholinergic effects and their clinical impact on cognitive function. A panel of clinical pharmacologists and geriatricians reviewed and assigned a score from 0 (no

known anticholinergic activity) to 3 (definite anticholinergic effects with clinical evidence of cognitive impairment). The process prioritized reproducibility and relevance to older populations, using data from in vitro receptor-binding studies, clinical pharmacology reports, and observational studies linking drug exposure to adverse cognitive outcomes. As a result, this ACB scale reflects both pharmacodynamic properties and real-world clinical risks.

For our project, we started from this list, consisting of names of single active substances, each associated with comprehensive score, as described above. From this, we identified all corresponding ATC codes, including those referring to combination drugs. If an ATC code represented a combination product, and at least one of its components had a score, the ATC code was included. All included ATC codes, including combination products identified through this method, and their scores are listed in **Appendix 4**.

3.3.6 Sedative Load (SL score)

Sedative medications are widely used across among older adults for managing conditions such as anxiety, insomnia, agitation, and chronic pain. However, in aging individuals, the pharmacodynamic and pharmacokinetic changes associated with senescence- such as increased CNS sensitivity, slower hepatic metabolism, and altered blood-brain barrier permeability- make them particularly vulnerable to the adverse effects of sedative agents. These effects include impaired attention, daytime somnolence, increased risk of falls, delirium, and cognitive decline ^{92,93}.

Unlike drug classes defined by a shared mechanism of action or a specific receptor target, sedative medications do not necessarily act through a defined pharmacological pathway. Instead, what groups them together under the concept of Sedative Load is their common clinical effect that can arise from various mechanisms such as benzodiazepines enhance GABAergic transmission, tricyclic antidepressants block histaminergic and muscarinic receptors, opioids bind to mu-opioid receptors, and muscle relaxants often act through poorly defined central pathways. Despite these diverse mechanisms, the functional endpoint- a reduction in CNS arousal- is what

contributes cumulatively to a patient's overall sedative burden. This is particularly relevant in older adults, whose diminished physiological reserve makes them more vulnerable to the additive effects of different sedatives, regardless of how each drug works at the molecular level. Although sedation is a clinically relevant concern in older adults, the number of validated tools available to quantify sedative burden remains limited.

To date, only two sedative burden scales have been widely referenced in the literature: the Sedative Load Model (SLM) ⁹⁴ and the Sloane model ⁹⁵. The most used, SLM, classifies drugs based on expert consensus into four levels of sedative potency: none, low, moderate, or high. A key strength of this model lies in its broad coverage-encompassing over 900 medications- and its integration with ATC classification codes, facilitating ease of use in both pharmacological research and routine clinical care. In this model, each drug's potency score is summed to calculate a patient's total Sedative Load. This quantitative approach enables a practical method to assess cumulative exposure, particularly useful in older adults who are more susceptible to adverse outcomes from combined sedative effects. The modified version of the SLM, proposed by Sloane et al. in 2008, was developed to suit specific medications used in their clinical trials. However, this adaptation included a narrower range of drugs and introduced only minor variations in how certain agents were categorized compared to the original SLM. As such, while it offers simplicity, its limited scope may reduce its applicability in broader clinical practice.

The SLM remains the most validated and pragmatic option available for assessing sedative exposure and for evaluating the cumulative risk associated with sedative medication use- particularly in geriatric populations prone to polypharmacy and functional decline. This limits its adaptability to the evolving pharmaceutical landscape and highlights the need for continued refinement and validation of sedative burden instruments.

As for ACB scale, Al Rihani et al. developed a comprehensive SL table was constructed through a structured review of the literature combined with expert consensus ⁹¹. Initially, researchers conducted a systematic search of published pharmacologic data to identify drugs with known or suspected anticholinergic activity.

These drugs were then categorized according to the strength of evidence supporting their sedative effects. A panel of clinical pharmacologists and geriatricians reviewed and assigned a score from 0 (no known sedative activity) to 3 (definite sedative effects with clinical evidence of impairment). The process prioritized reproducibility and relevance to older populations, using data from in vitro receptor-binding studies, clinical pharmacology reports, and observational studies linking drug exposure to adverse cognitive outcomes. As a result, the SL scale reflects both pharmacodynamic properties and real-world clinical risks.

From this list of individual active ingredients, each linked to a specific score, as previously outlined, we systematically identified all relevant ATC codes, extending the selection to include combination therapies. An ATC code was retained if it corresponded to a product in which at least one component appeared in the original list and carried an associated score. The final compilation of ATC codes-encompassing both single agents and combination products identified through this approach- and their respective scores is provided in **Appendix 5**.

3.4 Operational definitions of selected indicators

Six different PIIIs were defined to capture the main dimensions of pharmacological inappropriateness among older adults. Each indicator corresponds to a specific pattern of medication use that has been associated in literature with increased risk of adverse outcomes. Once the indicator lists were defined, it was necessary to develop operational definitions capable of identifying whether a subject was classified as *exposed* or *non-exposed* to each of them.

3.4.1 PIMs

In most cases, a single redeemed prescription (dispensation) of the drugs listed in **Appendix 1** during the study period is sufficient to define a PIM event. However, as illustrated in **Figure 17**, in certain instances the redemption of a drug is required but not alone sufficient to classify an event as a PIM. Drugs used for treatment of gastro-

oesophageal reflux disease (GORD/GERD), specifically proton pump inhibitors (PPIs), were considered PIMs if the patient redeemed prescriptions which duration was more than 8 weeks without the co-exposure to other medications such as ATC code M01A (NSAIDs) but also with ATC codes B01AC56, B01AC06, N02BA, and H02, considering the first day out of the 8 weeks as the index date. Moreover, combinations used for the eradication of *Helicobacter pylori* (ATC code A02BD) were considered PIMs if used for more than 14 days, considering as index day the 15th day of exposure. The M01A drug class includes anti-inflammatory and antirheumatic products that are non-steroidal, which were considered PIMs if used continuously for more than 3 months. For this evaluation, the index date was defined as the first day immediately following the 3-month period of continuous use.

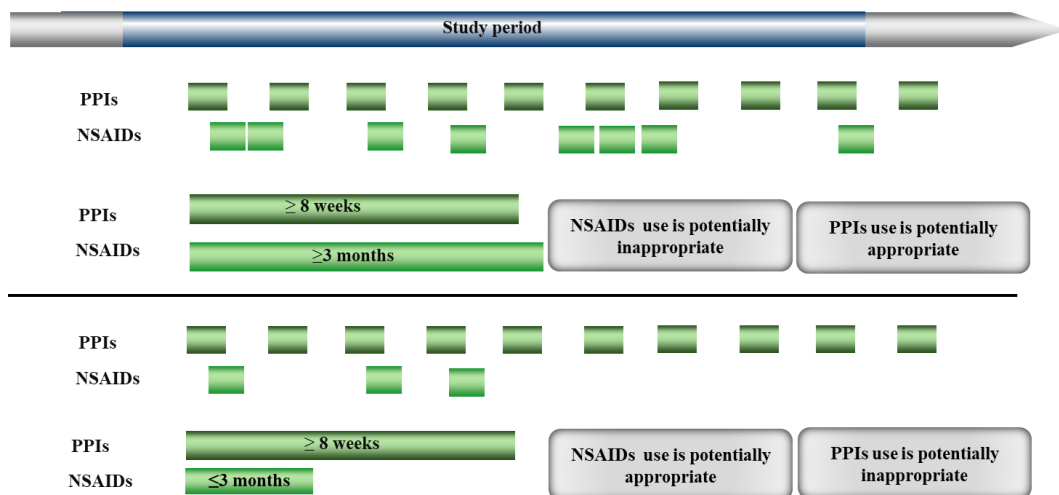


Figure 17- Example of co-exposure assessment PPIs/NSAIDs.

To complete the 14 days, you need 2 boxes for an amount of 20 days of coverage. This does not mean that patients are necessary inappropriate with 2 prescribed boxes, because we cannot assume the complete intake of the pills, but the redemption of a higher number of pills (coverage higher than 20 days) is a marker of potential inappropriateness which means an intake of pills higher than the 2 dispensed boxes that a patient can get due to prescriptions according to the defined treatment. For example, in **Figure 18**, the treatment of *Helicobacter Pylori* requires 14 days of medication, but a single box of the available drugs covers only 10 days of treatment.

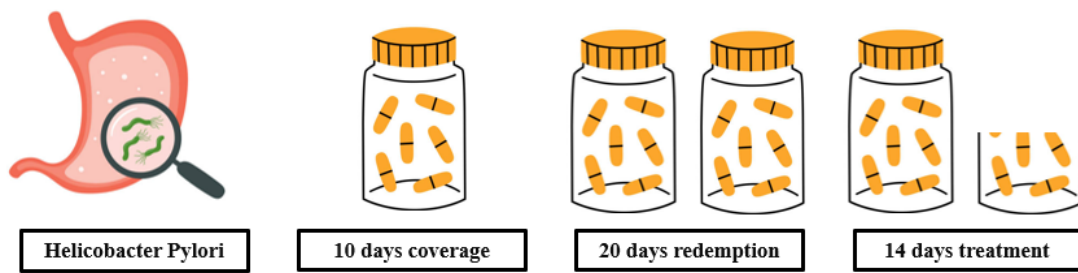


Figure 18- Graphical example the relationship between single box coverage and treatment requirements.

Drugs with ATC code A10AB, specifically referring to fast-acting insulins and analogues for injection, were considered PIMs if patients were exposed only to short- or rapid-acting insulin without co-exposure to long-acting insulin, considering as index date the first day of redemption of fast acting insulin. For these specific cases, we defined the duration of each medication event using the defined daily dose (DDD) ⁹⁶, with the assumption that 1 DDD was 1 day of treatment and based on the pharmacological and epidemiological considerations provided by Pazzagli et al.⁹⁷. The assessment of co-exposure to multiple drug classes- particularly for determining time-based appropriateness criteria- was conducted following the methodological approach as described by Barbieri et al. ⁹⁸. This method involves constructing individual treatment episodes based on dispensation data and evaluating overlapping periods of drug use. In our study, we applied a similar logic to assess co-exposure to specific drug combinations.

3.4.2 pDDI

A pDDI was identified when two medications, listed among those specified in **Appendix 2**, had overlapping coverage periods based on the dispensation date and the number of DDDs supplied (**Figure 19**). To ensure clinical relevance, the overlap between the two drugs had to persist for a minimum of 3 consecutive days.

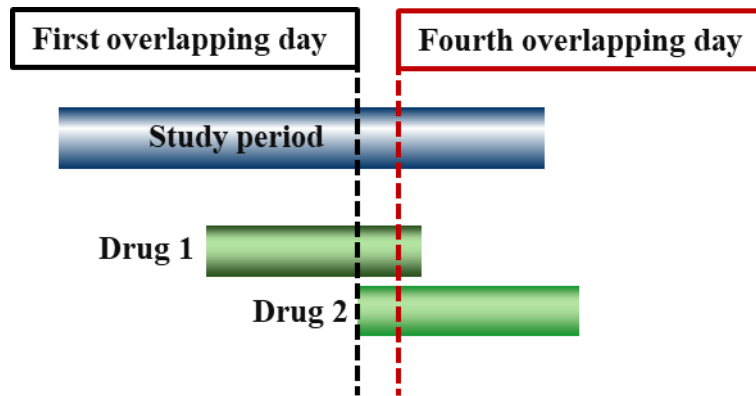


Figure 19- Operational definition of a potential drug-drug interaction (pDDI). The index date is set on the fourth consecutive day of therapeutic overlap, which meets the minimum 3-day requirement.

Although there is no established gold standard for defining the exposure time window, the chosen timeframe of 3 days was selected primarily to align with the relatively short follow-up period of only 3 months, making longer co-exposure windows less convenient for our analysis. This approach allowed us to capture acute, subacute and chronic cumulative effects, reflecting patterns more likely to translate into clinically observable harm. In this case, the fourth day of concurrent coverage was designated as the index date, marking the beginning of the potentially inappropriate pharmacological condition.

3.4.3 FRIDs

Exposure to FRIDs was defined as the prescription of at least one medication from the predefined list in **Appendix 3** during the observation period, using the earliest date of drug redemption as first day of potential inappropriate condition.

3.4.4 TDs

When at least two drugs of the same therapeutic class are simultaneously present and overlap for more than 3 days (as previously explained). To identify duplicates, we considered the fourth level of the ATC code ⁹⁹ selecting as first day of potential

inappropriate condition the earliest fourth day of co-exposure of the same therapeutic class (**Figure 20**).

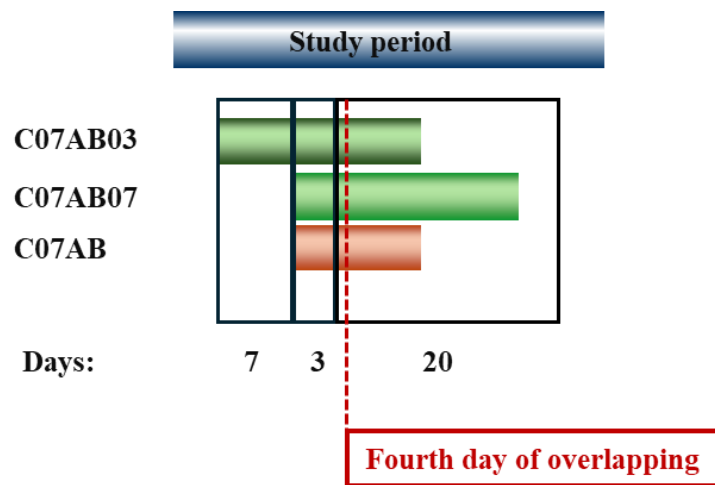


Figure 20- Example of a therapeutic duplication (TD). The index date is defined as the fourth day of overlap between two drugs of the same therapeutic class (4th level ATC).

The minimum 4 overlapping days of two medications sharing the same 4th level ATC code (C07AB, selective beta blocking agents), but with different 5th level ATC code (C07AB03 and C07AB07, atenolol and bisoprolol respectively) were considered indicative as therapeutic duplicates.

3.4.5 ACB score and SL score

The lists of drugs and their assigned scores used to calculate ACB and SL are provided in **Appendix 4** and **Appendix 5**, respectively. To assess the cumulative exposure to medications with anticholinergic or sedative properties, we applied the two validated scoring calculating, for each patient, the daily cumulative score from all concurrently prescribed medications during the observational window. Specifically, we identified patients who reached a cumulative ACB or SL score respectively ≥ 3 for at least 3 consecutive days (**Figure 21**). When this threshold was met, the indicator was considered present, and the fourth day – making the first day beyond the sustained exposure- was considered as index date.

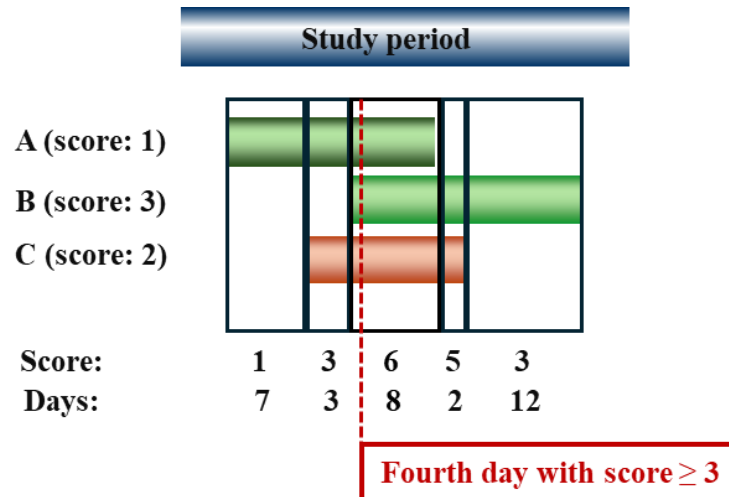


Figure 21- Operational definition of a high cumulative burden score (ACB or SL). An event is flagged when the daily cumulative score from concurrent medications among A, B and C is ≥ 3 for at least three consecutive days. The fourth day meeting this condition is designated as the index date.

3.4.6 Potential Inappropriateness Indicators (PIIs)

Table 3 summarize the number of drug and drug classes and general conditions included in each indicator. Each indicator is based on a specific operational definition aimed at maximizing both clinical relevance and feasibility within administrative data. The presence of any single fulfilled condition is sufficient to classify a patient as exposed to the corresponding PII.

Table 3- Number of drugs, drug classes and conditions summarized for each indicator

	Drugs	Drug classes	Rationale
PIMs	180	19	Redemption and/or coexposure and/or period of exposure
pDDI	474	0	Minimum 4 overlapping days of the 2.653 possible combination
FRIDs	0	5	Redemption of at least one of the 5 drug classes
TDs	-	-	Minimum 4 overlapping days of two equal 4th level ATC code but different 5th level ATC code
ACB score	202	0	Minimum 4 days with score ≥ 3
SL score	476	0	Minimum 4 days with score ≥ 3

CHAPTER 4

All-cause hospitalization risk estimation

Understanding the association between drug exposure and adverse outcomes in real-world settings requires robust study designs capable of capturing temporal relationships, accounting for confounders, and reflecting clinical complexity. Cohort studies, particularly when based on large healthcare administrative databases, provide a powerful tool for estimating risk in observational contexts. This chapter presents the core methodological framework of the research, including the construction of the study population, the design of the retrospective matched cohort study, and the approach to risk assessment. It builds on the previous chapter by operationalizing the predefined criteria and indicators into a structured, real-world analytic setting.

4.1 Methods

4.1.1 Data source and study population

The study population refers to the group of individuals selected for analysis based on predefined eligibility criteria. Carefully defining the study population is essential to ensure that the study results are valid, representative, and generalizable to the wider target population. The selection process sets the foundation for all subsequent analyses, providing the context in which exposures, outcomes, and potential confounders are measured and interpreted. A well-defined study population minimizes selection bias, which occurs when individuals included in the study are not representative of the target population, and enhances internal validity by including individuals who are relevant to the research question and have sufficient data available for accurate measurement of key variables. Additionally, clarity in population definition facilitates comparison across studies and improves the applicability of findings in clinical or public health settings. In cohort studies, particularly in pharmacoepidemiology, the study population often consists of individuals meeting specific clinical or demographic criteria, such as age groups, disease status, or medication use patterns.

Defining these criteria with precision allows to focus on populations at risk, understand heterogeneity in treatment effects, and identify subgroups with differing risk profiles. Furthermore, an adequately characterized study population supports the use of

statistical methods to adjust for confounding factors and enhances the interpretation of causal relationships between exposures and outcomes.

The analysis conducted in this study rely on administrative healthcare databases from the Italian NHS. Since 1997, NHS has managed healthcare delivery through a system based on electronically linkable databases containing information on NHS-reimbursable health services.

The databases include:

- Demographic databases: this is an inhabitant registry where the GP chosen by each subject is recorded. It stores information on residents who receive NHS assistance, including birth date, sex, district of residence, and (GP) code and information on GPs, such as birth date, sex, and number of patients;
- Pharmacy databases: information based on dispensing records of prescribed drugs reimbursable by the NHS, including prescription date, dispensing date, the name of each drug dispensed, WHO Anatomical Therapeutic Classification (ATC) code, marketing authorization code (AIC), dose(s), number of boxes, and cost for NHS;
- Hospital databases: information on all hospitalizations at public or private hospitals of the LHUs, including admission date, primary and secondary diagnoses, that are expressed ICD-9 or ICD-10 codes, and date of discharge.

Although primarily designed for administrative and reimbursement purposes, these databases are routinely updated, legally validated, and known for their high accuracy, especially in domains such as drug dispensations and hospitalizations. Despite their lack of clinical granularity (e.g., laboratory values or outpatient diagnoses not linked to reimbursed services), previous studies have demonstrated their utility in assessing medication exposure, adherence, and healthcare utilization patterns¹⁰⁰.

In Italy, administrative healthcare data are managed at the local level by individual LHUs, which are responsible for collecting and updating information capturing healthcare-related events for nearly the entire resident population who access services through the SSN. However, data collection processes follow standardized national guidelines, ensuring consistency across LHUs. This standardization enables the

integration and evaluation of data at the regional level, supporting large-scale analyses and healthcare planning.

These databases offer several strengths: they ensure near-complete population coverage, and large-scale, longitudinal analyses on heterogeneous and unselected populations. Moreover, given their standardised structure across regions, claims data from multiple LHUs can be pooled with relative ease. One limitation in data management is the lack of information on specific classes of medications. For example, administrative databases do not capture OTC drugs- medications purchased without a prescription- or medications that are not reimbursed by the NHS and therefore not tracked in claims data.

Data used in this thesis were obtained from the EDU.RE.DRUG (Effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients) study, which have been described in detail elsewhere ⁵⁶. Briefly, this prospective, multicentre, open-label, parallel-arm, controlled, pragmatic trial has been designed to deeply investigate the practice of prescribing among general practitioners in two Italian regions, to highlight the most frequent events of inappropriateness, and to plan tailored intervention for GPs and patients focused on this critical issue. The primary objective was to assess the effectiveness of informative and/or educational interventions addressed to general practitioners and their patients, aimed at improving the prescribing quality and promoting proper medication use. Eight LHUs were enrolled: four in the Campania region, in the southern part of Italy, and four in the Lombardy region, in the north of Italy. The clinical setting of the study was the general practice. The study population was composed of all GPs and all their adult patients aged ≥ 40 years from the eight LHUs involved, and data were retrieved from health-related administrative databases.

For this thesis, data from the northern LHUs (Bergamo, Lecco, Mantova, and Monza Brianza) in the Lombardy region were used (**Figure 22**). Among the population aged 65 years and older in each LHU, between 76% and 95% of over 65 citizens received at least one reimbursed drug dispensation, depending on the LHU and year (**Table 4**).

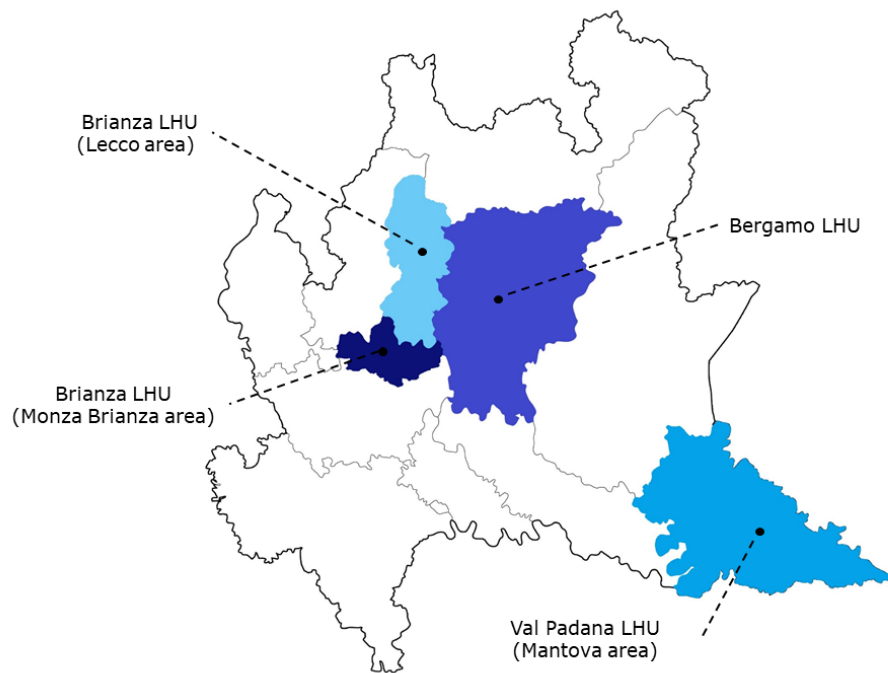


Figure 22 -. *Geographical location of the four Local Health Units in the Lombardy region (Italy) from which the study population was drawn.*

This prescription coverage underscores the completeness of the data and enhances confidence in the representativeness of the older population. This ensures near-complete representativeness and minimizes selection bias.

Table 4- *Proportion of citizens captured within the prescription database. “Citizens” refers to the total resident population aged ≥ 65 years¹⁰¹ while “Patients” refers to the subset of citizens with at least one reimbursed drug prescription during the year.*

LOMBARDY	2014	2015	2016	2017	2018
LHU Over65 Citizens, N					
BG					
	210,102	213,831	213,996	218,049	218,761
LC					
	75,475	77,052	78,498	82,341	83,006
MB					
	186,162	189,702	189,806	199,357	202,680
MN					
	95,193	95,901	96,865	102,007	102,661

LHU Over65 Patients, N					
BG					
	193,487	196,811	196,633	206,940	207,604
LC					
	57,774	61,809	68,076	72,318	73,033
MB					
	142,480	151,820	164,192	177,931	182,597
MN					
	85,852	86,525	85,217	89,467	89,759
Patient/Citizens, %					
BG	92.1%	92.0%	91.9%	94.9%	94.9%
LC	76.5%	80.2%	86.7%	87.8%	88.0%
MB	76.5%	80.0%	86.5%	89.3%	90.1%
MN	90.2%	90.2%	88.0%	87.7%	87.4%

**Bergamo (BG), Lecco (LC), Monza Brianza (MB), Mantova (MN)*

4.1.2 Study design

A retrospective matched cohort study was conducted using healthcare administrative databases. Retrospective cohort studies utilizing administrative healthcare databases have become increasingly valuable for pharmacoepidemiological research, enabling large-scale analysis of medication use, health outcomes, and risk factors in real-world populations. In a retrospective matched cohort study, individuals are grouped based on exposure status and followed over time using historical data. Matching is applied to ensure comparability between exposed and unexposed groups with respect to key confounding variables, thereby improving internal validity and reducing bias in effect estimation- systematic errors that cause the estimated effect of an exposure on an outcome to be either overestimated or underestimated.

The exposed cohort included individuals who, during the study period (2015-2018), redeemed at least one medication meeting the predefined indicators. The index date was defined as the first day the individual fulfilled any of the specified conditions, such as the date of medication redemption or a date determined by a required observation period. The year 2014, although available in the dataset, was not included in the main analysis as it was used as a washout period- that is, a timeframe preceding

cohort entry used to verify the absence of prior inappropriate prescriptions, and for the accurate assessment of covariates and comorbidities prior to the index date. This approach aimed to improve the accuracy of identifying first occurrences of inappropriate medication use.

To reduce confounding, a risk-set matching approach was used for the selection of the control group ¹⁰². For each exposed individual, one unexposed control was selected from the pool of eligible patients who:

- had no evidence of predefined criteria to the same index date
- had the same biological sex and age
- remained at risk of being exposed at that time point

This matching method is dynamic, meaning that a person who serves as a control at one point in time can later become part of the exposed group if they meet the criteria. This approach helps reduce biases- like healthy user bias and selection bias- by ensuring that the groups being compared are similar not only in age and sex but also in when they were exposed.

Both exposed and unexposed individuals were followed for 3 months after the index date. In addition, a 12-month baseline period prior to the index date was adopted to assess patient characteristics, comorbidities, and healthcare utilization. The 365-day lookback period is widely recognized as sufficient to capture chronic conditions and risk factors reliably in real-world settings ¹⁰³.

The 3-month follow-up window was chosen to evaluate short-term outcomes - specifically, the risk of hospitalization - following exposure. Since aging is associated with increasing frailty and comorbidity burden, longer follow-up periods could introduce bias due to evolving health status. A shorter window therefore provides a clearer temporal link between exposure and outcome.

As an additional methodological clarification to what has been described above, individuals were included if their index date occurred between January 1, 2015, and September 30, 2018. Although data were available through December 2018, setting

the latest permissible index date at the end of September ensured a complete 3-month follow-up period for all participants.

Finally, to avoid immortal time bias - a type of bias that occurs when individuals must survive long enough to be classified into the exposure group, potentially leading to misleading risk estimates - we required that deceased patients had sufficient medication coverage, based on the date and duration of their last recorded dispensation, to fully cover the three-month period preceding death. Patients who died but whose therapeutic coverage did not extend through the entire three-month period preceding death were excluded from the analysis. This step ensures that all included patients had a standardized exposure window of at least three months, mitigating any bias related to an undefined or truncated observation time.

Figure 23 provides a summary of the study design, including the definition of the two cohorts of exposed and not exposed individuals and the definition of follow-up.

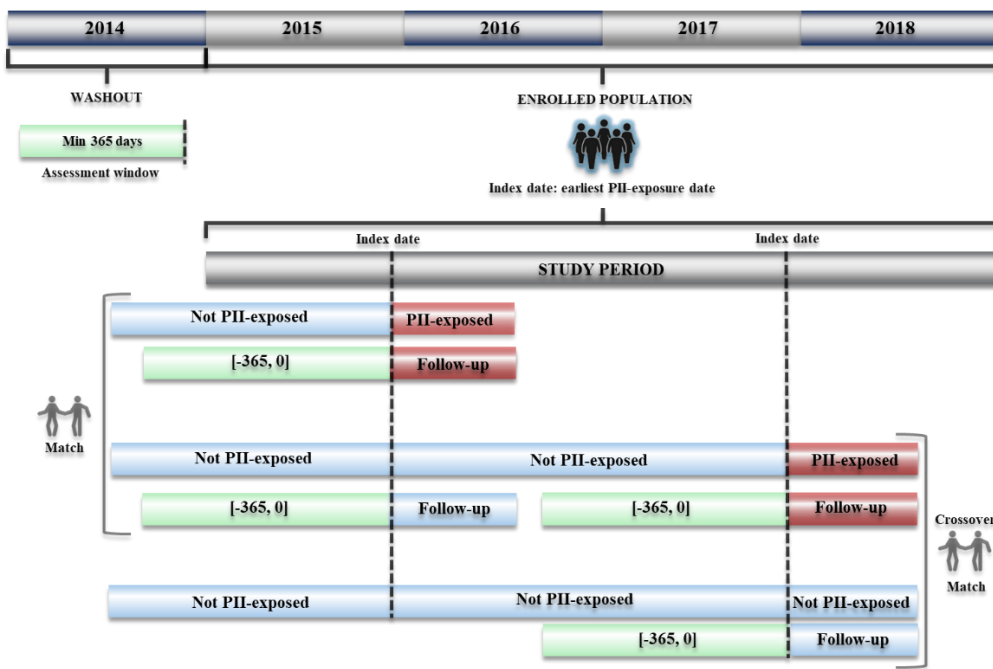


Figure 23- Graphical representation of the study design and matching strategy

The study protocol of this study was drafted according to the HARPER guidelines ⁶⁹ and registered in the European catalogue of real-world studies (EUPAS1000000472, <https://catalogues.ema.europa.eu/>).

4.1.3 Outcome definition: all-cause hospitalizations

The outcome defines the event or condition the research aims to investigate in relation to exposures. Outcomes should be clearly defined, measurable, and clinically relevant to ensure meaningful interpretation and applicability of the study findings.

All-cause hospitalization identified through hospital discharge records using ICD-9 codes was selected as the primary outcome (within 90 days from the index date) due to its clinical relevance, reliability of measurement, and suitability for use in administrative healthcare databases. All-cause hospitalizations capture the full spectrum of potential adverse of drug exposure events, both direct and indirect effects, that may be related- either directly or indirectly- to medication use in older adults, including those not easily attributed to a single condition or diagnosis^{104 105 106}.

4.1.4 Analytical strategy and model development

Risk assessment refers to the process of estimating the likelihood of an outcome occurring as a result of a specific exposure. This includes calculating measures such as risk differences, risk ratios, or hazard ratios depending on the study design and type of data available. In the context of cohort studies, risk assessment commonly aims to quantify the association between exposure and subsequent outcomes while accounting for potential confounding variables.

The primary objective was to estimate the risk of all-cause hospitalization associated with exposure to PIMs, pDDIs, FRIDs, TDs, ACB score, and SL score in individuals aged 65 years and older, assessed as defined in **paragraph 3.4**.

To address potential confounding and to refine risk estimates, a rigorous statistical approach was employed. A conditional logistic regression model was used to estimate the association between exposure and the risk of hospitalization. This method, suitable for matched data, is mathematically equivalent to a Cox proportional hazards model stratified by matched pairs. Conditional logistic regression allows for the analysis of binary outcomes within matched sets, ensuring that comparisons are made between individuals with similar baseline characteristics and thus helping reduce confounding.

Adjustment was performed for a predefined set of covariates that could influence the risk of hospitalization. This included age, sex, drugs dispensed and hospitalization diagnosis in the prior 12 months. This information was used as a proxy to estimate individuals' overall health status, allowing for comparisons across groups in terms of chronic disease burden. All covariates were identified using data from the 12-month baseline period through hospital discharge records and drug dispensations. Detailed information on the type of adjustment is provided in the following paragraph.

The model applied in this thesis estimates the probability of hospitalization associated with exposure to inappropriate prescriptions compared to individuals not exposed to such inappropriate prescribing.

In observational studies, treatment or exposure allocation is not random, as in a trial, and may be influenced by patients' characteristics. This creates potential confounding, where differences in baseline factors can bias the estimated association between exposure and outcome.

To address this issue the high-dimensional propensity score (HDPS) methodology was employed to control for confounding when utilizing large healthcare databases. Traditional propensity score methods rely on manually selected confounders and are often insufficient to control for the vast number of potential confounders such as in healthcare databases. In contrast, HDPS semi-automates the identification and prioritization of hundreds or thousands of potential confounding variables, such as diagnoses, procedures, and medications. This capability is particularly crucial given the complexity and volume of the administrative claims data employed in this study.

This data-driven approach helps to minimize residual confounding by systematically adjusting for a vast array of covariates, including proxies for unmeasured confounders. By reducing the impact of these biases, HDPS enhances the validity and reliability of estimated treatment effects, making it an invaluable tool for drawing more accurate causal inferences from complex real-world data ¹⁰⁸.

By integrating these diverse data points - demographics, chronic medication use, and hospital diagnoses - the HDPS model aimed to create a robust adjustment for

confounding, mimicking randomization and allowing for more accurate estimations of treatment effects.

HDPS was derived using logistic regression. The predictors incorporated into this model were:

- Sex and age: demographic characteristics were included to account for their influence on both medication prescription patterns and patient health outcomes;
- ATC codes: these codes classify medications based on their therapeutic action and chemical characteristics. Including them allowed us to capture information about patients' long-term medication profiles, which serve as a "proxy" for their underlying chronic health conditions and comorbidities. For example, a patient consistently taking anti-diabetic medication is likely to have diabetes. This provides a comprehensive, data-driven overview of a patient's health status;
- Hospital discharge diagnoses: these codes represent the diagnoses recorded at the time of hospital discharge. They offer additional detailed insights into acute and chronic health issues a patient has experienced, further enriching our understanding of their clinical complexity.

Before proceeding with the calculation of the HDPS for each subject in our sample, an additional data processing step was necessary.

In high-dimensional observational studies using administrative healthcare data, it is common to work with a large number of candidate covariates. While this rich set of variables offers a more granular description of patient characteristics, it can also introduce redundancy and noise into the modelling process. The method used for dimensionality reduction was the removal of near-zero variance (NZV) variables. NZV predictors are those that exhibit little to no variation across the study population - such as binary indicators where almost all individuals fall into the same category. These variables typically:

- Provide limited or no discriminative power;
- Increase model complexity unnecessarily;
- May introduce numerical instability or multicollinearity;

- Can contribute to overfitting, particularly in penalized or regularized models.

By filtering out NZV variables before estimating the HDPS, we reduce the risk of model distortion and enhance computational efficiency. This step is especially relevant when the covariate space includes thousands of binary indicators derived from drug dispensations or diagnostic codes, as is common in real-world datasets.

Thus, the final set of covariates for HDPS estimation includes only those with sufficient variability to meaningfully differentiate between exposed and unexposed individuals. This approach aligns with best practices in high-dimensional data analysis and contributes to the transparency and replicability of the model-building process

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4.1.5 Statistical analysis

Age was categorized in groups (65–74 years, 75–84 years, and 85 years or older). Statistically significant differences were assessed for age, age groups, and biological sex of individuals who fulfilled the conditions to be classified as exposed to a PII and those who had not redeemed at the index date. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Variables with a normal distribution were presented as mean $\pm$ standard deviation (SD) and compared using the t-test.

As reported previously, logistic regression analysis was performed to estimate the OR and the corresponding 95% confidence interval (95% CI) for the risk of all-cause hospitalization during the follow-up period, comparing individuals who met PII conditions to those who did not. Individuals were censored at death, the end of data availability, or the occurrence of the study outcome.

Moreover, stratified analyses by sex and age were conducted to explore potential effect modification, as these factors are known to influence both prescribing patterns and hospitalization risk.

Both the primary analysis models and the stratified analysis models were implemented separately for each LHU to account potential variability across different health areas. Subsequently, the overall LHU-specific OR estimation was pooled to derive a single, robust risk estimate for each PII (these pooled ORs were then used as described in section 5.2.4).

To obtain a pooled estimate, a meta-analysis was conducted. The log-transformed OR and its standard error (SE) for each LHU were combined using the DerSimonian–Laird method. Effect measures were expressed as ORs with their corresponding 95%CI. For data visualization, a forest plot was generated. To assess the impact of heterogeneity on the meta-analysis results, the I-squared (I^2) statistic was calculated. I^2 values were interpreted as follows: 0% indicated no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity¹⁰⁹. When heterogeneity exceeded 50%, random estimates from the model were considered to account for variability between LHUs.

Data analysis was performed using R software version R version 4.4.1, and two-tailed $p < 0.05$ was considered for statistical significance in all analyses.

Appendix 6 provides a comprehensive overview of all R packages used in the analysis, along with a detailed description of the information required by each function and the specific scripts developed for the study. This documentation aims to ensure full transparency and reproducibility of the analytical procedures.

4.2 Results

This section presents the main findings regarding the risk of hospitalization associated with exposure to each PII.

4.2.1 The study population

The final study cohort comprised 664,893 individuals aged 65 years or older, with at least one drug prescription between January 1, 2014, and December 31, 2018.

Descriptive analysis of the study population is reported in **Table 5**. The largest population of individuals aged 65 years and older was observed in the LHU of Bergamo, followed by Monza Brianza, Lecco, and Mantova. In all four LHUs, the distribution by sex was relatively balanced, with a slight predominance of females. Regarding age groups, the intermediate category (65–74 years) was the most represented across the LHUs.

Considering the requirement for a one-year covariate assessment period prior to the index date and a minimum of three months of follow-up, the population eligible for our analysis includes individuals with at least one prescription between January 1, 2015, and September 1, 2018 (**Table 6**). This cohort is balanced in terms of age and sex, and reflects the broader population observed from 2014 to 2018. The mean age across LHUs ranges from 73.8 to 74.5 years. The 65–74 age group represents the largest proportion, ranging from 53.9% in Mantova to 57.7% in Bergamo. The 75–84 group accounts for 31.4% in Bergamo up to 33.0% in Monza Brianza, while individuals aged 85 and older comprise between 10.9% in Bergamo and 13.4% in Mantova.

Table 5- Characteristics of the population (from 2014 to 2018) of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

		2014	2015	2016	2017	2018
BG						
N		193.487	196.811	196.633	206,940	207.604
Female sex, N (%)		109,989 (56.8%)	111,325 (56.6%)	110,960 (56.4%)	115,826 (56%)	115,821 (55.8%)
Age, mean (SD)		75.2 (7.3)	75.2 (7.3)	75.3 (7.3)	75.7 (7.5)	75.8 (7.6)
Age group, N (%)	65-74 yy	98,766 (51.0%)	99,331 (50.5%)	98,452 (50.1%)	100,904 (48.8%)	101,122 (48.7%)
	75-84 yy	70,442 (36.4%)	72,208 (36.7%)	72,459 (36.8%)	76,058 (36.8%)	75,963 (36.6%)
	≥85 yy	24,279 (12.5%)	25,272 (12.8%)	25,722 (13.1%)	29,978 (14.5%)	30,519 (14.7%)
LC						
N		57.774	61.809	68.076	72.318	73.033
Female sex, N (%)		33,109 (57.3%)	35,129 (56.8%)	38,414 (56.4%)	40,564 (56.1%)	40,792 (55.9%)
Age, mean (SD)		74.7 (7)	75.1 (7.2)	75.6 (7.4)	76 (7.6)	76.1 (7.6)
Age group, N (%)	65-74 yy	30,842 (53.4%)	31,588 (51.1%)	33,077 (48.6%)	34,147 (47.2%)	34,490 (47.2%)
	75-84 yy	21,028 (36.4%)	22,952 (37.1%)	25,561 (37.5%)	26,966 (37.3%)	27,031 (37%)
	≥85 yy	5,904 (10.2%)	7,269 (11.8%)	9,438 (13.9%)	11,205 (15.5%)	11,512 (15.8%)
MB						
N		142,480	151,820	164.192	177.931	182.597
Female sex, N (%)		81,549 (57.2%)	86,471 (57%)	92,824 (56.5%)	100,177 (56.3%)	102,496 (56.1%)
Age, mean (SD)		74.6 (6.8)	75 (7)	75.5 (7.3)	75.9 (7.5)	76 (7.5)
Age group, N (%)	65-74 yy	76,071 (53.4%)	77,455 (51.0%)	79,174 (48.2%)	83,318 (46.8%)	85,381 (46.8%)
	75-84 yy	53,311 (37.4%)	58,009 (38.2%)	63,572 (38.7%)	68,635 (38.6%)	69,652 (38.1%)
	≥85 yy	13,098 (9.2%)	16,356 (10.8%)	21,446 (13.1%)	25,978 (14.6%)	27,564 (15.1%)
MN						
N		85.852	86.525	85.217	89.467	89.759
Female sex, N (%)		49,703 (57.9%)	49,850 (57.6%)	48,861 (57.3%)	51,113 (57.1%)	50,992 (56.8%)
Age, mean (SD)		75.9 (7.6)	76(7.6)	76 (7.6)	76.4 (7.8)	76.4 (7.8)
Age group, N (%)	65-74 yy	40,543 (47.2%)	40,456 (46.8%)	39,788 (46.7%)	40,762 (45.6%)	41,246 (46.0%)
	75-84 yy	32,203 (37.5%)	32,650 (37.7%)	32,148 (37.7%)	33,320 (37.2%)	33,119 (36.9%)
	≥85 yy	13,106 (15.3%)	13,419 (15.5%)	13,281 (15.6%)	15,385 (17.2%)	15,394 (17.2%)

* SD=Standard Deviation, yy=years.

Table 6- *Characteristics of the eligible population (from 2015 to 2018) of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.*

	BG	LC	MB	MN	p-value
Over65 population with at least one prescription, N	246,267	83,764	205,792	105,407	
Female sex, N (%)	136,783 (55.5)	46,667 (55.7)	89,229 (57.4)	59,833 (56.8)	<0.0001
Age, mean (SD)	73.8 (7.6)	74.2 (7.8)	74 (7.6)	74.5 (8)	<0.0001
Age group, N (%)					
65-74 yy	142,017 (57.7)	47,025 (56.1)	115,324 (56.0)	56,860 (53.9)	<0.0001
75-84 yy	77,306 (31.4)	26,713 (31.9)	67,862 (33.0)	34,407 (32.6)	
≥85 yy	26,944 (10.9)	10,026 (12.0)	22,606 (11.0)	14,140 (13.4)	

*SD=Standard Deviation, yy=years.

4.2.2 PIMs

The annual prevalence of PIMs is reported in **Table 7**. Overall, 39.7% of patients have redeemed a first PIM between 2025 and 2018. The annual prevalence of patients with at least one PIM ranged from 39.5% to 40.0%.

Table 7 – Annual prevalence of PIMs.

	2015	2016	2017	2018	p-value
Over65 population with at least one prescription, N	496,965	513,917	546,656	552,993	
Individuals with at least one PIM, N (%)	196,468 (34.1%)	203,289 (39.6%)	218,549 (40.0%)	220,402 (39.9%)	0.03
Individuals with one PIM, N (%)	126,515 (64.4%)	131,799 (64.8%)	138,794 (63.5%)	139,397 (63.2%)	<0.0001
Individuals with two PIMs, N (%)	49,261 (25.1%)	50,542 (24.9%)	55,346 (25.3%)	56,556 (25.7%)	<0.0001
Individuals with three PIMs, N (%)	15,233 (7.8%)	15,318 (7.5%)	17,678 (8.1%)	17,947 (8.1%)	<0.0001
Individuals with four or more PIMs, N (%)	5,459 (2.8%)	5,630 (2.8%)	6,731 (3.1%)	6,502 (3.0%)	<0.0001

Table 8 summarizes the five most frequent PIMs. Although the relative ranking of the top four potentially inappropriate medications remained stable throughout the observed years, their overall prevalence showed a gradual increase. Specifically, N06AB (SSRIs) increased from 15.1% in 2015 to 15.9% in 2016 and 2018; G04CA02 (tamsulosin) rose from 13.2% in 2015 to 14.6% in 2018; N06AX (other antidepressant) grew from 10.5% in 2015 to 13.5% in 2018; and A02BC (PPI) increased from 7.3% in 2016 to 9.3% in 2018. The fifth most frequent PIM varied across the years. Specifically, it alternated among B01AC05 (ticlopidine, 7.2% in 2015), G04CA04 (tamsulosin, 7.2% in 2016 and 8.1% in 2018), and B03AA07 (ferrous sulphate, 8.1% in 2017).

Table 8 – *Five most frequent PIMs by patients*

	2015	2016	2017	2018
1.	N06AB (15.1%)	N06AB (15.9%)	N06AB (15.8%)	N06AB (15.9%)
2.	G04CA02 (13.2%)	G04CA02 (13.9%)	G04CA02 (14.1%)	G04CA02 (14.6%)
3.	N06AX (10.5%)	N06AX (11.4%)	N06AX (12.5%)	N06AX (13.2%)
4.	A02BC (8.1%)	A02BC (7.3%)	A02BC (8.8%)	A02BC (9.3%)
5.	B01AC05 (7.2%)	G04CA04 (7.2%)	B03AA07 (7.7%)	G04CA04 (8.1%)

*N06AB Selective serotonin reuptake inhibitors, G04CA02 Tamsulosin, N06AX Other Antidepressant, A02BC Proton pump inhibitors, B01AC05 Ticlopidine, G04CA04 Silodosin, B03AA07 Ferrous sulphate.

Baseline characteristics of this cohort are presented in **Table 9**. As expected, following the matching approach, the two groups were perfectly balanced in terms of sex, age, and age group distribution within each LHU. Females consistently represented a slight majority of the population, ranging from 54.0% to 55.5%, while the average age ranged from 76.5 to 77.3 years across LHUs. In all LHUs, the most represented age group was 65–74 years, followed by 75–84 and ≥ 85 years. A marked difference in hospitalization rates was observed between the matched groups. Individuals exposed to at least one potentially inappropriate prescription consistently showed a higher incidence of all-cause hospitalization across LHUs. For example, hospitalization occurred in 10.2% of PIM users vs. 6.0% of controls in Bergamo, and in 8.6% vs. 5.1% in Mantova, respectively. These differences were statistically significant in all LHUs

($p < 0.0001$), suggesting a consistent association between PIM exposure and increased hospitalization risk, even after matching.

Table 9 – Characteristics of the PIMs matched cohorts at the enrolment. LHUs of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

Covariates	Presence of at least one PIM		p-value
	No	Yes	
BG	N= 94,110		
N [matched]	47,055	47,055	
Female sex, N (%)	25,754 (50.0)	25,754 (50.0)	-
Age, mean (SD)	76.5 (7.8)	76.5 (7.8)	-
Age class, N (%)			
65-74 yy	21,382 (45.4)	21,382 (45.4)	-
75-84 yy	17,378 (36.9)	17,378 (36.9)	
≥85 yy	8,295 (17.6)	8,295 (17.6)	
Hospitalization, N (%)	2,800 (36.8)	4,804 (63.2)	<0.0001
LC	N= 36,518		
N [matched]	18,259	18,259	
Female sex, N (%)	9,853 (50.0)	9,853 (50.0)	-
Age, mean (SD)	77.2 (8.3)	77.2 (8.3)	-
Age class, N (%)			
65-74 yy	7,800 (42.7)	7,800 (42.7)	-
75-84 yy	6,550 (35.6)	6,550 (35.6)	
≥85 yy	3,909 (21.4)	3,909 (21.4)	
Hospitalization, N (%)	1,099 (37.9)	1,797 (62.1)	<0.0001
MB	N= 85,630		
N [matched]	42,815	42,815	
Female sex, N (%)	23,442 (50.0)	23,442 (50.0)	-
Age, mean (SD)	77.3 (8.0)	77.3 (8.0)	-
Age class, N (%)			
65-74 yy	17,809 (41.6)	17,809 (41.6)	-
75-84 yy	16,272 (38.0)	16,272 (38.0)	
≥85 yy	8,734 (20.4)	8,734 (20.4)	
Hospitalization, N (%)	2,299 (39.1)	3,581 (60.9)	<0.0001
MN	N=39,868		
N [matched]	19,934	19,934	
Female sex, N (%)	11,065 (50.0)	11,065 (50.0)	-
Age, mean (SD)	76.7 (8.2)	76.7 (8.2)	-
Age class, N (%)			
65-74 yy	9,088 (45.6)	9,088 (45.6)	-
75-84 yy	6,969 (35.0)	6,969 (35.0)	
≥85 yy	3,877 (19.4)	3,877 (19.4)	
Hospitalization, N (%)	1,023 (37.5)	1,705 (62.5)	<0.0001

* SD=Standard Deviation, yy=years.

The estimated association (OR and 95% CI) between exposure and all-cause hospitalization is summarized in **Figure 24**. Across all LHUs, exposure to at least one PIM was consistently associated with a significantly increased risk of hospitalization. Specifically, the risk increased by 49% in Monza Brianza, 51% in Mantova, 58% in Lecco, and 62% in Bergamo. The pooled estimate showed a 55% overall increase in the odds of hospitalization for patients receiving PIMs compared to matched controls not exposed to such medications (OR 1.55, 95% CI: 1.48–1.62). The Qb test for heterogeneity across LHUs indicated no significant variability ($p = 0.13$), supporting the consistency of the association across the four LHUs. To explore potential effect modification, stratified analyses were conducted by sex and age group.

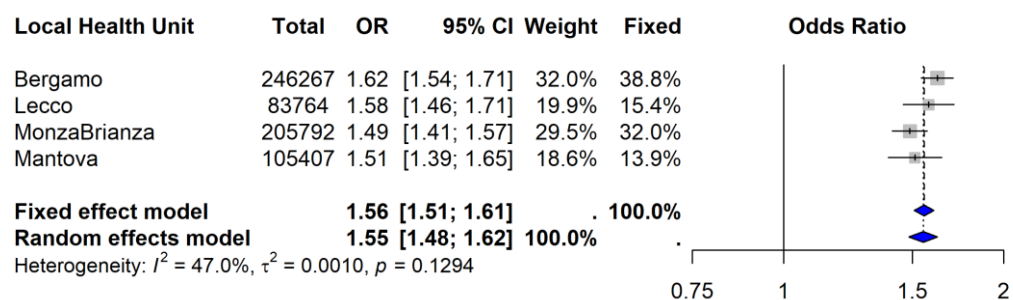
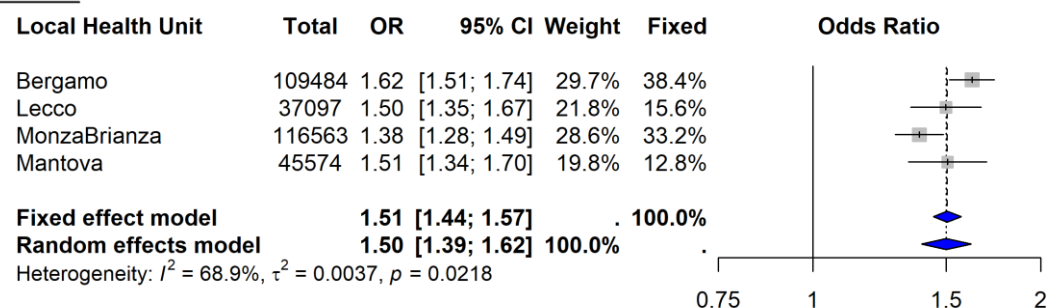


Figure 24 – Pooled results of association between PIMs and hospitalization across the LHUs.

As shown in **Figure 25**, both male and female individuals exposed to PIMs had a significantly higher risk of hospitalization. The pooled OR was 1.50 (95% CI: 1.39–1.62) for males and 1.62 (95% CI: 1.55–1.70) for females. Significant heterogeneity ($p=0.02$) across LHUs was observed for females, but not for males ($p=0.65$).

PANEL A



PANEL B

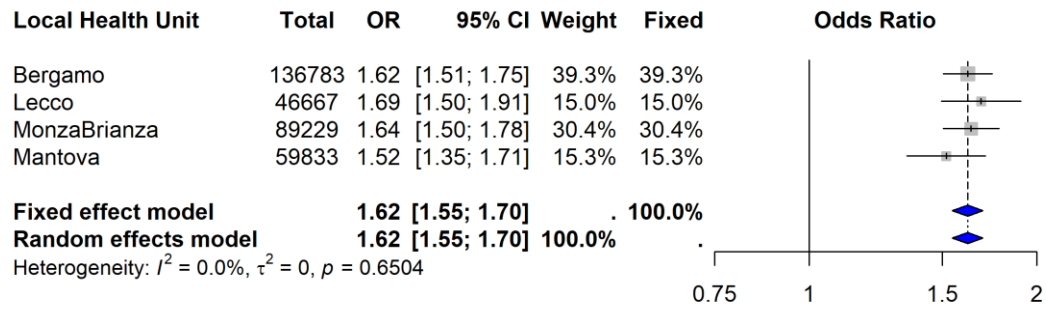


Figure 25 – Pooled results of association between PIM and hospitalization across the LHUs – stratification by sex (PANEL A: Male; PANEL B: Female).

No statistically significant heterogeneity was found between sexes ($p=0.09$), suggesting a broadly similar effect across genders, despite the point estimate was slightly higher in females (**Figure 26**).

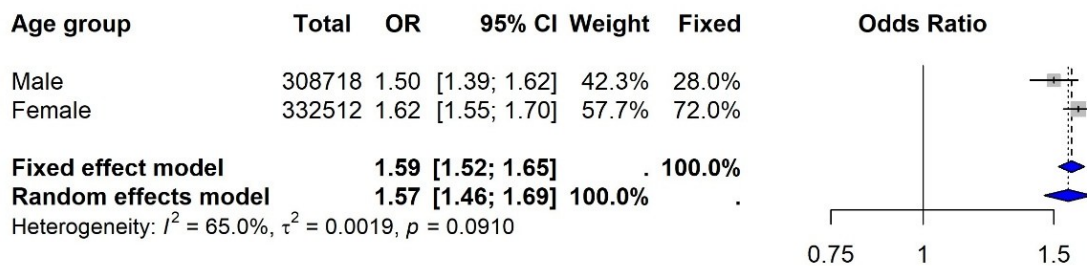
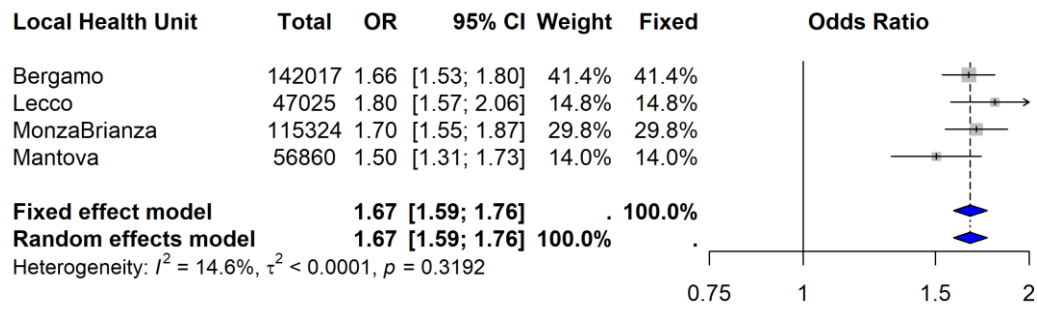


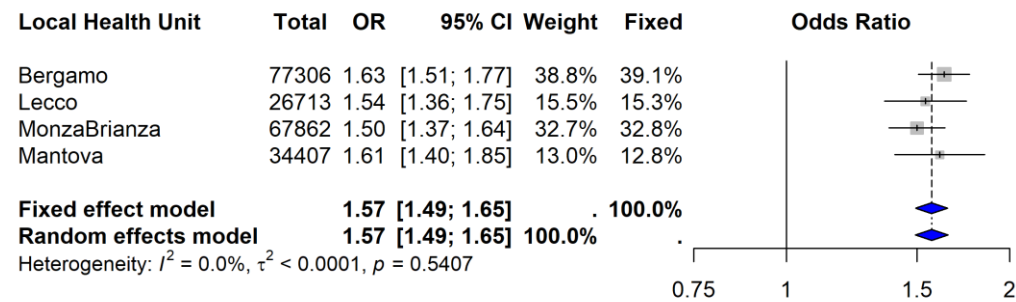
Figure 26 – Heterogeneity test between PIMs and hospitalization by sex

Age-stratified analysis (**Figure 27**) revealed substantial differences in the strength of association between PIM exposure and hospitalization risk across LHUs. The pooled OR was 1.67 (95% CI: 1.59–1.76) for individuals aged 65–74 years, 1.57 (95% CI: 1.49–1.65) for those aged 75–84 years, and 1.36 (95% CI: 1.22–1.52) for individuals aged 85 years or older. No Significant heterogeneity across LHUs was observed for individuals aged 65-74 and 75-84-year-old ($p=0.32$ and $p=0.54$ respectively), but significant heterogeneity across LHUs was found in individuals aged 85 years or older ($p=0.03$).

PANEL A



PANEL B



PANEL C

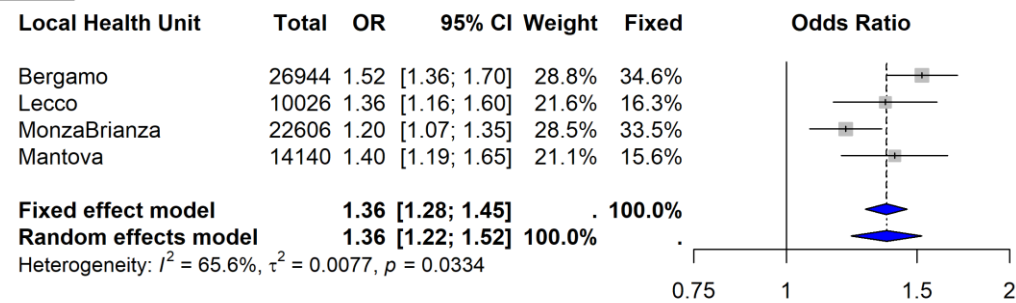


Figure 27- Pooled results of association between PII and hospitalization across the LHUs – stratification by age groups (PANEL A: 65-74 years old; PANEL B: 75-84 years old; PANEL C: ≥ 85 years old)

Figure 28 shows the pooled odds ratios across the four LHUs by age group, along with the test for heterogeneity, which assesses whether the risk differs significantly between age groups. The forest plot in **Figure 28** clearly highlights a difference in the risk of hospitalization associated with PIMs across age groups ($p=0.004$). Overall, the findings suggest that the risk of hospitalization related to PIMs is more pronounced in the younger-old population and tends to decrease in the oldest age group.

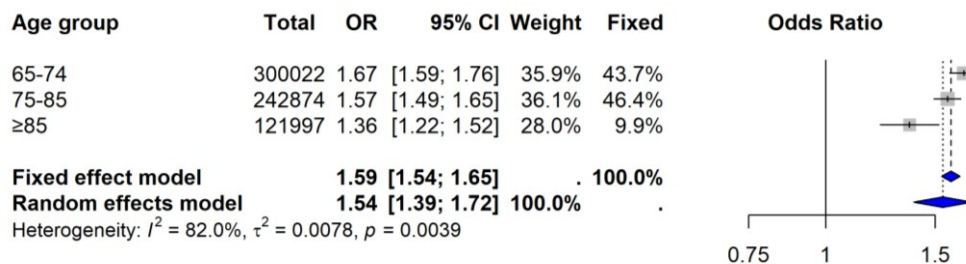


Figure 28 – Heterogeneity test between PIMs and hospitalization by age groups

4.2.3 pDDIs

The annual prevalence of pDDIs is reported in **Table 10**. Overall, 24.1% patients from 2015 to 2018 had a first potentially drug drug interaction. The annual prevalence of patients with at least one occurrence of pDDIs ranged from 23.7% to 24.6% over the study period.

Table 10 – Annual prevalence of pDDIs

	2015	2016	2017	2018	p-value
Over65 population with at least one prescription, N	496,965	513,917	546,656	552,993	
Individuals with at least one pDDI, N (%)	117,936 (24.6%)	122,155 (23.7%)	133,060 (24.3%)	131,376 (23.8%)	<0.0001
Individuals with one pDDI, N (%)	67,464 (57.2%)	70,179 (57.5%)	75,921 (57.1%)	75,654 (57.6%)	0.03
Individuals with two pDDIs, N (%)	25,695 (21.8%)	26,444 (21.6%)	29,141 (21.9%)	28,999 (22.1%)	0.06
Individuals with three pDDIs, N (%)	11,831 (10%)	12,193 (10%)	13,180 (9.9%)	13,012 (9.9%)	0.66
Individuals with four or more pDDIs, N (%)	12,946 (11%)	13,339 (10.9%)	14,818 (11.1%)	13,711 (10.4%)	<0.0001

Table 11 summarizes the five most frequent pDDIs among individuals with at least one PII exposure in the year. The combination A02BC02-H03AA01 (pantoprazole-levothyroxine sodium) consistently ranked first throughout the study period, with an increased trend from 1.1% in 2015 to 1.5% in 2018. The second and third most frequent combinations varied across the years, alternating between B01AC06-

M01AE01 (acetylsalicylic acid-ibuprofen) and H02AB07-J01MA12 (prednisone-levofloxacin). Similarly, the fourth and fifth positions showed some fluctuation, involving combinations such as B01AA03-C01BD01 (warfarin-amiodarone), C01BD01-C10AA05 (amiodarone-digoxin), and B01AA03-B01AC06 (warfarin-acetylsalicylic acid). Despite these variations, all the most frequent pDDIs remained stable in terms of annual prevalence, with values ranging from 0.7% to 1.5% over the four-year period.

Table 11 – *Five most frequent pDDIs by patients*

	2015	2016	2017	2018
1.	A02BC02- H03AA01 (1.1%)	A02BC02- H03AA01 (1.3%)	A02BC02- H03AA01 (1.4%)	A02BC02- H03AA01 (1.5%)
2.	B01AC06- M01AE01 (1.0%)	B01AC06- M01AE01 (0.9%)	H02AB07- J01MA12 (1.0%)	H02AB07- J01MA12 (0.9%)
3.	H02AB07- J01MA12 (0.9%)	H02AB07- J01MA12 (0.9%)	B01AC06- M01AE01 (0.9%)	B01AC06- M01AE01 (0.8%)
4.	B01AA03- C01BD01 (0.9%)	B01AA03- C01BD01 (0.8%)	B01AA03- C01BD01 (0.8%)	C01BD01- C10AA05 (0.7%)
5.	B01AA03- B01AC06 (0.9%)	B01AA03- B01AC06 (0.8%)	C01BD01- C10AA05 (0.7%)	B01AA03- C01BD01 (0.7%)

*A02BC02 Pantoprazole, H03AA01 Levothyroxine sodium, B01AC06 Acetylsalicylic acid, M01AE01 Ibuprofen, H02AB07 Prednisone, J01MA12 Levofloxacin, B01AA03 Warfarin, C01BD01 Amiodarone, C10AA05 Digoxin.

The final matched cohort, comprising 99,594 pairs of individuals who met the pDDIs criteria and subjects which did not, and it forms the basis for the risk analysis. Baseline characteristics of this cohort are presented in **Table 12**. Females consistently represented a slight majority of the population, ranging from 59.7% to 50.5%, while the average age ranged from 77.6 to 78.4 years across LHUs. In all settings, the most represented age group was 75–84 years, followed by 65–74 and ≥85 years.

A marked difference in hospitalization rates was observed between the matched groups. Individuals exposed to at least one pDDIs condition consistently showed a higher incidence of all-cause hospitalization across LHUs. For example, hospitalization occurred in 11.6% of PIM users vs. 5.9% of controls in Bergamo, and in 9.8% vs. 5.0% in Mantova. These differences were statistically significant in all LHUs ($p < 0.0001$), suggesting a consistent association between pDDIs exposure and increased hospitalization risk, even after matching.

Table 12 – Characteristics of the pDDIs matched cohorts at the enrolment. LHUs of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

Covariates	Presence of at least one pDDI		P-value
	No	Yes	
BG	N= 77,398		
N [matched]	38,699	38,699	
Female sex, N (%)	23,413 (60.5)	23,413 (60.5)	-
Age, mean (SD)	77.6 (7.7)	77.6 (7.7)	-
Age class, N (%)			
65-74 yy	14,902 (38.5)	14,902 (38.5)	-
75-84 yy	15,700 (40.6)	15,700 (40.6)	
≥85 yy	8,097 (20.9)	8,097 (20.9)	
Hospitalization, N (%)	2,295 (5.9)	4,488 (11.6)	<0.0001
LC	N= 26,216		
N [matched]	13,108	13,108	
Female sex, N (%)	7,822 (59.7)	7,822 (59.7)	-
Age, mean (SD)	78.1 (7.9)	78.1 (7.9)	-
Age class, N (%)			
65-74 yy	4,780 (36.5)	4,780 (36.5)	-
75-84 yy	5,343 (40.8)	5,343 (40.8)	
≥85 yy	2,985 (22.8)	2,985 (22.8)	
Hospitalization, N (%)	685 (5.2)	1,422 (10.8)	<0.0001
MB	N= 63,516		
N [matched]	31,758	31,758	
Female sex, N (%)	19,208 (60.5)	19,208 (60.5)	-
Age, mean (SD)	77.8 (7.7)	77.8 (7.7)	-
Age class, N (%)			
65-74 yy	11,851 (37.3)	11,851 (37.3)	-
75-84 yy	13,145 (41.4)	13,145 (41.4)	
≥85 yy	6,762 (21.3)	6,762 (21.3)	
Hospitalization, N (%)	1,590 (5.0)	3,265 (10.3)	<0.0001
MN	N=32,058		
N [matched]	16,029	16,029	
Female sex, N (%)	9,844 (61.4)	9,844 (61.4)	-
Age, mean (SD)	78.4 (8)	78.4 (8)	-
Age class, N (%)			
65-74 yy	5,705 (35.6)	5,705 (35.6)	-
75-84 yy	6,459 (40.3)	6,459 (40.3)	
≥85 yy	3,865 (24.1)	3,865 (24.1)	
Hospitalization, N (%)	794 (5.0)	1,575 (9.8)	<0.0001

* SD=Standard Deviation, yy=years.

The estimate association between exposure and all-cause hospitalization is summarized in **Figure 29**. Across all LHUs, exposure to at least one pDDIs was consistently associated with a significantly increased risk of hospitalization. Specifically, the risk increased by 43% in Bergamo, 47% in Mantova, 54% in Monza Brianza, and 59% in Lecco. The pooled estimate showed a 50% overall increase in the odds of hospitalization for patients receiving PIMs compared to matched controls not exposed to such medications (OR 1.50, 95% CI: 1.43–1.57). The Qb test for heterogeneity across LHUs indicated no significant variability ($p=0.29$), supporting the consistency of the association across the four LHU.

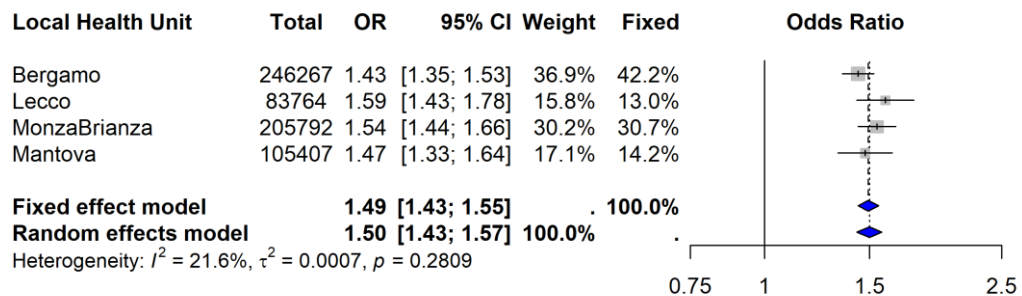
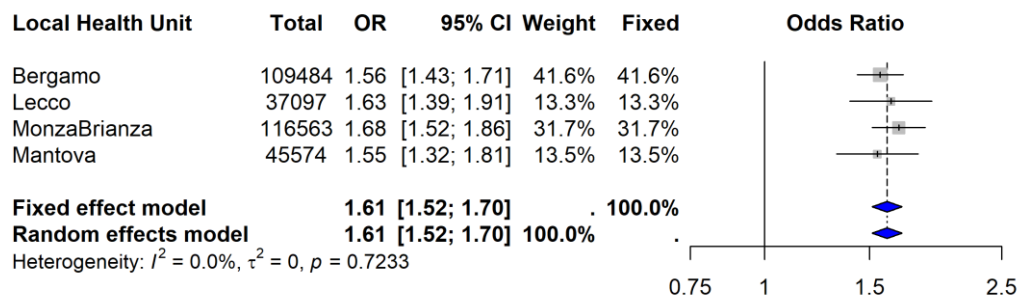


Figure 29 – Pooled results of association between pDDIs and hospitalization across the LHUs.

As shown in **Figure 30**, both male and female individuals exposed to pDDIs had a significantly higher risk of hospitalization. The pooled OR was 1.61 (95% CI: 1.52–1.70) in males and 1.40 (95% CI: 1.31–1.49) in females. No significant heterogeneity across LHUs was observed for both males and females ($p=0.72$ and $p=0.29$ respectively).

PANEL A



PANEL B

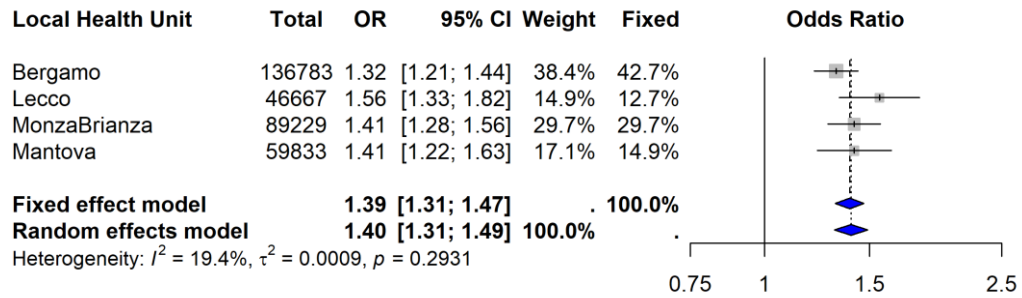


Figure 30 – Pooled results of association between pDDIs and hospitalization across the LHUs – stratification by sex (PANEL A: Male; PANEL B: Female).

Statistically significant heterogeneity was found between sexes ($p = 0.0016$), suggesting different effect across genders (**Figure 31**), with a higher risk in males.

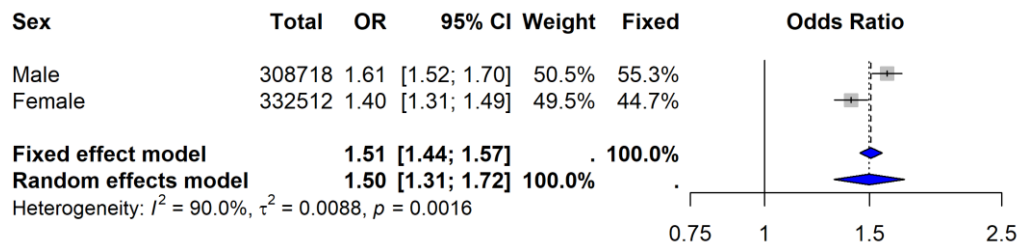
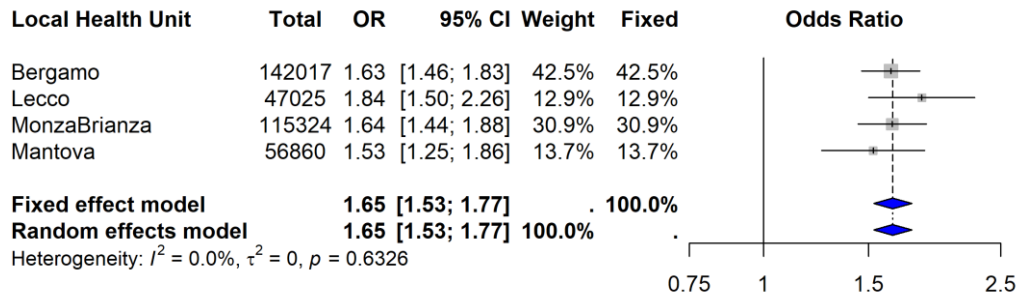


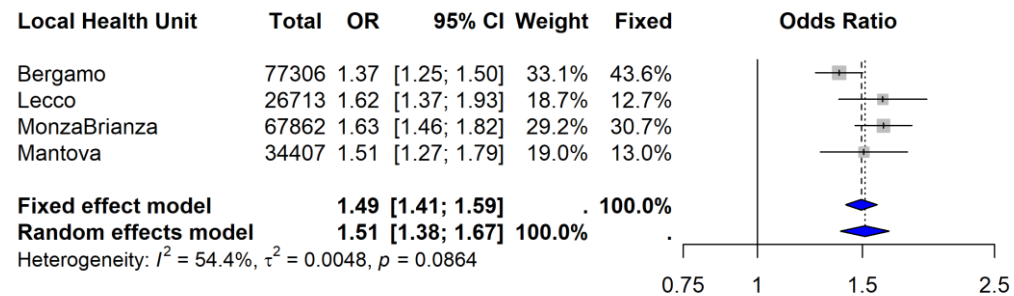
Figure 31 – Heterogeneity test between pDDIs and hospitalization by sex

Age-stratified analysis (**Figure 32**) revealed substantial differences in the strength of association between pDDIs exposure and hospitalization risk across LHUs. The pooled OR was 1.65 (95% CI: 1.53–1.77) for individuals aged 65–74 years, 1.51 (95% CI: 1.38–1.67) for those aged 75–84 years, and 1.33 (95% CI: 1.23–1.43) for individuals aged 85 years or older. No Significant heterogeneity across LHUs was observed for individuals aged 65-74, 75-84-year-old, and 85 years or older ($p=0.6326$, $p=0.09$ and $p=0.96$ respectively).

PANEL A



PANEL B



PANEL C

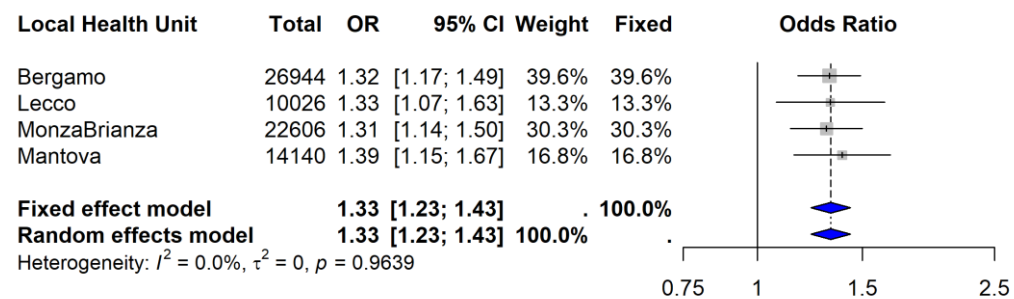


Figure 32- Pooled results of association between pDDIs and hospitalization across the LHUs – stratification by age groups (PANEL A: 65-74 years old; PANEL B: 75-84 years old; PANEL C: ≥ 85 years old)

Figure 33 shows the pooled odds ratios across the four LHUs by age group. The forest plot in clearly highlights a difference in the risk of hospitalization associated with pDDIs across age groups ($p=0.0003$). Overall, the findings suggest that the risk of hospitalization related to pDDIs is more pronounced in the younger-old population and tends to decrease in the oldest age group.

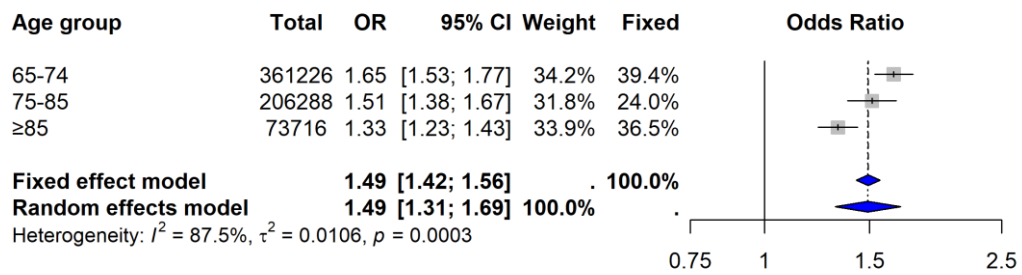


Figure 33 – Heterogeneity test between pDDIs and hospitalization by age groups

4.2.4 FRIDs

The annual prevalence of FRIDs is reported in **Table 13**. Overall, 23.3% patients from 2015 to 2018 have redeemed FRIDs. The annual prevalence of patients with at least one FRID ranged from 22.2% to 24.2% over the study period.

Table 13 – Annual prevalence of FRIDs

	2015	2016	2017	2018	p-value
Over65 population with at least one prescription, N	496,965	513,917	546,656	552,993	
Individuals with at least one FRIDs, N (%)	110,396 (22.2%)	117,629 (22.9%)	131,173 (24.0%)	133,749 (24.2%)	<0.0001
Individuals with one FRIDs, N (%)	89,809 (81.4%)	95,146 (80.9%)	104,613 (79.8%)	106,377 (79.5%)	<0.0001
Individuals with two FRIDs, N (%)	18,387 (16.7%)	19,974 (17%)	23,263 (17.7%)	24,107 (18.0%)	<0.0001
Individuals with three FRIDs, N (%)	2,089 (1.9%)	2,385 (2.0%)	3,125 (2.4%)	3,089 (2.3%)	<0.0001
Individuals with four FRIDs, N (%)	111 (0.1%)	124 (0.1%)	172 (0.1%)	176 (0.1%)	0.04

Table 14 summarizes the five most frequent FRIDs among individuals with at least one PII exposure in the year. The ranking remained stable throughout the study period, with N06A (antidepressant) consistently in first position and increasing in prevalence from 13.0% in 2015 to 14.0% in 2018. This was followed by N02A (opioids, from 9.3% to 10.1%), N05A (antipsychotics, from 2.7% to 3.7%), and N04B (dopaminergic

agents, from 1.8% to 2.1%). Overall, the prevalence the FRID categories showed a modest upward trend.

Table 14 –FRIDs frequency by patients

	2015	2016	2017	2018
1.	N06A (13.0%)	N06A (13.4%)	N06A (13.7%)	N06A (14.0%)
2.	N02A (9.3%)	N02A (9.5%)	N02A (10.1%)	N02A (10.0%)
3.	N05A (2.7%)	N05A (3.0%)	N05A (3.6%)	N05A (3.7%)
4.	N04B (1.8%)	N04B (2.0%)	N04B (2.1%)	N04B (2.1%)

*N06A Antidepressant, N02A Opioids, N05A Antipsychotics, N04B Dopaminergic agents.

The final matched cohort, comprising 119,743 pairs of individuals who met the FRIDs criteria and subjects which did not and it forms the basis for the risk analysis. Baseline characteristics of this cohort are presented in **Table 15**. Females consistently represented a slight majority of the population, ranging from 60.1% to 62.5%, while the average age ranged from 77.3 to 78.1 years across LHUs. In all settings, the most represented age groups were 65–74 and 75–84 years, followed by and ≥85 years.

A marked difference in hospitalization rates was observed between the matched groups. Individuals exposed to at least one potentially inappropriate prescription consistently showed a higher incidence of all-cause hospitalization across LHUs. For example, hospitalization occurred in 10.7% of PIM users vs. 6.2% of controls in Bergamo, and in 9.8% vs. 5.3% in Mantova. These differences were statistically significant in all LHUs ($p < 0.0001$), suggesting a consistent association between FRIDs exposure and increased hospitalization risk, even after matching.

Table 15 – Characteristics of the FRIDs matched cohorts at the enrolment. LHUs of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

	Presence of at least one FRID		
Covariates	No	Yes	p-value
BG	N= 95,780		
N [matched]	47,890	47,890	
Female sex, N (%)	28,769 (60.1)	28,769 (60.1)	-
Age, mean (SD)	77.3 (7.9)	77.3 (7.9)	-
Age class, N (%)			
65-74 yy	19,429 (40.6)	19,429 (40.6)	-
75-84 yy	18,777 (39.2)	18,777 (39.2)	
≥85 yy	9,684 (20.2)	9,684 (20.2)	
Hospitalization, N (%)	2,956 (6.2)	5,103 (10.7)	<0.0001
LC	N= 30,870		
N [matched]	15,435	15,435	
Female sex, N (%)	9,553 (61.9)	9,553 (61.9)	-
Age, mean (SD)	78.1 (8.1)	78.1 (8.1)	-
Age class, N (%)			
65-74 yy	5,688 (36.9)	5,688 (36.9)	-
75-84 yy	6,051 (39.2)	6,051 (39.2)	
≥85 yy	3,696 (23.9)	3,696 (23.9)	
Hospitalization, N (%)	872 (5.6)	1,626 (10.5)	<0.0001
MB	N= 75,274		
N [matched]	37,637	37,637	
Female sex, N (%)	23,505 (62.5)	23,505 (62.5)	-
Age, mean (SD)	78.1 (8)	78.1 (8)	-
Age class, N (%)			
65-74 yy	13,544 (36.0)	13,544 (36.0)	-
75-84 yy	15,308 (40.7)	15,308 (40.7)	
≥85 yy	8,785 (23.3)	8,785 (23.3)	
Hospitalization, N (%)	2,028 (5.4)	3,278 (8.7)	<0.0001
MN	N=37,562		
N [matched]	18,781	18,781	
Female sex, N (%)	11,718 (62.4)	11,718 (62.4)	-
Age, mean (SD)	78.0 (8.2)	78.0 (8.2)	-
Age class, N (%)			
65-74 yy	7,197 (38.3)	7,197 (38.3)	-
75-84 yy	7,110 (37.9)	7,110 (37.9)	
≥85 yy	4,474 (23.8)	4,474 (23.8)	
Hospitalization, N (%)	989 (5.3)	1,832 (9.8)	<0.0001

* SD=Standard Deviation, yy=years.

The estimate association between exposure and all-cause hospitalization is summarized in **Figure 34**. Across all LHUs, exposure to at least one FRIDs was consistently associated with a significantly increased risk of hospitalization. Specifically, the risk increased by 49% in Monza Brianza, 59% in Bergamo, 69% in Mantova, and 75% in Lecco. The pooled estimate showed a 62% overall increase in the odds of hospitalization for patients receiving FRIDs compared to matched controls not exposed to such medications (OR 1.62, 95% CI: 1.51–1.73). The Qb test for heterogeneity across LHUs indicated significant variability ($p=0.01$), indicating that the strength of the association between FRIDs exposure and all-cause hospitalization varied across the four regions, rather than being consistent.

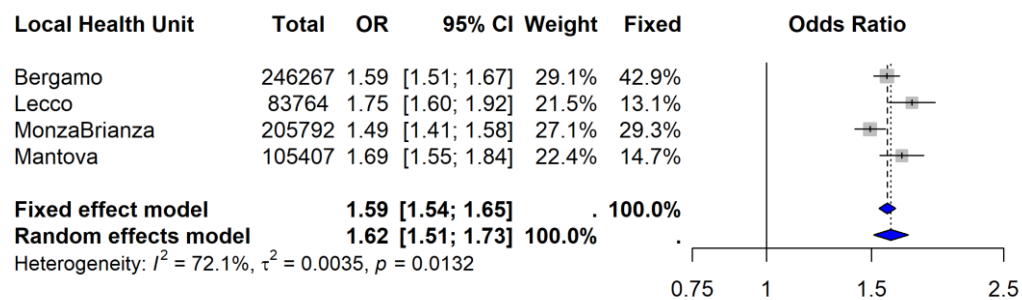
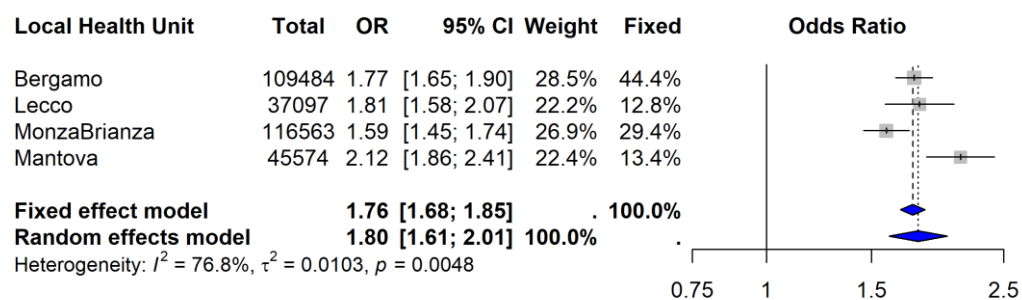


Figure 34 – Pooled results of association between FRIDs and hospitalization across the LHUs.

As shown in **Figure 35**, both male and female individuals exposed to FRIDs had a significantly higher risk of hospitalization. The pooled OR was 1.80 (95% CI: 1.62–2.01) for males and 1.48 (95% CI: 1.37–1.59) for females. Significant heterogeneity ($p=0.0048$) across LHUs was observed for males, but not for females ($p=0.06$).

PANEL A



PANEL B

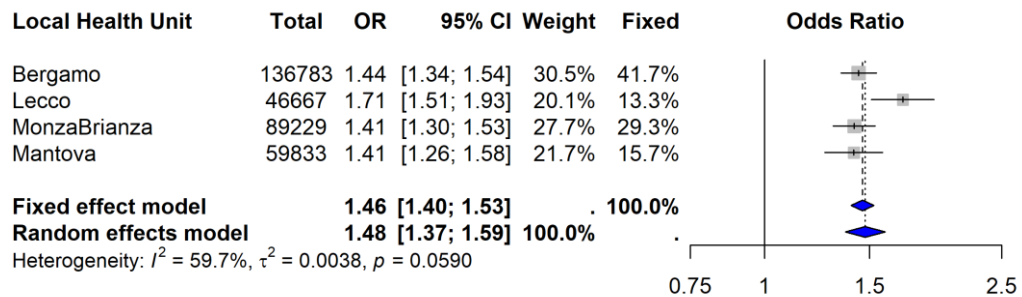


Figure 35 – Pooled results of association between FRIDs and hospitalization across the LHUs – stratification by sex (PANEL A: Male; PANEL B: Female).

Statistically significant heterogeneity was found between sexes ($p=0.0046$), suggesting different effect across genders (**Figure 36**), with a higher risk in males.

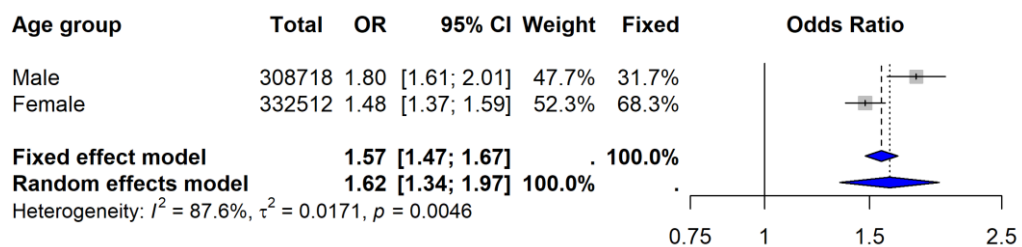
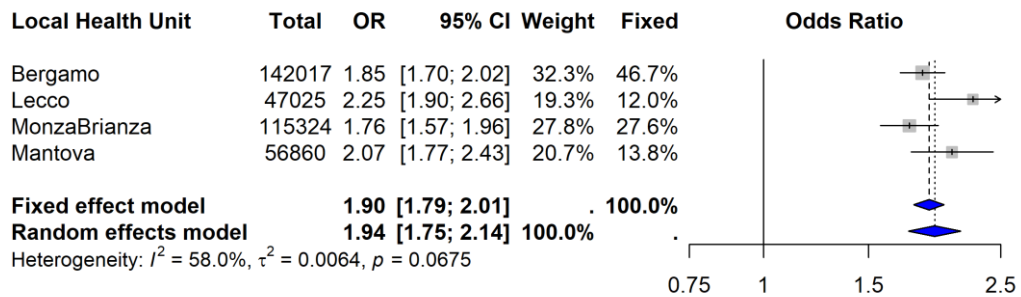


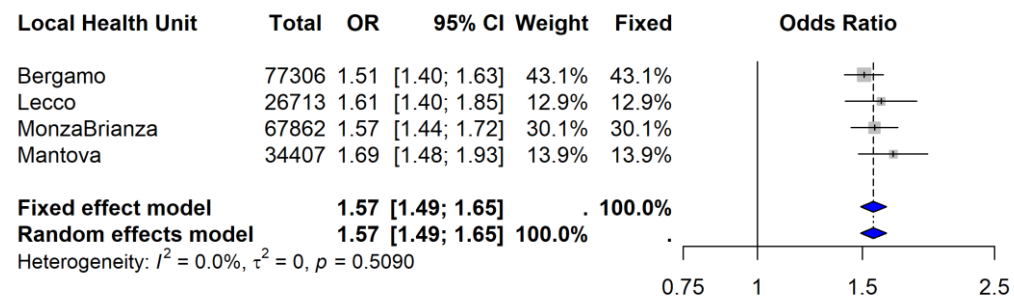
Figure 36 – Heterogeneity test between FRIDs and hospitalization by sex

Age-stratified analysis (**Figure 37**) revealed substantial differences in the strength of association between FRIDs exposure and hospitalization risk across LHUs. The pooled OR was 1.94 (95% CI: 1.74–2.14) for individuals aged 65–74 years, 1.57 (95% CI: 1.49–1.65) for those aged 75–84 years, and 1.39 (95% CI: 1.19–1.54) for individuals aged 85 years or older. No Significant heterogeneity across LHUs was observed for individuals aged 65-74 and 75-84-year-old ($p=0.07$ and $p=0.51$ respectively), but significant heterogeneity across LHUs was found in individuals aged 85 years or older ($p=0.01$).

PANEL A



PANEL B



PANEL C

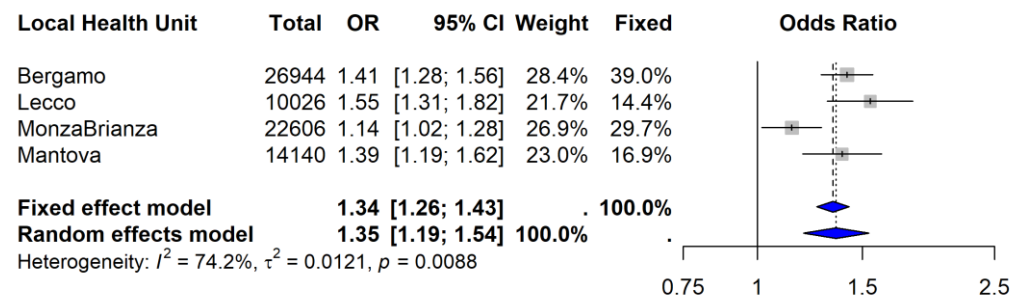


Figure 37- Pooled results of association between FRIDs and hospitalization across the LHUs – stratification by age groups (PANEL A: 65-74 years old; PANEL B: 75-84 years old; PANEL C: ≥ 85 years old)

Figure 38 shows the pooled odds ratios across the four LHUs by age group. The forest plot in **Figure 38** clearly highlights a difference in the risk of hospitalization associated with FRIDs across age groups ($p < 0.0001$). Overall, the findings suggest that the risk

of hospitalization related to FRIDs is more pronounced in the younger-old population and tends to decrease in the oldest age group.

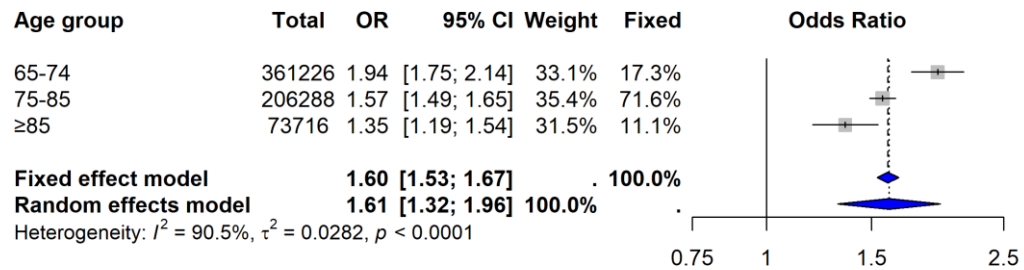


Figure 38 – Heterogeneity test between FRIDs and hospitalization by age groups

4.2.5 TDs

The annual prevalence of TDs is reported in **Table 16**. Overall, 9.0% patients from 2015 to 2018 have redeemed a potential TD. The annual prevalence of patients with at least one TD ranged from 8.8% to 9.1% over the study period.

Table 16 – Annual prevalence of TDs

	2015	2016	2017	2018	p-value
Over65 population with at least one prescription, N	496,965	513,917	546,656	552,993	
Individuals with at least one TD, N (%)	44,605 (9.0%)	45,158 (8.8%)	49,017 (9.0%)	50,472 (9.1%)	<0.001
Individuals with one TD, N (%)	37,980 (85.1%)	38,681 (85.7%)	41,851 (85.4%)	43,376 (85.9%)	0.03
Individuals with two TDs, N (%)	4,909 (11.0%)	4,844 (10.7%)	5,295 (10.8%)	5,243 (10.4%)	0.02
Individuals with three TDs, N (%)	1,287 (2.9%)	1,196 (2.6%)	1,371 (2.8%)	1,372 (2.7%)	0.15
Individuals with four or more TDs, N (%)	429 (1.0%)	437 (1.0%)	500 (1.0%)	481 (1.0%)	0.71

Table 17 summarizes the five most frequent TDs among individuals with at least one PII exposure in the year. The combination B01AC04-B01AC06 (clopidogrel-acetylsalicylic acid) was the most frequent TD across all years, with a stable

prevalence of 1.3% from 2015 to 2017 and a slight decrease to 1.2% in 2018. The remaining combinations showed lower and relatively stable frequencies. A02BC02-A02BC05 (pantoprazole-esomeprazole) ranked second from 2015 to 2018, increasing slightly from 0.3% to 0.4%. A11CC04-A11CC05 (calcitriol-colecalciferol) and A02BC02-A02BC03 (pantoprazole-lansoprazole) alternated among the third, fourth, and fifth positions, all maintaining prevalence between 0.2% and 0.3%. Overall, the observed TDs remained consistent over time and occurred with relatively low frequency, ranging from 0.2% to 1.3%.

Table 17 – Five most frequent TDs by patients

	2015	2016	2017	2018
1.	B01AC04- B01AC06 (1.3%)	B01AC04- B01AC06 (1.3%)	B01AC04- B01AC06 (1.3%)	B01AC04- B01AC06 (1.2%)
2.	A02BC02- A02BC05 (0.3%)	A02BC02- A02BC05 (0.3%)	A02BC02- A02BC05 (0.4%)	A02BC02- A02BC05 (0.4%)
3.	A02BC02- A02BC03 (0.2%)	A11CC04- A11CC05 (0.3%)	A11CC04- A11CC05 (0.3%)	A11CC04- A11CC05 (0.3%)
4.	A11CC04- A11CC05 (0.2%)	B01AC06- B01AC24 (0.2%)	B01AC06- B01AC24 (0.2%)	B01AC06- B01AC24 (0.3%)
5.	B01AC06- B01AC24 (0.2%)	A02BC02- A02BC03 (0.2%)	A02BC02- A02BC03 (0.2%)	A02BC02- A02BC03 (0.2%)

*B01AC04 Clopidogrel, B01AC06 Acetylsalicylic acid, A02BC02 Pantoprazole, A02BC05 Esomeprazole, A02BC03 Lansoprazole, A11CC04 Calcitriol, A11CC05 Colecalciferol, B01AC24 Ticagrelor.

The final matched cohort, comprising 94,984 pairs, forms the basis for the risk analysis. Baseline characteristics of this cohort are presented in **Table 18**. Females consistently represented a slight majority of the population, ranging from 51.9% to 53.9%, while the average age ranged from 77.3 to 78.3 years across LHUs. In all settings, the most represented age group were 65–74 and 75–84 years, followed by ≥85 years.

A marked difference in hospitalization rates was observed between the matched groups. Individuals exposed to at least one potentially inappropriate prescription consistently showed a higher incidence of all-cause hospitalization across LHUs. For example, hospitalization occurred in 12.4% of TDs users vs. 5.8% of controls in Bergamo, and in 10.2% vs. 5.2% in Monza Brianza. These differences were statistically significant in all LHUs ($p < 0.0001$), suggesting a consistent association between TDs exposure and increased hospitalization risk, even after matching.

Table 18 – Characteristics of the TDs matched cohorts at the enrolment. LHUs of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

	Presence of at least one TD		
Covariates	No	Yes	p-value
BG	N=73,096		
N [matched]	36,548	36,548	
Female sex, N (%)	19,092 (52.2)	19,092 (52.2)	-
Age, mean (SD)	77.3 (7.5)	77.3 (7.5)	-
Age class, N (%)			
65-74 yy	14,541 (39.8)	14,541 (39.8)	-
75-84 yy	15,141 (41.4)	15,141 (41.4)	
≥85 yy	6,866 (18.8)	6,866 (18.8)	
Hospitalization, N (%)	2,118 (5.8)	4,514 (12.4)	<0.0001
LC	N= 23,850		
N [matched]	11,925	11,925	
Female sex, N (%)	6,192 (51.9)	6,192 (51.9)	-
Age, mean (SD)	77.3 (7.4)	77.3 (7.4)	-
Age class, N (%)			
65-74 yy	4,746 (39.8)	4,746 (39.8)	-
75-84 yy	4,993 (41.9)	4,993 (41.9)	
≥85 yy	2,186 (18.3)	2,186 (18.3)	
Hospitalization, N (%)	632 (5.3)	1,297 (10.9)	<0.0001
MB	N= 62,164		
N [matched]	14,865	14,865	
Female sex, N (%)	16,217 (52.2)	16,217 (52.2)	-
Age, mean (SD)	77.3 (7.3)	77.3 (7.3)	-
Age class, N (%)			
65-74 yy	12,181 (39.2)	12,181 (39.2)	-
75-84 yy	13,161 (42.3)	13,161 (42.3)	
≥85 yy	5,740 (18.5)	5,740 (18.5)	
Hospitalization, N (%)	1,609 (5.2)	3,184 (10.2)	<0.0001
MN	N=30,858		
N [matched]	15,429	15,429	
Female sex, N (%)	8,309 (53.9)	8,309 (53.9)	-
Age, mean (SD)	78.3 (7.7)	78.3 (7.7)	-
Age class, N (%)			
65-74 yy	5,517 (35.8)	5,517 (35.8)	-
75-84 yy	6,422 (41.6)	6,422 (41.6)	
≥85 yy	3,490 (22.6)	3,490 (22.6)	
Hospitalization, N (%)	844 (5.5)	1,671 (10.8)	<0.0001

* SD=Standard Deviation, yy=years.

The estimate association between exposure and all-cause hospitalization is summarized in **Figure 39**. Across all LHUs, exposure to at least one TDs was consistently associated with a significantly increased risk of hospitalization. Specifically, the risk increased by 44% in Mantova, 50% in Monza Brianza, 52% in Lecco, and 56% in Bergamo. The pooled estimate showed a 52% overall increase in the odds of hospitalization for patients receiving TDs compared to matched controls not exposed to such medications (OR 1.52, 95% CI: 1.46–1.58). The Qb test for heterogeneity across LHUs indicated no significant variability ($p = 0.56$), supporting the consistency of the association across the four regions.

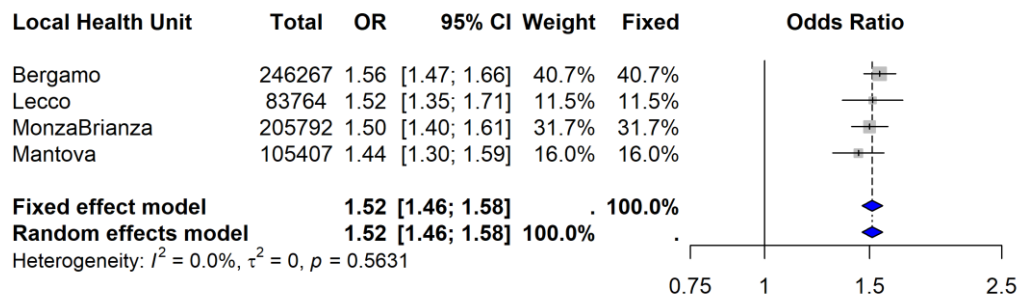
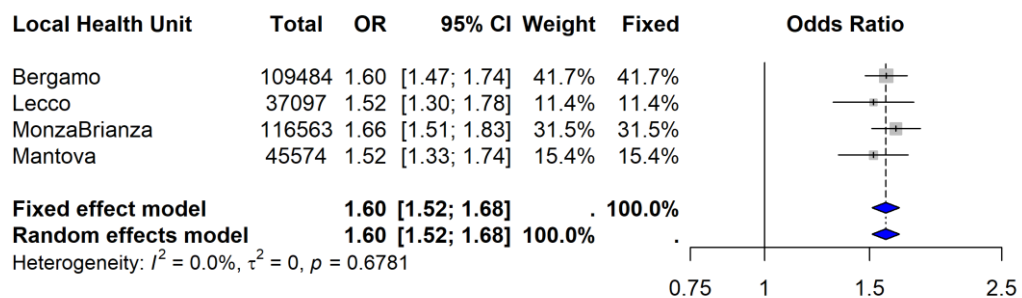


Figure 39 – Pooled results of association between TDs and hospitalization across the LHUs.

As shown in **Figure 40**, both male and female individuals exposed to TDs had a significantly higher risk of hospitalization. The pooled odds ratio was 1.60 (95% CI: 1.52–1.68) in males and 1.41 (95% CI: 1.30–1.52) in females. No significant heterogeneity across LHUs was observed for both females ($p=0.22$) and males ($p=0.68$).

PANEL A



PANEL B

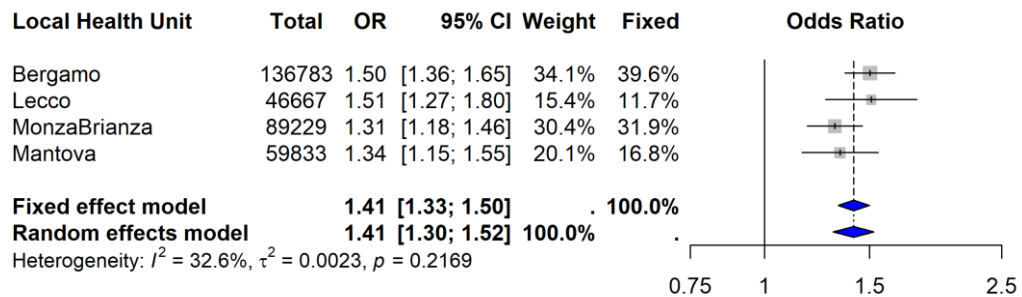


Figure 40 – Pooled results of association between TDs and hospitalization across the LHUs – stratification by sex (PANEL A: Male; PANEL B: Female).

Statistically significant heterogeneity was found between sexes ($p=0.01$), suggesting a different effect between sexes (**Figure 41**), with a higher risk in males.

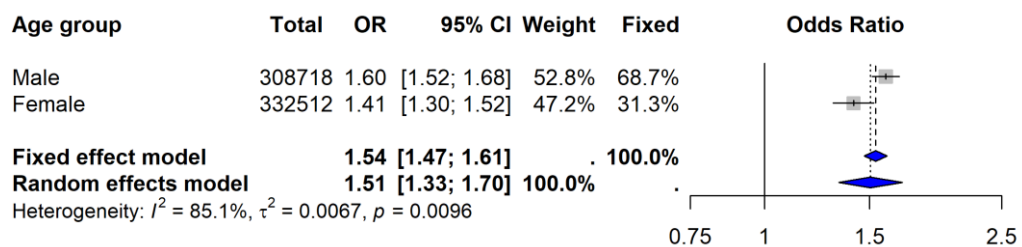
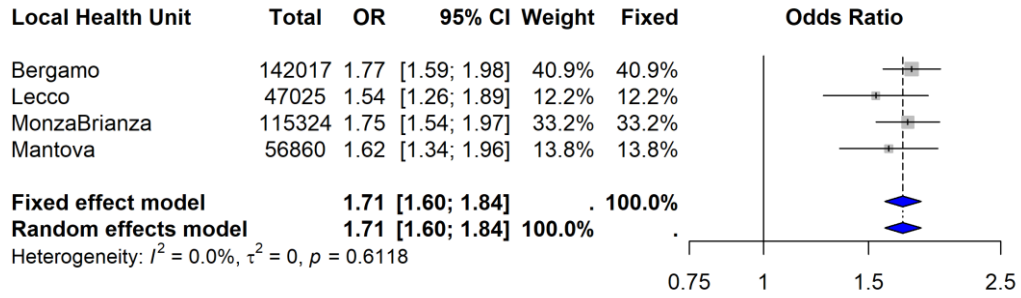


Figure 41 – Heterogeneity test between TDs and hospitalization by sex

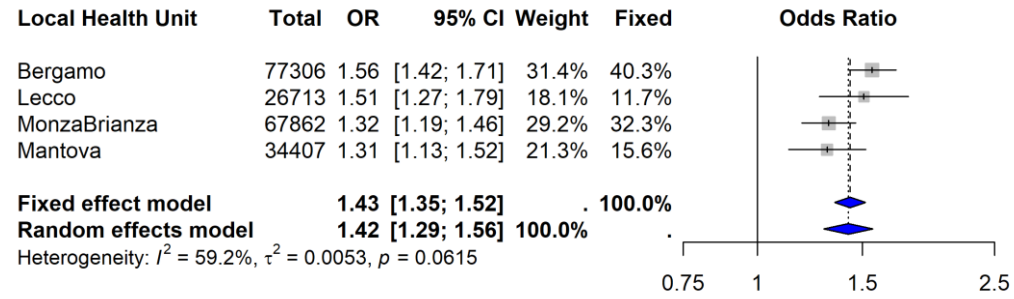
Age-stratified analysis (**Figure 42**) revealed substantial differences in the strength of association between TDs exposure and hospitalization risk. The pooled OR was 1.71 (95% CI: 1.60–1.84) for individuals aged 65–74 years, 1.42 (95% CI: 1.29–1.56) for those aged 75–84 years, and 1.43 (95% CI: 1.29–1.59) for individuals aged 85 years or older. No Significant heterogeneity across LHUs was observed for individuals aged 65-74, 75-84-year-old and 85 years or older ($p=0.61$, $p=0.06$ and $p=0.29$ respectively).

Figure 43 shows the pooled odds ratios across the four LHUs by age group. The forest plot in **Figure 43** clearly highlights a difference in the risk of hospitalization associated with FRIDs across age groups ($p=0.002$). Overall, the findings suggest that the risk of hospitalization related to FRIDs is more pronounced in the younger-old population followed by the 75–84 and ≥ 85 age groups.

PANEL A



PANEL B



PANEL C

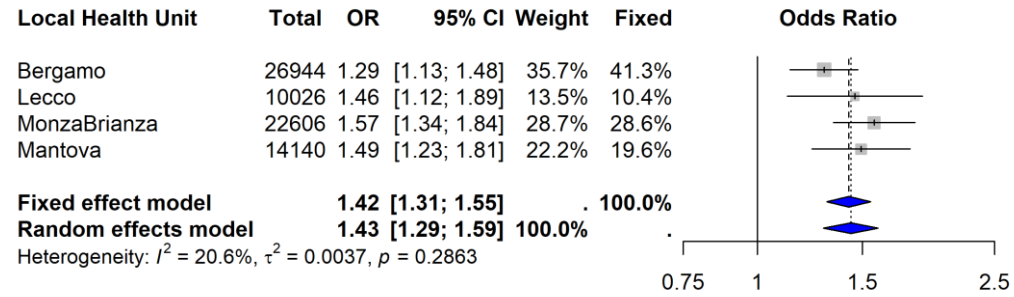


Figure 42- Pooled results of association between TDs and hospitalization across the LHUs – stratification by age groups (PANEL A: 65-74 years old; PANEL B: 75-84 years old; PANEL C: ≥ 85 years old)

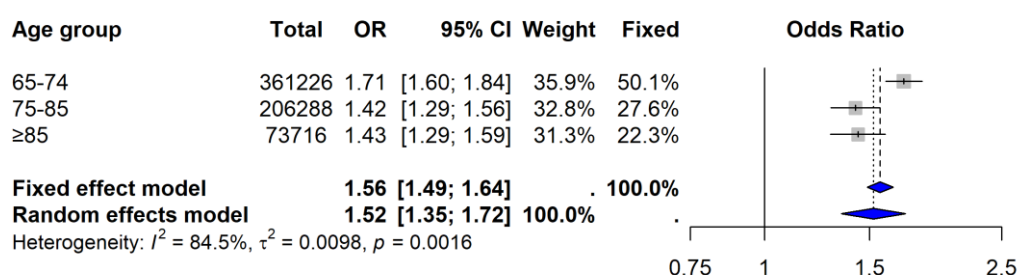


Figure 43 – Heterogeneity test between TDs and hospitalization by age groups

4.2.6 ACB score

The annual prevalence of ACB score ≥ 3 is reported in **Table 19**. Overall, 7.5% patients from 2015 to 2018 had an occurrence of ACB score ≥ 3 . The annual prevalence of patients with at least one PIM ranged from 7.0% to 7.9% over the study period.

Table 19 – Annual prevalence of ACB score ≥ 3 .

	2015	2016	2017	2018	p-value
Over65 population with at least one prescription, N	496,965	513,917	546,656	552,993	
Individuals with at least one ACB score ≥ 3 , N (%)	39,174 (7.9%)	38,296 (7.5%)	40,202 (7.4%)	38,711 (7.0%)	<0.0001
Individuals with one ACB score ≥ 3 , N (%)	25,222 (64.4%)	24,640 (64.3%)	25,740 (64.0%)	24,953 (64.5%)	0.60
Individuals with two ACB score ≥ 3 , N (%)	6,226 (15.9%)	5,962 (15.6%)	6,480 (16.1%)	6,272 (16.2%)	0.07
Individuals with three ACB score ≥ 3 , N (%)	3,340 (8.5%)	3,337 (8.7%)	3,473 (8.6%)	3,293 (8.5%)	0.71
Individuals with four or more ACB score ≥ 3 , N (%)	4,386 (11.2%)	4,357 (11.4%)	4,509 (11.2%)	4,193 (10.8%)	0.10

Table 20. summarizes the five most frequent ACB score ≥ 3 conditions among individuals with at least one PII exposure in the year. The ATC code N06AA09 (amitriptyline) appeared consistently in the first position across all years, with a stable prevalence of 0.5%. Other combinations showed lower and relatively stable

frequencies. C03CA01-N03AX16 (furosemide-pregabalin) and C03CA01-N05AH04 (furosemide-quetiapine) alternated between the second and third ranks, both reaching up to 0.3% in the later years. The triple combination B01AA03-C01AA05-C03CA01 (warfarin-digoxin-furosemide) appeared in 2015 and 2016, while A02BC03-N06AB05 (lansoprazole-paroxetine) and C03CA01-N06AB05 (furosemide-paroxetine) were reported from 2015 onward. Overall, the most common prescribing combinations showed limited variation over time and occurred with low prevalence, ranging between 0.2% and 0.5%.

Table 20 – Five most frequent ACB score ≥ 3 by patients

	2015	2016	2017	2018
1.	N06AA09 (0.5%)	N06AA09 (0.5%)	N06AA09 (0.5%)	N06AA09 (0.5%)
2.	C03CA01-N03AX16 (0.2%)	C03CA01-N03AX16 (0.3%)	C03CA01-N05AH04 (0.3%)	C03CA01-N05AH04 (0.3%)
3.	B01AA03-C01AA05- C03CA01 (0.2%)	C03CA01-N05AH04 (0.2%)	C03CA01-N03AX16 (0.3%)	C03CA01-N03AX16 (0.3%)
4.	A02BC03-N06AB05 (0.2%)	B01AA03-C01AA05- C03CA01 (0.2%)	C03CA01-N06AB05 (0.2%)	C03CA01-N06AB05 (0.2%)
5.	C03CA01-N05AH04 (0.2%)	A02BC03-N06AB05 (0.2%)	A02BC03-N06AB05 (0.2%)	A02BC03-N06AB05 (0.2%)

*N06AA09 amitriptyline, C03CA01 Furosemide, N03AX16 Pregabalin, B01AA03 Warfarin, C01AA05 Digoxin, A02BC03 Lansoprazole, N06AB05 Paroxetine, N05AH04 Quetiapine.

The final matched cohort, comprising 60,699 pairs, forms the basis for the risk analysis. Baseline characteristics of this cohort are presented in **Table 21**. Females consistently represented a slight majority, ranging from 61.2% to 62.6%, while the average age ranged from 78.6 to 79.6 years across LHUs. In all settings, the most represented age group was 75–84 years, followed by 65–74 and ≥ 85 years.

A marked difference in hospitalization rates was observed between the matched groups. Individuals exposed to at least one occurrence of ACB score ≥ 3 consistently showed a higher incidence of all-cause hospitalization across LHUs. For example, hospitalization occurred in 12.5% of ACB drugs users vs. 5.6% of controls in Bergamo, and in 10.3% vs. 4.6% in Monza Brianza. These differences were statistically significant in all LHUs ($p < 0.0001$).

Table 21– Characteristics of the ACB score ≥ 3 matched cohorts at the enrolment. LHUs of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

	Presence of at least one occurrence of ACB score ≥ 3		
Covariates	No	Yes	p-value
BG	N= 50,170		
N [matched]	25,085	25,085	
Female sex, N (%)	15,345 (61.2)	15,345 (61.2)	-
Age, mean (SD)	78.6 (8)	78.6 (8)	-
Age class, N (%)			
65-74 yy	8,479 (33.8)	8,479 (33.8)	-
75-84 yy	10,217 (40.7)	10,217 (40.7)	
≥ 85 yy	6,389 (25.5)	6,389 (25.5)	
Hospitalization, N (%)	1,416 (5.6)	3,126 (12.5)	<0.0001
LC	N= 15,552		
N [matched]	7,776	7,776	
Female sex, N (%)	4,820 (62.0)	4,820 (62.0)	-
Age, mean (SD)	79.3 (8.1)	79.3 (8.1)	-
Age class, N (%)			
65-74 yy	2,431 (31.3)	2,431 (31.3)	-
75-84 yy	3,167 (40.7)	3,167 (40.7)	
≥ 85 yy	2,178 (28.0)	2,178 (28.0)	
Hospitalization, N (%)	431 (5.5)	905 (11.6)	<0.0001
MB	N= 35,814		
N [matched]	17,907	17,907	
Female sex, N (%)	11,182 (62.4)	11,182 (62.4)	-
Age, mean (SD)	79.1 (7.9)	79.1 (7.9)	-
Age class, N (%)			
65-74 yy	5,610 (31.3)	5,610 (31.3)	-
75-84 yy	7,479 (41.8)	7,479 (41.8)	
≥ 85 yy	4,818 (26.9)	4,818 (26.9)	
Hospitalization, N (%)	818 (4.6)	1,850 (10.3)	<0.0001
MN	N=19,862		
N [matched]	9,931	9,931	
Female sex, N (%)	6,216 (62.6)	6,216 (62.6)	-
Age, mean (SD)	79.6 (8)	79.6 (8)	-
Age class, N (%)			
65-74 yy	2,957 (29.8)	2,957 (29.8)	-
75-84 yy	4,046 (40.7)	4,046 (40.7)	
≥ 85 yy	2,928 (29.5)	2,928 (29.5)	
Hospitalization, N (%)	568 (5.7)	1,166 (11.7)	<0.0001

* SD=Standard Deviation, yy=years.

The estimate association between exposure and all-cause hospitalization is summarized in **Figure 44**. Across all LHUs, exposure to ACB score ≥ 3 was consistently associated with a significantly increased risk of hospitalization. Specifically, the risk increased by 44% in Mantova, 48% in Bergamo, 52% in Lecco, and 64% in Monza Brianza. The pooled estimate showed a 52% overall increase in the odds of hospitalization for patients with at least 4 days with ACB score ≥ 3 compared to matched controls not exposed to such condition (OR 1.52, 95% CI: 1.43–1.61). The Qb test for heterogeneity across LHUs indicated no significant variability ($p=0.43$), supporting the consistency of the association across the four LHUs.

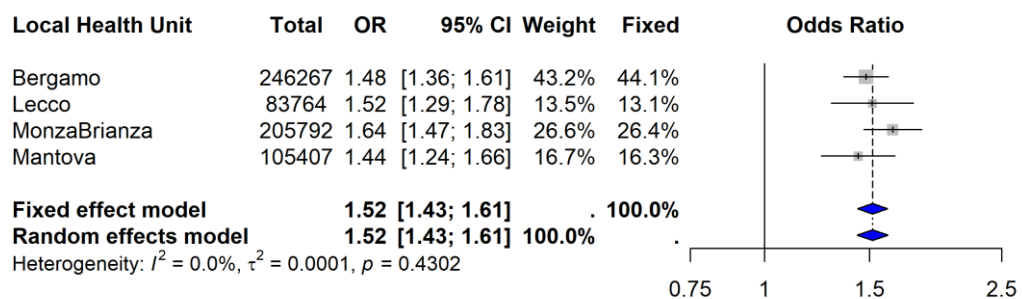
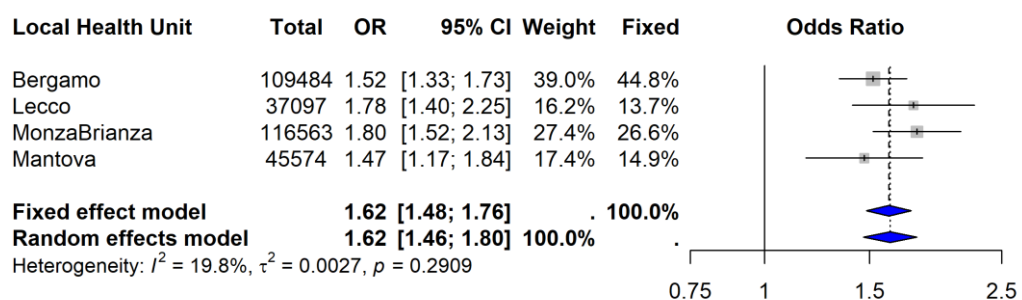


Figure 44 – Pooled results of association between ACB score ≥ 3 for more than 3 days and hospitalization across the LHUs.

As shown in **Figure 45**, both male and female individuals exposed to ACB score condition of selection had a significantly higher risk of hospitalization. The pooled odds ratio was 1.62 (95% CI: 1.46–1.80) in males and 1.45 (95% CI: 1.34–1.56) in females. Significant heterogeneity ($p=0.75$) across LHUs was observed for females, but not for males ($p=0.03$).

PANEL A



PANEL B

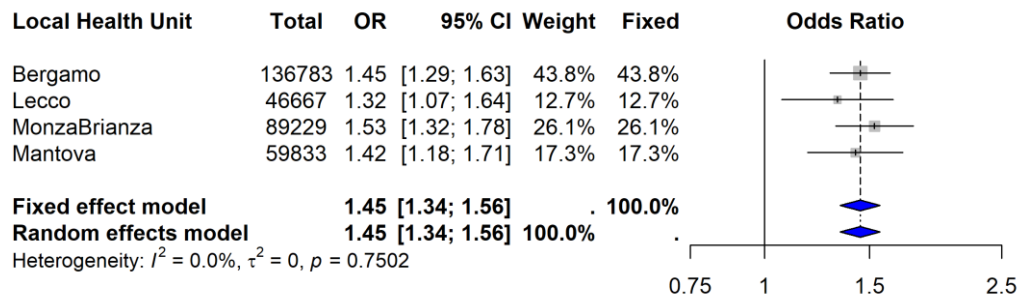


Figure 45 – Pooled results of association between ACB score ≥ 3 and hospitalization across the LHUs – stratification by sex (PANEL A: Male; PANEL B: Female).

No statistically significant heterogeneity was found between sexes ($p=0.08$), suggesting a broadly similar effect across genders, despite the point estimate was slightly higher in males (**Figure 46**).

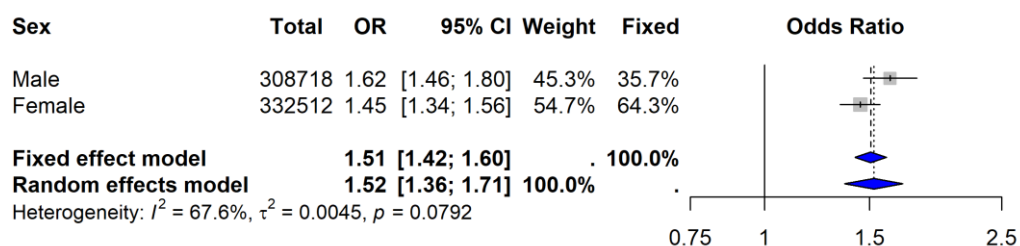
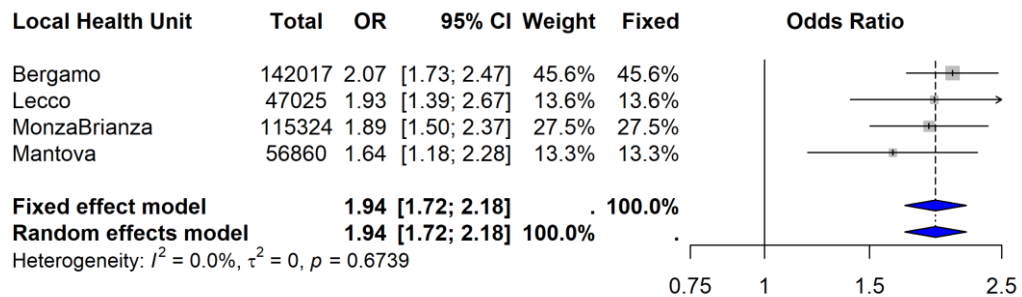


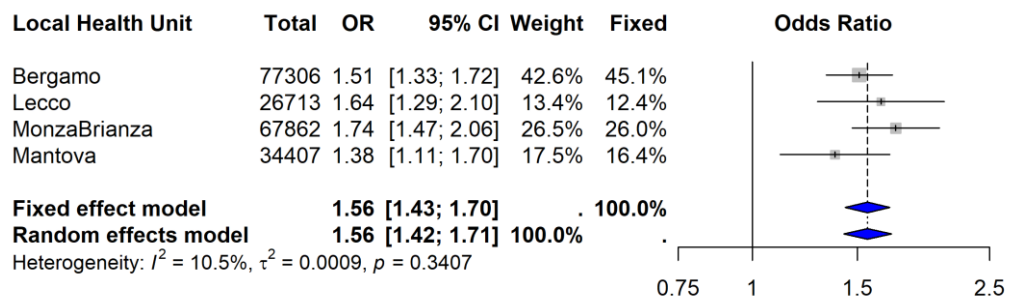
Figure 46 – Heterogeneity test between ACB score ≥ 3 and hospitalization by sex

Age-stratified analysis (**Figure 47**) revealed substantial differences in the strength of association between ACB score exposure and hospitalization risk. The pooled OR was 1.94 (95% CI: 1.72–2.18) for individuals aged 65–74 years, 1.56 (95% CI: 1.42–1.71) for those aged 75–84 years, and 1.25 (95% CI: 1.09–1.45) for individuals aged 85 years or older. No Significant heterogeneity across LHUs was observed for individuals aged 65-74, 75-84-year-old and 85 years or older ($p=0.67$, $p=0.34$ and $p=0.06$ respectively).

PANEL A



PANEL B



PANEL C

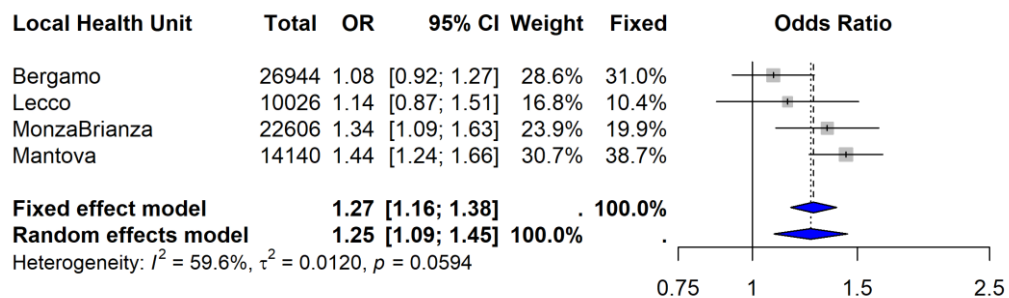


Figure 47- Pooled results of association between ACB score ≥ 3 and hospitalization across the LHUs – stratification by age groups (PANEL A: 65-74 years old; PANEL B: 75-84 years old; PANEL C: ≥ 85 years old)

Figure 48 shows the pooled odds ratios across the four LHUs by age group. The forest plot in **Figure 48** clearly highlights a difference in the risk of hospitalization associated with ACB drugs across age groups ($p < 0.0001$). Overall, the findings suggest that the risk of hospitalization related to ACB drugs is more pronounced in the younger-old population and tends to decrease in the oldest age group.

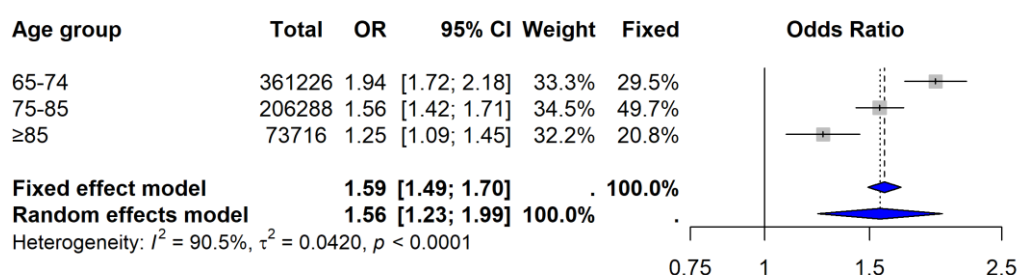


Figure 48 – Heterogeneity test between ACB score ≥ 3 and hospitalization by age groups

4.2.7 SL score

Annual prevalence of SL score ≥ 3 is reported in **Table 22**. Overall, 37.7% patients from 2015 to 2018 had an occurrence of SL score ≥ 3 . The annual prevalence of patients with at least one SL score ≥ 3 occurrence ranged from 37.4% to 38.4% over the study period.

Table 22 – Annual prevalence of SL score ≥ 3 .

	2015	2016	2017	2018	p-value
Over65 population with at least one prescription, N	496,965	513,917	546,656	552,993	
Individuals with at least one SL score ≥ 3 , N (%)	189,799 (38.2%)	197,558 (38.4%)	204,818 (37.5%)	201,764 (36.5%)	<0.001
Individuals with one SL score ≥ 3 , N (%)	70,901 (37.4%)	73,566 (37.2%)	77,303 (37.7%)	77,440 (38.4%)	<0.001
Individuals with two SL score ≥ 3 , N (%)	34,691 (18.3%)	35,566 (18.0%)	38,020 (18.6%)	37,680 (18.7%)	<0.001
Individuals with three SL score ≥ 3 , N (%)	22,467 (11.8%)	23,016 (11.7%)	24,136 (11.8%)	23,721 (11.8%)	<0.001
Individuals with four or more SL score ≥ 3 , N (%)	61,740 (32.5%)	65,410 (33.1%)	65,359 (31.9%)	62,923 (31.2%)	<0.001

Table 23 summarizes the five most frequent SL score ≥ 3 conditions among individuals with at least one PII exposure in the year. The combination A02BC02-C09AA05-C10AA05 (ramipril-atorvastatin) appeared consistently in the top position

across all years, with a stable prevalence of 0.3%. Other frequent combinations included A02BC02-C03CA01-C09AA05 (pantoprazole-furosemide-ramipril) and A02BC02-C07AB07-C10AA05 (pantoprazole-bisoprolol-atrovastatin), both showing relatively stable frequencies between 0.2% and 0.3% over time. Overall, the most common prescribing combinations showed limited variation over time and occurred with low prevalence, ranging between 0.2% and 0.3%.

Table 23 – Five most frequent SL score ≥ 3 by patients

	2015	2016	2017	2018
1.	A02BC02- C09AA05- C10AA05 (0.3%)	A02BC02- C09AA05- C10AA05 (0.3%)	A02BC02- C09AA05- C10AA05 (0.3%)	A02BC02- C09AA05- C10AA05 (0.3%)
2.	A02BC02- C03CA01- C09AA05 (0.2%)	A02BC02- C03CA01- C09AA05 (0.3%)	A02BC02- C03CA01- C09AA05 (0.2%)	A02BC02- C03CA01- C07AB07 (0.3%)
3.	A02BC02- C07AB07- C10AA05 (0.2%)	A02BC02- C07AB07- C10AA05 (0.2%)	A02BC02- C03CA01- C07AB07 (0.2%)	A02BC02- C07AB07- C10AA05 (0.3%)
4.	A02BC02- C03CA01- C07AB07 (0.2%)	A02BC02- C03CA01- C07AB07 (0.2%)	A02BC02- C07AB07- C10AA05 (0.2%)	A02BC02- C03CA01- C10AA05 (0.2%)
5.	C03CA01- C09AA05- C10AA05 (0.2%)	C03CA01- C09AA05- C10AA05 (0.2%)	A02BC02- C03CA01- C10AA05 (0.2%)	A02BC02- C03CA01- C09AA05 (0.2%)

*A02BC02 Pantoprazole, C09AA05 Ramipril, C10AA05 Atrovastatin, C03CA01 Furosemide, C07AB07 Bisoprolol.

Baseline characteristics of this cohort are presented in **Table 24**. The final matched cohort, comprising 143,113 pairs, forms the basis for the risk analysis. Females consistently represented a slight majority of the population, ranging from 55.7% to 57.0%, while the average age ranged from 76.1 to 76.9 years across LHUs. In all settings, the most represented age group was 65–74 years, followed by 75–84 and ≥ 85 years.

A marked difference in hospitalization rates was observed between the matched groups. Individuals exposed to at least one potentially inappropriate prescription consistently showed a higher incidence of all-cause hospitalization across LHUs. For example, hospitalization occurred in 11.7% of drugs with potential sedative effect users vs. 5.7% of controls in Mantova, and in 8.2% vs. 5.3% in Monza Brianza. These differences were statistically significant in all LHUs ($p < 0.0001$), suggesting a

consistent association between SL score ≥ 3 exposure and increased hospitalization risk, even after matching.

Table 24 – Characteristics of the SL score ≥ 3 matched cohorts at the enrolment. LHUs of Bergamo (BG), Lecco (LC), Monza Brianza (MB) and Mantova (MN) LHUs.

Covariates	Presence of at least one occurrence of SL score ≥ 3		p-value
	No	Yes	
BG	N= 103,210		
N [matched]	51,605	51,605	
Female sex, N (%)	28,918 (56.0)	28,918 (56.0)	-
Age, mean (SD)	76.1 (7.7)	76.1 (7.7)	-
Age class, N (%)			
65-74 yy	24,477 (47.4)	24,477 (47.4)	-
75-84 yy	18,744 (36.3)	18,744 (36.3)	
≥ 85 yy	8,384 (16.2)	8,384 (16.2)	
Hospitalization, N (%)	2,965 (5.7)	4,982 (9.7)	<0.0001
LC	N= 41,780		
N [matched]	20,890	20,890	
Female sex, N (%)	11,570 (55.4)	11,570 (55.4)	-
Age, mean (SD)	76.8 (8.1)	76.8 (8.1)	-
Age class, N (%)			
65-74 yy	9,264 (44.3)	9,264 (44.3)	-
75-84 yy	7,618 (36.5)	7,618 (36.5)	
≥ 85 yy	4,008 (19.2)	4,008 (19.2)	
Hospitalization, N (%)	1,128 (5.4)	1,890 (9.0)	<0.0001
MB	N= 96,898		
N [matched]	48,449	48,449	
Female sex, N (%)	27,160 (56.1)	27,160 (56.1)	-
Age, mean (SD)	76.9 (7.9)	76.9 (7.9)	-
Age class, N (%)			
65-74 yy	20,817 (43.0)	20,817 (43.0)	-
75-84 yy	18,610 (38.4)	18,610 (38.4)	
≥ 85 yy	9,022 (18.6)	9,022 (18.6)	
Hospitalization, N (%)	2,576 (5.3)	3,965 (8.2)	<0.0001
MN	N=44,338		
N [matched]	22,169	22,169	
Female sex, N (%)	12,637 (57.0)	12,637 (57.0)	-
Age, mean (SD)	76.4 (8.1)	76.4 (8.1)	-
Age class, N (%)			
65-74 yy	10,499 (47.4)	10,499 (47.4)	-
75-84 yy	7,639 (34.5)	7,639 (34.5)	

	≥85 yy	4,031 (18.2)	4,031 (18.2)	
Hospitalization, N (%)		568 (5.7)	1,166 (11.7)	<0.0001

* SD=Standard Deviation, yy=years.

The estimate association between exposure and all-cause hospitalization is summarized in **Figure 49**. Across all LHUs, exposure to SL score ≥ 3 for more than 3 days was consistently associated with a significantly increased risk of hospitalization. Specifically, the risk increased by 26% in Mantova, 41% in Monza Brianza, 51% in Lecco, and 54% in Bergamo. The pooled estimate showed a 43% overall increase in the odds of hospitalization (OR 1.43, 95% CI: 1.31–1.56). The Qb test for heterogeneity across LHUs indicated significant variability ($p = 0.0007$), indicating that the strength of the association varied across the four regions, rather than being consistent.

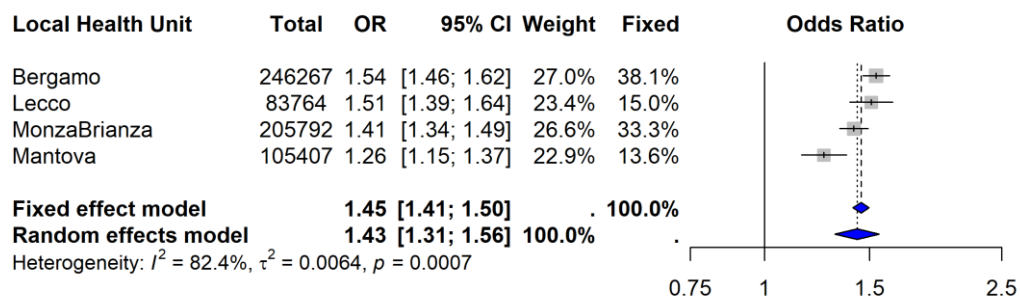
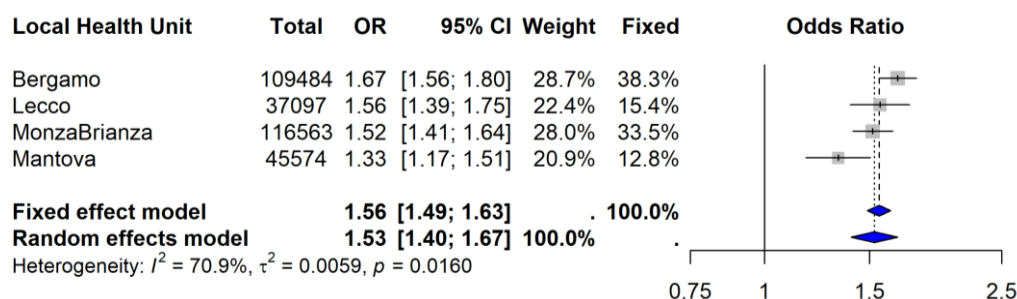


Figure 49 – Pooled results of association between SL score ≥ 3 for more than 3 days and hospitalization across the LHUs.

To explore potential effect modification, stratified analyses were conducted by sex and age group. As shown in **Figure 50**, both male and female individuals exposed to SL score had a significantly higher risk of hospitalization. The pooled odds ratio was 1.53 (95% CI: 1.40–1.67) in males and 1.34 (95% CI: 1.24–1.45) in females. Significant heterogeneity ($p=0.02$) across LHUs was observed for males, but not for females ($p=0.06$).

PANEL A



PANEL B

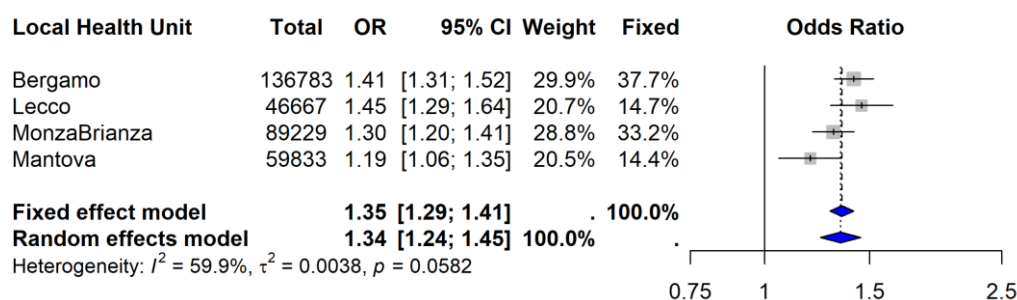


Figure 50 – Pooled results of association between SL score ≥ 3 and hospitalization across the LHUs – stratification by sex (PANEL A: Male; PANEL B: Female).

No statistically significant heterogeneity was found between sexes ($p = 0.0309$), suggesting no different effect across genders, despite the point estimate was slightly higher in males (**Figure 51**).

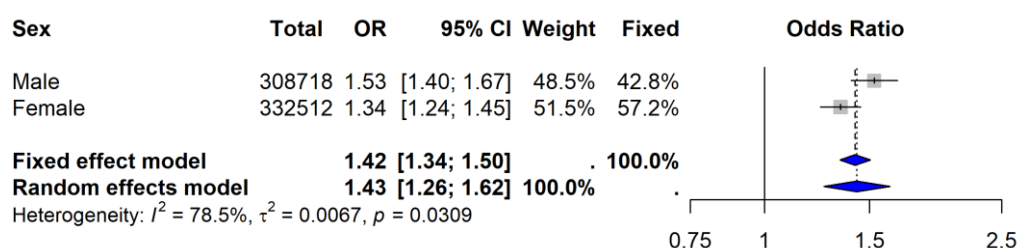
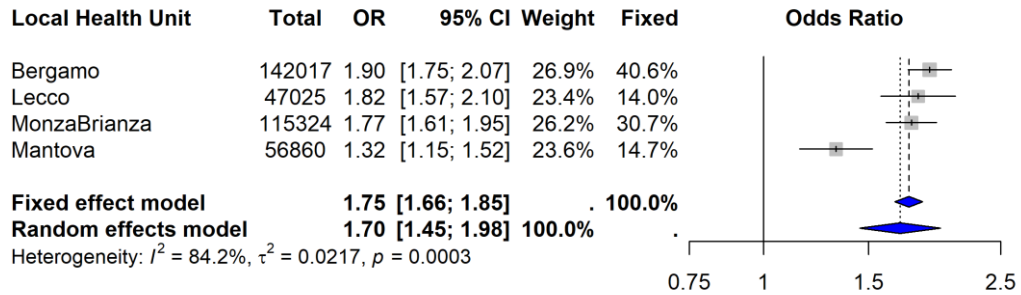


Figure 51 – Heterogeneity test between SL score ≥ 3 and hospitalization by sex

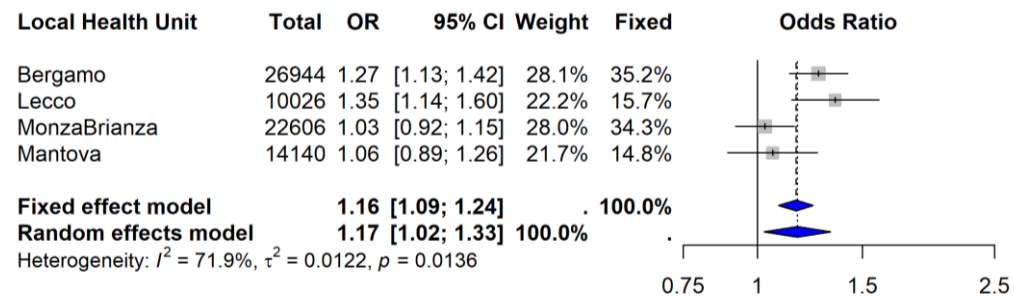
Age-stratified analysis (**Figure 52**) revealed substantial differences in the strength of association between SL score ≥ 3 exposure and hospitalization risk across LHUs. The pooled OR was 1.70 (95% CI: 1.45–1.98) for individuals aged 65–74 years, 1.17 (95% CI: 1.02–1.33) for those aged 75–84 years, and 1.40 (95% CI: 1.33–1.47) for individuals aged 85 years or older. No Significant heterogeneity across LHUs was

observed for individuals aged 85 years or older ($p=0.92$), but significant heterogeneity across LHUs was found in individuals aged 65-74 and 75-84-year-old ($p=0.0003$ and $p=0.01$ respectively).

PANEL A



PANEL B



PANEL C

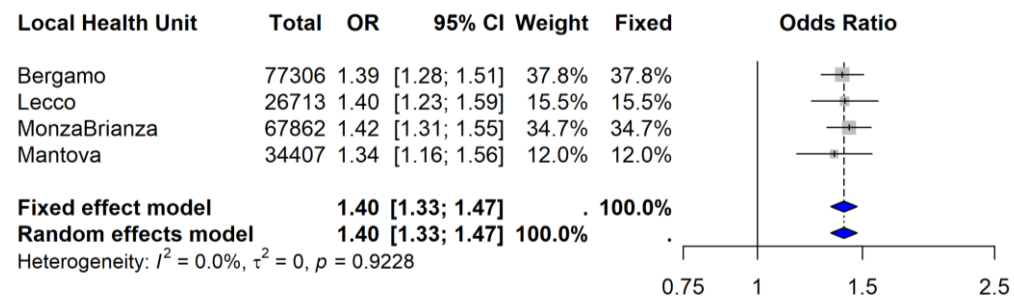


Figure 52- Pooled results of association between SL score ≥ 3 and hospitalization across the LHUs – stratification by age groups (PANEL A: 65-74 years old; PANEL B: 75-84 years old; PANEL C: ≥ 85 years old)

Figure 53 shows the pooled odds ratios across the four LHUs by age group. The forest plot in **Figure 53** clearly highlights a difference in the risk of hospitalization associated with PIMs across age groups ($p=0.0013$). Overall, the findings suggest that the risk of

hospitalization related to $SL \geq$ score is more pronounced in the younger-old population and tends to decrease in the oldest age group.

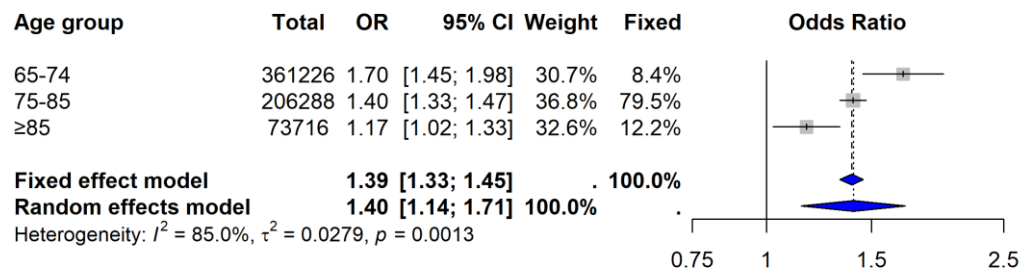


Figure 53 – Heterogeneity test between SL score ≥ 3 and hospitalization by age groups

CHAPTER 5

Development of the prioritization algorithm

The methodological framework developed to identify subgroups of older adults at increased risk of hospitalization was based on Machine Learning techniques (ML). Specifically, a data-driven approach based on Conditional Inference Trees (CITs) was applied to stratify the exposed population according to the risk profiles.

5.1 Artificial Intelligence, Machine Learning and decision trees

The concept of Artificial Intelligence (AI) traces back when humans imagined the possibility of creating artificial beings capable of thought and action, reflecting early human fascination with artificial agents ¹¹⁰. However, even though the concept of AI came from ancient time ¹¹¹ the formal study of AI as a scientific discipline began only in the mid-20th century. The term “artificial intelligence” was coined in 1956 during the Dartmouth Summer Research Project on Artificial Intelligence, where pioneers like John McCarthy, Marvin Minsky, Allen Newell, and Herbert Simon gathered to define the field ¹¹².

5.1.1 Artificial intelligence

Early AI research focused on symbolic reasoning and rule-based systems, aiming to replicate human logical thought processes through explicit programming.

Over the decades, AI has evolved through several phases:

- Symbolic AI (Good Old-Fashioned AI- GOFAI): In the 1950s-70s, AI was largely rule-based, relying on hand-coded knowledge and logic inference systems ¹¹³;
- Expert Systems (1980s): Systems that encoded domain-specific knowledge to make decisions, widely used in medical diagnosis and other applied fields ¹¹⁴;
- Machine Learning (from the 1990s): A paradigm shift occurred with the development of statistical learning algorithms, enabling computers to learn from data rather than explicit rules ¹¹⁵;

- Deep Learning (2010s onwards): Inspired by the structure of the human brain, deep neural networks allowed for unprecedented performance in complex tasks such as image and speech recognition ¹¹⁶.

At its core, AI relies on mathematical concepts such as probability theory, statistics, optimization, and linear algebra.

AI applications span a wide range of domains, including healthcare, finance, scientific research, computer vision, and natural language processing. These diverse applications often leverage different branches of AI (**Figure 54**) depending on the complexity of the task, the nature of the data and the goal:

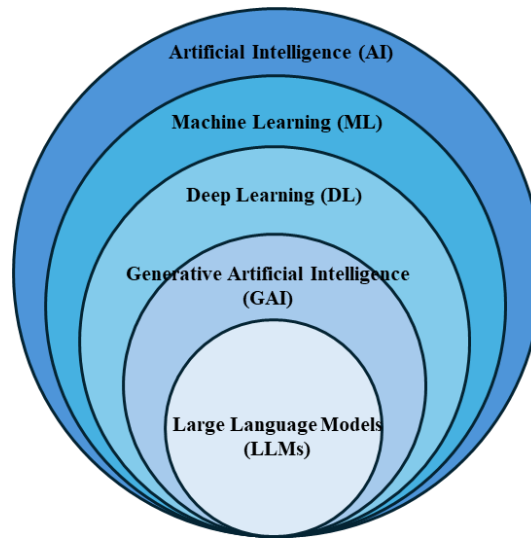


Figure 54 – *The subsets of AI*

Artificial Intelligence can be understood as a set of nested circles, each representing conceptual relationships between its key areas:

- The outermost circle represents AI: all technologies enabling machines to mimic human intelligence, emulate human behaviours, enabling them to learn, make decisions, solve problems and recognize patterns;
- Inside this lies ML, which uses data-driven algorithms to improve performance on tasks. ML uses advance algorithms to detect patterns in large datasets, allowing machines to learn and adapt;
- Nested within ML is Deep Learning, which employs layered neural networks to model complex data processing and analytics;

- A recent and impactful development is Generative AI (GAI), a category of DL models that generate new content (e.g., text, images, audio) based on provided input;
- Within GAI, Large Language Models (LLMs) specialize in understanding and generating human language.

While this visual metaphor is helpful, it is important to clarify that these domains are not strict subsets of one another in a mathematical sense. Rather, they represent overlapping methodologies and paradigms that differ in approach, complexity, and level of specific techniques.

5.1.2 Machine Learning

ML encompasses a variety of approaches that enable algorithms to learn patterns from data and make predictions or decisions without being explicitly programmed. ML methods can be broadly categorized into four main *learning paradigms* (Figure 55) based on how a model learn from data ¹¹⁷.

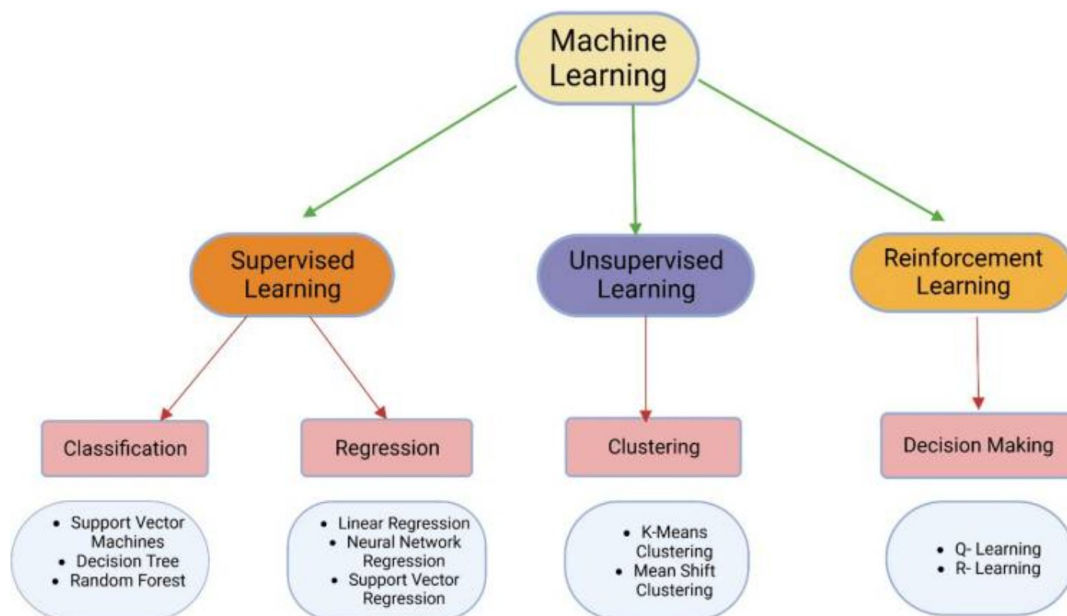


Figure 55 – The four types of ML

Supervised learning type relies on labelled data- where each input is paired with a known output- to predict outcomes, making it ideal for tasks where past results are

known., while *unsupervised learning* explores unlabelled data to find hidden patterns or groupings without predefined outcomes. Lastly, the *reinforcement learning* involves learning optimal actions through trial and error by interacting with an environment.

These paradigms can also be understood in terms of their goals classifying models into three main types:

- Descriptive models aim to summarize and understand historical patterns;
- Predictive models are designed to forecast future outcomes;
- Prescriptive models go further by recommending actions to optimize specific objectives.

Decision tree methods are within ML techniques spectrum. These models recursively partition data based on feature values to create a tree-like structure that facilitates both classification and regression tasks. This technique is presented in the following paragraph.

5.1.3 Decision tree: Conditional Inference Trees

Decision trees are a class of supervised learning algorithms applicable to both classification and regression tasks. **Figure 56** represents a basic tree-like structure.

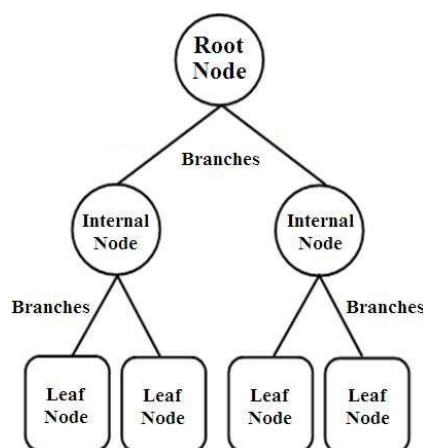


Figure 56 – Basic tree-like structure and components of decision tree ¹¹⁸

In the structure, the *nodes* represent the possible attributes associated with an event. The first *node* is called root and represents the attribute with largest information gain; *branches* represent the attributes values where data split into subsets (decision rule is applied to divide the dataset based on a single variable); and *leaves* represent the outcome prediction. When building a decision tree, it is possible to create a set of rules written considering the trajectory of the *root node* to the *leaf nodes*.

Traditional decision tree algorithms, such as CART (Classification and Regression Trees) ¹¹⁹, have long been used for supervised learning due to their intuitive structure and their ability to model non-linear associations. However, these classical methods present several well-known limitations. In particular, they tend to suffer from selection bias, favouring predictor variables with many possible split points (e.g. continuous variables or categorical variables with many levels), and the splits are based solely on impurity measures (such as Gini index- a measure of node impurity used in decision trees, quantifying how often a randomly chosen element would be incorrectly classified if it were randomly labelled according to the node's class distribution) without any formal statistical inference, which can result in overfitting and questionable interpretability, especially in high-dimensional or noisy datasets. CITs, introduced as a statistically alternative, overcome these issues. Hothorn et al. (2006) ¹²⁰ proposed this method, which uses permutation-based significance testing at each node to select predictors- a global null hypothesis of independence is tested, and only predictors significantly associated with the outcome are considered for splitting. The algorithm then selects the variable with the smallest p-value, and chooses an optimal split point, proceeding recursively. This approach removes selection bias and provides a formal statistical basis for each decision in the tree construction process. Compared with traditional trees, CITs also incorporate an automatic stopping criterion: the splitting process halts when no predictor strongly associated with the outcome remains (i.e. no p-value passes the predefined threshold), reducing the risk of overfitting and yielding more parsimonious, generalizable models.

This approach was particularly suited to our objective, as we aimed to identify, among patients exposed to a PII, those at highest risk based on their clinical history. The need to combine multiple variables- such as age, comorbidities, and healthcare utilization-

required a methodology capable of capturing complex interactions to effectively prioritize patients for targeted intervention.

5.2 Development of CITs

To implement this modelling framework, we constructed dedicated training datasets that included only individuals exposed to each PII during the study period (from 2015 to 2018). These datasets served as the empirical foundation for CITs development, enabling the algorithm to learn from real-world patterns of hospitalization following exposure.

5.2.1 Creation of the training dataset

For each PII, tree-based machine learning models were trained on the entire dataset in order to maximize sample size, a crucial factor for the robustness of this analytical approach. This choice was supported by the findings from the previous step, which did not reveal any significant heterogeneity among the participating LHUs, thereby justifying the use of a pooled dataset for model development. All-cause hospitalization within 90 days after the first PII prescription, as binary outcome variable, served as classification target in the learning model.

The training datasets used for CITs construction included also a comprehensive set of covariates derived from administrative health records. These covariates were selected to reflect demographic, pharmacological and clinical aspects relevant to hospitalization risk. Specifically, we included age groups (65–74, 75–84, and ≥ 85 years old) to reflect meaningful shifts in geriatric risk and healthcare needs, and sex, as binary variable (male-female), due to known sex-based differences in both prescribing patterns and health outcomes. In addition, we incorporated hospitalization diagnostic codes (ICD-9) and prescriptions information (i.e. ATC codes), each transformed into binary variables (present/absent) based on whether the patient had a record of the condition or dispensation. ICD-9 codes were assessed over the 12 months preceding the index date to capture acute and chronic conditions. The information on

pharmaceutical exposure was collected both in the 12 months preceding the index date and throughout the follow-up period (up to 3 months, or shorter if hospitalization occurred), in order to monitor exposures during the follow-up period. To minimize redundancy and reduce multicollinearity- particularly the risk of overrepresenting multiple drugs from the same therapeutic class as separate predictors- the pharmaceutical exposures were aggregated using 4th level ATC codes. This approach allows for a more stable and interpretable model by grouping medications with similar pharmacological properties. **Figure 57** provides a schematic representation of how the available information was used to describe the characterization of the included patients.

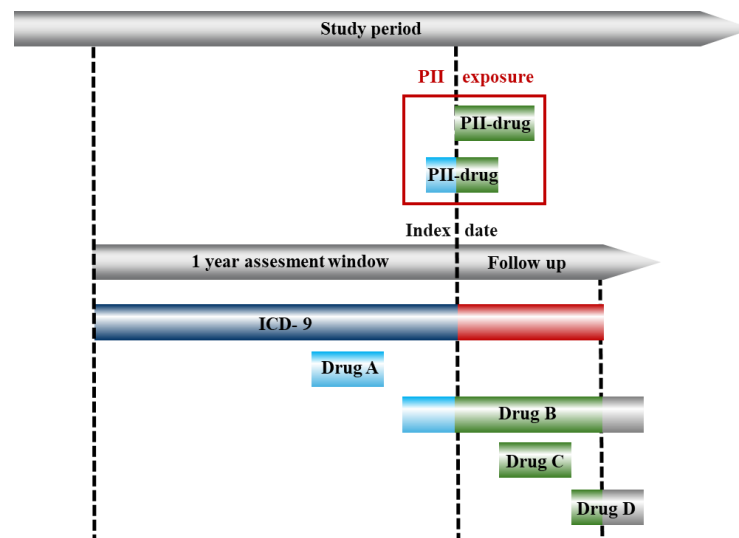


Figure 57 – ICD-9 and ATC codes incorporation in the training dataset. ICD-9 codes characterize patients only prior the index date (blue). In light blue, prescriptions characterizing the patient prior the index date; in green, prescriptions characterizing the patient during the followup period. NB drug A, B, C, and D are drugs that do not satisfy the PII- exposure condition or are not drugs PII lists.

For example, following a PII exposure, an index date is established (either at the first dispensation or after a specific time requirement has been met). This date marks two critical timeframes for the creation of the dataset: a one-year covariate assessment window prior to the index date, and a three-month follow-up period after it. During the 12-month assessment window, both ICD-9 codes (dark blue) and drug prescription coverages (ATC 4th level, in light blue) were incorporated as baseline covariates to characterize the patient's clinical history. Similarly, all drug prescription coverages

(ATC 4th level) occurring within the follow-up period (green) were also incorporated into the model.

5.2.2 CITs development

A CIT produced a visually interpretable model consisting of binary splits (branches) leading to terminal nodes (leaves), each representing a subgroup of exposed individuals characterized by specific attributes (**Figure 58**).

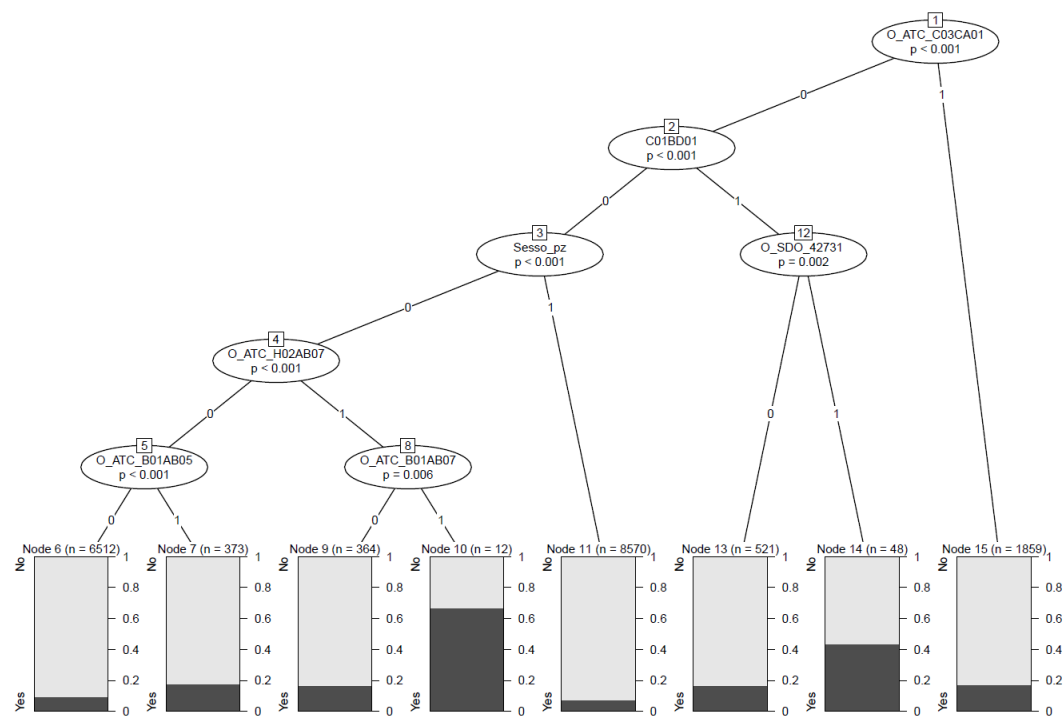


Figure 58. Example of CIT

At each internal node, the algorithm selected the most significant predictor variable (based on permutation p-values) and applied a binary split (0/1, No/Yes) that maximized the difference in hospitalization (outcome) probability between resulting branches. The outcome is displayed at the terminal leaves accompanied by the number of cases.

For example, based on the **Figure 59**, let's consider a hypothetical patient exposed to a PII, and follow their path through the tree to illustrate how the algorithm classifies risk based on clinical and pharmacological characteristics.

The first node in the tree considers the variable C03CA01 (bendroflumethiazide, a thiazide diuretic). The patient is split based on whether he was exposed to this medication (1 = yes, 0 = no). In this case, this hypothetical patient was not exposed (0), so we follow the branch labelled 0, which leads us to node 2. At node 2, the tree checks for exposure to C01BD01 (isosorbide dinitrate with hydralazine, a drug combination used for heart failure). Again, this patient is not exposed, so we follow the 0 branch to node 3. Node 3 splits based on sex (0 = male, 1 = female). Let us assume the patient is male, so we move to node 4. At node 4, the tree evaluates whether the patient was treated with H02AB07 (prednisolone, a corticosteroid). This time, the patient was exposed, so we follow the 1 branch to node 8. At node 8, there is another split based on exposure to B04AB07 (bosentan, an endothelin receptor antagonist used in pulmonary hypertension). The patient was exposed, so we follow the 1 branch again. At this point, the patient falls into a terminal node that includes individuals who are male and treated with both prednisolone (H02AB07) and bosentan (B04AB07).

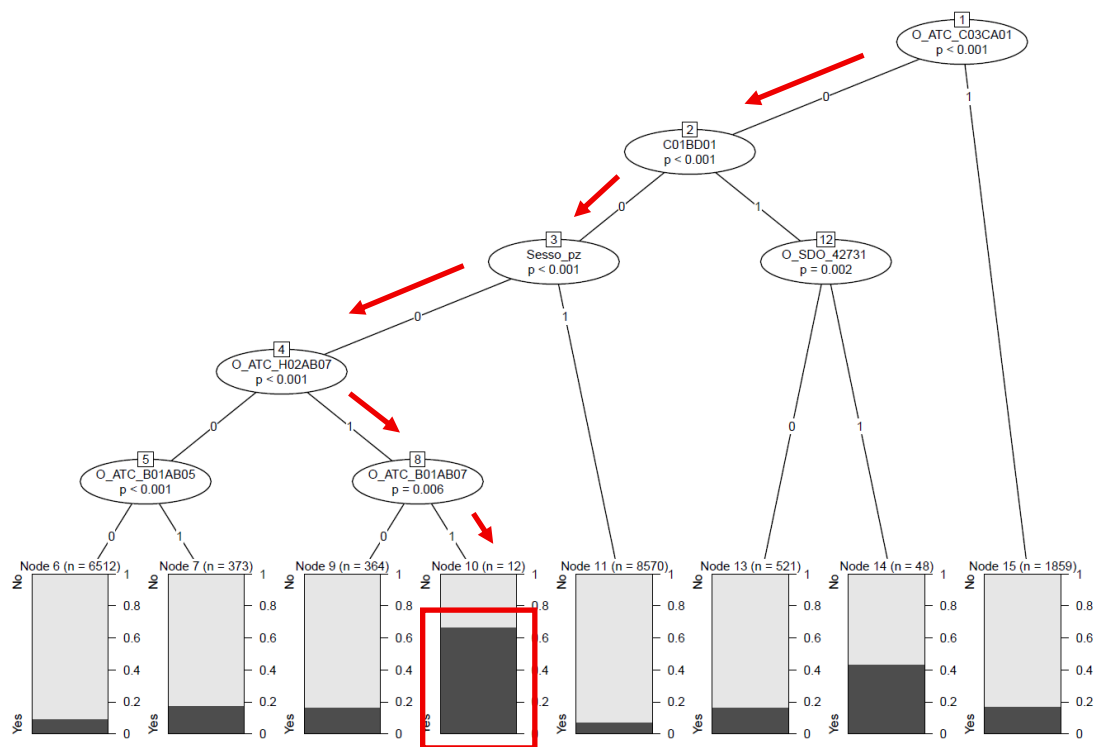


Figure 59. Example of patient-specific risk pathway in the CIT

As shown in **Figure 59**, the bar plot at this node reveals that more than 60% of the 12 individuals (red rectangle) presenting the scenario (red arrows) has been hospitalized

(black bar). This indicates that this specific combination of characteristics places the patient in a higher-risk group compared to other scenarios.

For the analysis presented in this thesis, a decision tree similar to the one shown in the previous figure was generated for each PII, with the aim of identifying subgroups of the population at higher risk. The specific code used for this analysis is provided in **Appendix 7**.

5.2.3 CITs reduction

Often, with complex models, CITs grow excessively. This complexity, while reflective of the data richness and high dimensionality, limited interpretability and increased the risk of overfitting. To mitigate these issues and to identify more stable, clinically meaningful decision patterns, very often a reduction strategy based on iterative subsampling is performed, in order to select those variables that appeared most frequently across iterations. To do this, we built CITs using small random samples of PII-selected patients, each with different percentages of hospitalized and non-hospitalized people. For each sample, we randomly picked 20% of the hospitalized patients and 20% of the non-hospitalized patients to make a tree. We repeated this process 10 times, each time choosing different patients. We did the same for samples with 30%, 40%, and 50% of patients, always repeating 10 times for each percentage. In the end, we checked which variables appeared most often in these trees. Only the variables that showed up at least 5 out of 10 times in at least 3 of the 5 percentage groups were kept for the final tree. This procedure leads to a reduction in the size of our tree by selecting variables (nodes) that are much more likely to be involved in determining the outcome, as shown in example **Figure 60**. For example, from the original CIT, only the nodes highlighted in yellow appeared more frequently. These nodes are therefore considered generally stable, and more reliable predictors. The branches are then redrawn accordingly (red lines). The resulting CIT consists of these selected nodes and the newly drawn branches.

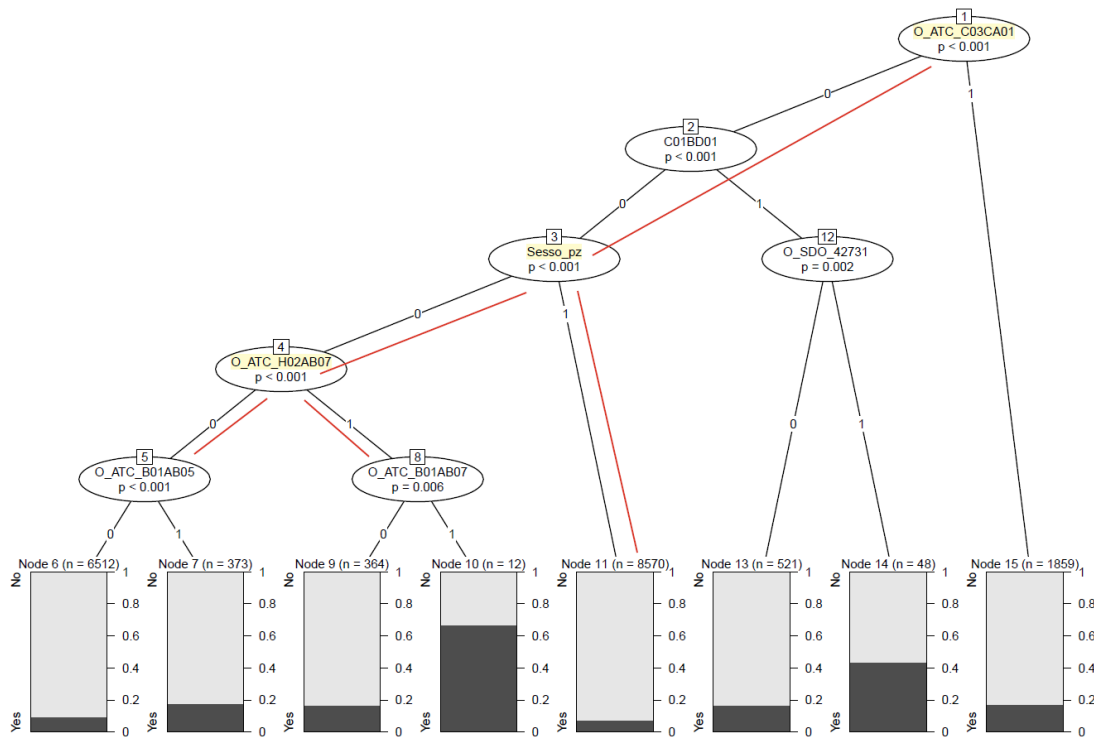


Figure 60. Example of CIT reduction

5.2.4 Subgroup risk profiling

We developed a quantitative assessment of each terminal branch emerging from the simplified trees. This analysis was conducted on the risk-matched datasets defined in the second phase of the project. Specifically, for each identified scenario, we fitted adjusted logistic regression models to estimate the OR for hospitalization related to PII, comparing the incidence of all-cause hospitalization with that one of respective controls selected through the matching process. These models accounted for potential confounding by including relevant covariates such as age, sex, and HDPS.

The OR of all-cause hospitalization for each scenario was then compared to the pooled overall risk associated with exposure to the specific PII (described in Section 4.1.5) in order to determine whether the scenario represents a higher-risk condition or not. Subgroups were retained only if their lower bound of the 95% CI for the OR was greater than or equal to the lower 95% CI of the OR for the corresponding PII. This filtering criterion was applied to exclude marginal or weak-risk profiles and to focus the interpretation on those patient subgroups that show a risk of hospitalization

comparable to- or greater than- the minimum effect observed from PII exposure alone. The retained subgroups thus represent refined, high-risk clusters.

For example, the overall OR for PIMs was 1.55 (95% CI: 1.48–1.62). The scenario where a patient is exposed to both B01AB (heparin group) and J01MA (fluoroquinolones) has an estimated OR of 2.01 (95% CI: 1.81–2.23). Since the lower bound of the scenario's 95% CI (1.81) is greater than the lower bound of the overall CI (1.48), this scenario was included as a high-risk profile. Conversely, for a male patient exposed to B01AB after the index date (but not prior) and not exposed to C03DA (aldosterone antagonists) and J01MA, the estimated OR was 1.50 (95% CI: 1.30–1.73). In this case, comparing the lower bounds of the 95% CI (1.30 vs. 1.48), the scenario was not considered to be at higher risk and was therefore excluded.

5.4 Results

Table 25 shows the size of the assessed dataset, one for each PII, once all the LHUs have been merged, including the number of the matched PII-exposed patients included in the model and the total number of variables considered (ICD-9 and ATC codes, age group, gender). The number of patients corresponds to the individuals identified by each specific indicator within the matched cohort. The number of variables reflects the different drugs or drug classes included in each indicator's list.

Table 25 – *Datasets' size presenting the matched PII-exposed patients*

	PIMs	pDDIs	FRIDs	TDs	ACB score	SL score
Patients, N	128,063	99,594	119,743	94,948	60,699	143,113
Variables, N	4,024	4,691	4,048	3,970	9,720	16,497
Nodes, N	29	36	30	39	24	33
Branches, N	42	56	46	61	34	62
Reduced nodes, N	10	9	11	9	6	15
Reduced branches, N	18	23	26	25	8	41
At risk branches, N	7	10	11	14	4	15
Branches reduction, %	83.3%	80.4%	76.1%	77.0%	88.2%	82.2%

The complexity of the resulting full-sample CITs- reflected by the number of nodes and branches- highlights the diversity of individual characteristics associated with each PII. For instance, the tree for TDs exhibited the highest number of nodes (n=39) and branches (n=61), in contrast, the ACB the lowest number of nodes (n=24) and branches (n=34).

Following the iterative reduction strategy at 20, 30, 40 and 50% sampling, the number of nodes and branches decreased substantially across all PIIs

For each those branches (row “Reduced branches” in the table), adjusted logistic regression models were fitted to estimate the OR for hospitalization. Only those subgroups meeting the risk profiling threshold were retained- that is, subgroups for which the lower bound of the 95% CI for the OR was equal to or greater than the lower 95% CI of the overall OR for the corresponding PII were consider at higher risk. The number of these retained high-risk branches/subgroups is reported in the final row, “At risk branches”. After applying the sampling-iterated process and evaluating them using OR thresholding, the number of original branches was reduced substantially by 88.2% for ACB score, 83.3% for PMIs, 82.2% for SL score, 80.4% for pDDIs, 77.0% for TDs and 76.1% for FRIDs.

5.4.1 PIMs

Based on the training dataset, **Figure 61** illustrates the full-sample CIT developed for PIMs, which includes 29 nodes (variables) that reached statistical significance ($p < 0.05$) and 42 branches (scenarios).

This comprehensive model highlights the full range of splitting variables considered by the algorithm and serves as the initial foundation for subsequent refinement.

After applying the iterative sampling strategy across different subsamples of the training dataset, we obtained a simplified version of the original CIT characterized by a reduced and more interpretable tree structure. **Figure 62** presents the resulting sample CIT developed for PIMs, where the most consistently selected nodes and branches (i.e., variables and scenarios) are highlighted in red.

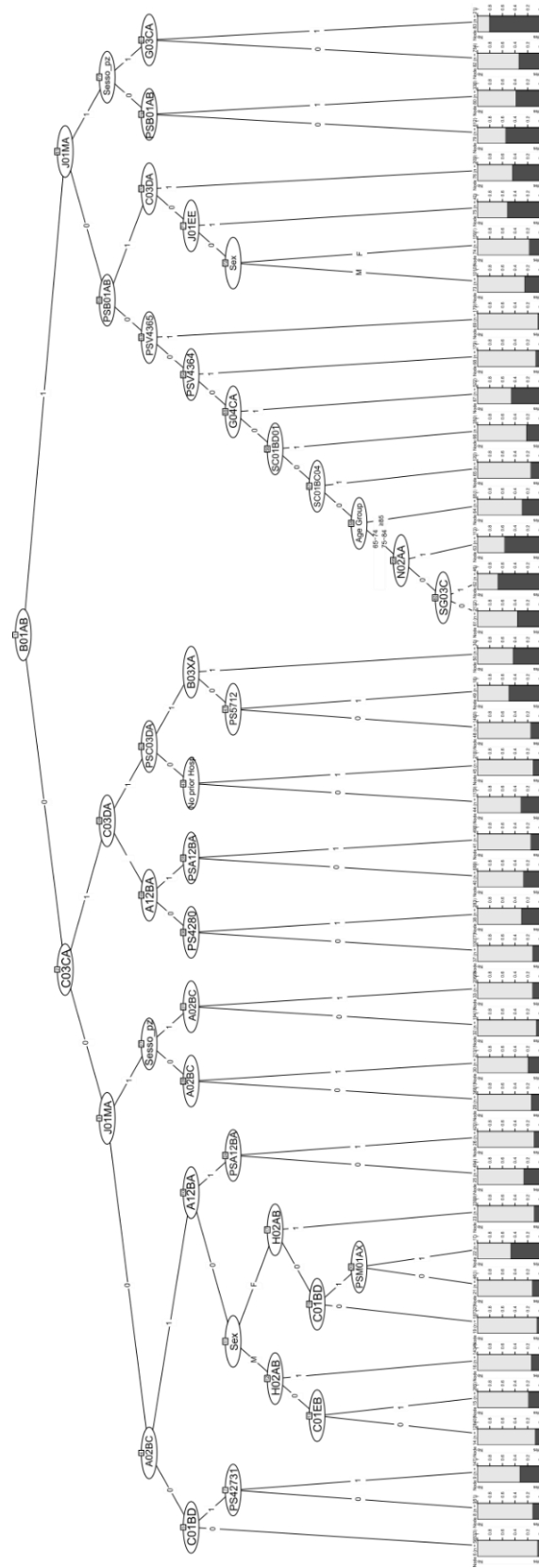


Figure 61 – full-sample CIT for PIMs

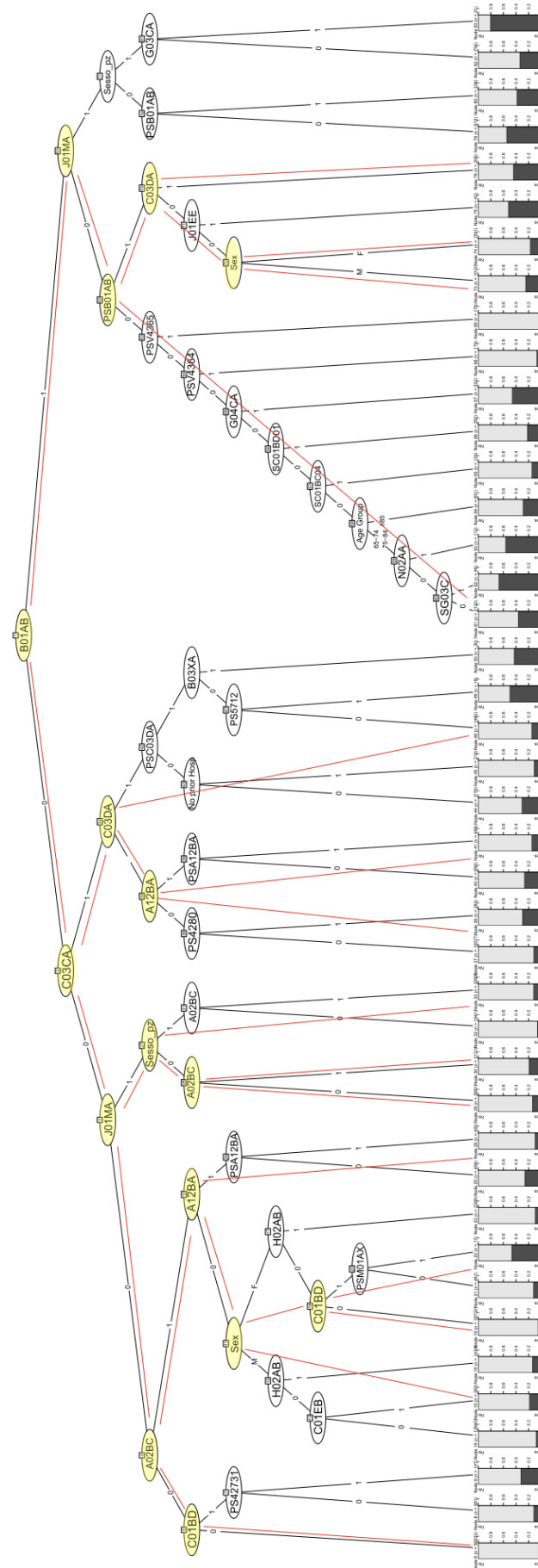


Figure 62 — sampled CIT for PIMs

Among the initial 29 nodes, 10 were retained after iteration: B01AB (heparin group, antithrombotic agents), J01MA (fluoroquinolones, antibacterials), Sex, PSB01AB (heparin group, antithrombotic agents – prior to the selection date), C03DA (aldosterone antagonists, diuretics), A12BA (potassium, a mineral supplement), A02BC (proton pump inhibitors, drugs for peptic ulcer and gastro-oesophageal reflux), C01BD (amiodarone, an antiarrhythmics), 42731 (hospitalization for atrial fibrillation prior to the selection date), and C03CA (sulphonamides, diuretics).

These nodes of the simplified model represent the most stable and reproducible splits in the PIM-related CIT highlighting the key combinations of variables that more robustly define at-risk subgroups. All the branches to the terminal nodes classified under these refined decision paths are reported in **Appendix 8**.

At this stage, we needed to verify whether the selected scenarios truly identified patients at a significantly higher risk of hospitalization compared to those identified by the general PIMs criterion alone, without additional stratification. To do so, we re-applied the same logistic regression models used earlier, this time restricting the analysis to the subset of patients who fell within the specific high-risk pathways previously identified by the decision tree. In this way, we re-estimated the hospitalization risk associated with PIM exposure, but only among patients included in the simplified decision tree–defined scenarios.

For each of these subgroups, the risk of hospitalization was quantified and reported in **Table 26** which shows the prioritized high-risk PIM-related scenarios, representing patient subgroups that exceed the baseline risk of hospitalization associated with overall PIM exposure.

The lower bounds of the 95% CI ORs for each selected scenario are greater than or equal to the lower bound of the overall PIMs OR (1.55, 1.48-1.62). These values range from 1.60 (95% CI: 1.49–1.73) to 3.32 (95% CI: 2.27–4.86), confirming that the selected branches represent meaningful high-risk profiles.

To clarify the selection of scenarios, a graphical version is presented, that integrates the risks calculated in the previous step. **Figure 63** presents the final selection

algorithm proposed for identifying prioritized PIM-exposed patients, based on these refined decision rules.

Table 26 – Prioritization of at higher risk PIMs possible scenarios.

Scenario	OR	Lower	Upper
PIMs	1.55	1.48	1.62
Currently exposed to: B01AB and C03DA Currently not exposed to: J01MA Prior exposed to: B01AB	3.32	2.27	4.86
Currently exposed to: B01AB Currently not exposed to: J01MA Not prior exposed to: B01AB	2.49	2.32	2.68
Currently exposed to: B01AB and J01MA	2.01	1.81	2.23
Currently exposed to: B01AB Currently not exposed to: J01MA and C03DA Prior exposed to: B01AB Sex: female	1.92	1.69	2.19
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB	1.76	1.61	1.93
Currently exposed to: J01MA and A02BC Currently not exposed to: B01AB and C03CA Sex: male	1.64	1.50	1.81
Currently exposed to: J01MA Currently not exposed to: B01AB, C03CA and A02BC Sex: female	1.60	1.49	1.73

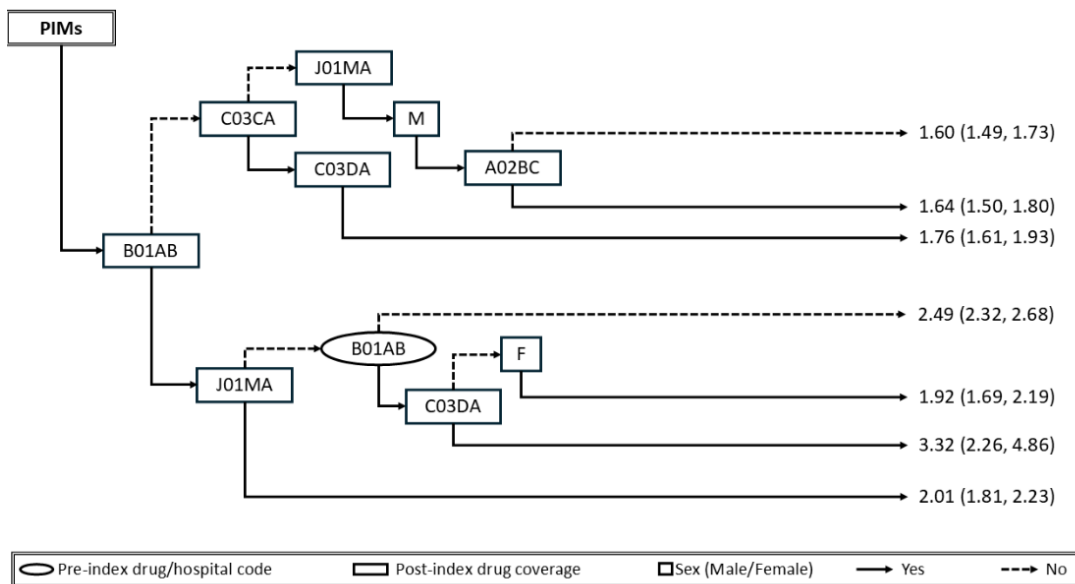


Figure 63 – PIMs prioritization algorithm illustration.

Specifically, the diagram illustrates how refined decision rules- derived from the most stable and clinically relevant CIT branches- can be operationalized to stratify patients based on their risk of hospitalization. This algorithm can be applied to PIM-selected patients by verifying their status on the variables used in the retained CIT branches (e.g., current exposure to B01AB and J01MA, prior exposure to B01AB, sex, etc.).

For example, a patient with a PIM dispensation, currently exposed to B01AB, but not exposed to J01MA, and with no exposure to B01AB prior the PIM selection date would fall into one of the high-risk branches (OR: 2.49, 2.32-2.68), making the individual a candidate for prioritized clinical intervention. A female patient, currently exposed to B01AB, but not exposed to J01MA and C03DA, who was already in treatment with B01AB, would fall into one of the high-risk branches (OR: 1.92, 1.69-2.19), making also this individual a candidate.

5.4.2 pDDIs

Based on the training dataset, **Figure 64** illustrates the full-sample CIT developed for pDDIs, which includes 36 nodes (variables) that reached statistical significance ($p < 0.05$) and 56 branches (scenarios).

Figure 65 presents the resulting sample CIT developed for pDDIs, where the most consistently selected nodes and branches (i.e., variables and scenarios) are highlighted in red.

Figure 64 – *full-sample CIT for pDDIs*



Figure 65 – *sampled CIT for pDDIs*

Among the initial 36 nodes, 10 were retained after iteration: A02BC (proton pump inhibitors, drugs for peptic ulcer and gastro-oesophageal reflux) A12BA (potassium, a mineral supplement), B01AB (heparin group, antithrombotic agents) B03AA (iron bivalent, an antianemic preparation), Sex, C01BD (amiodarone, an antiarrhythmics) C03CA (sulphonamides, diuretics), C03DA (aldosterone antagonists, diuretics) and J01MA (fluoroquinolones, antibacterials).

All the branches to the terminal nodes classified under the refined decision paths are reported in **Appendix 8**.

For each of these subgroups, the risk of hospitalization was quantified and reported in **Table 64** which shows the prioritized high-risk pDDIs-related scenarios, representing patient subgroups that exceed the baseline risk of hospitalization associated with overall pDDIs exposure.

The lower bounds of the 95% CI ORs for each selected scenario are greater than or equal to the lower bound of the overall pDDIs OR (1.50, 1.43-1.57). These values range from 1.61 (95% CI: 1.52–1.71) to 6.32 (95% CI: 4.64–8.61), confirming that the selected branches represent meaningful high-risk profiles.

Figure 66 presents the final selection algorithm proposed for identifying prioritized pDDIs-exposed patients, based on these refined decision rules.

Table 64 – *Prioritization of at higher risk pDDIs possible scenarios.*

Scenario	OR	Lower	Upper
pDDIs	1.50	1.43	1.57
Currently exposed to: B01AB and C03DA Currently not exposed to: J01MA	6.32	4.64	8.61
Currently exposed to: B01AB and C03DA	5.72	4.41	7.42
Currently exposed to: B01AB, C03DA and J01MA	4.48	2.75	7.30
Currently exposed to: C03CA, A02BC and A12BA Currently no exposed to: B01AB, C03DA, J01MA and B03AA	2.78	2.15	3.60
Currently exposed to: B01AB Currently not exposed to: C03DA	2.44	2.26	2.64
Currently exposed to: C03CA, C01BD Currently not exposed to: B01AB, C03DA and A02BC	2.31	1.67	3.20
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB and J01MA	2.16	1.94	2.42
Currently exposed to: C03CA, A02BC and J01MA Currently not exposed to: B01AB and C03DA	2.12	1.80	2.49
Currently exposed to: C03CA and A02BC Currently not exposed to: B01AB, C03DA, J01MA, B03AA and A12BA	1.63	1.50	1.77
Currently exposed to: C03CA Currently not exposed to: B01AB and C03DA	1.61	1.52	1.71

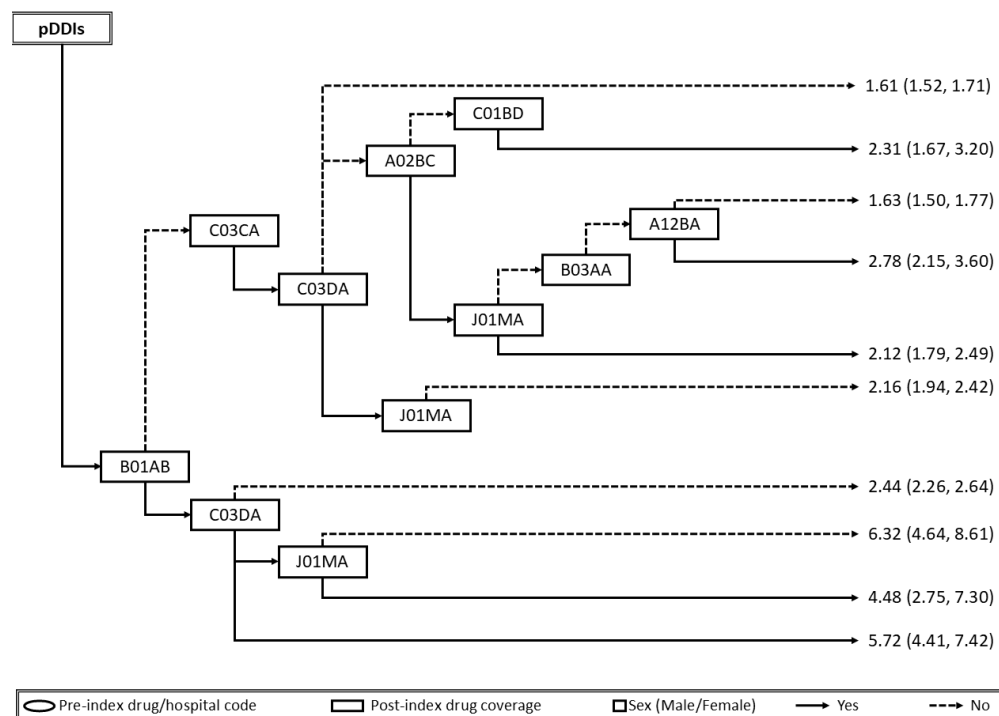


Figure 66 – *pDDIs prioritization algorithm illustration.*

This algorithm can be applied to pDDIs-selected patients by verifying their status on the variables used in the retained CIT branches (e.g., current exposure to B01AB and J01MA, exposure to A02BC, etc.).

For example, patient with a pDDIs occurrence, currently exposed to B01AB, but not exposed to C03DA, would fall into one of the high-risk branches (OR: 2.44, 2.26-2.64), making the individual a candidate for prioritized clinical intervention. A patient currently exposed to C03CA, C03DA but not to B01AB and J01MA, would fall into one of the high-risk branches (OR: 6.32, 4.64-8.61), making also this individual a candidate.

5.4.3 FRIDs

Based on the training dataset, **Figure 67** illustrates the full-sample CIT developed for FRIDs, which includes 30 nodes (variables) that reached statistical significance ($p < 0.05$) and 46 branches (scenarios).

Figure 68 presents the resulting sample CIT developed for FRIDs, where the most consistently selected nodes and branches (i.e., variables and scenarios) are highlighted in red.



Figure 67 – *full-sample CIT for FRIDs*

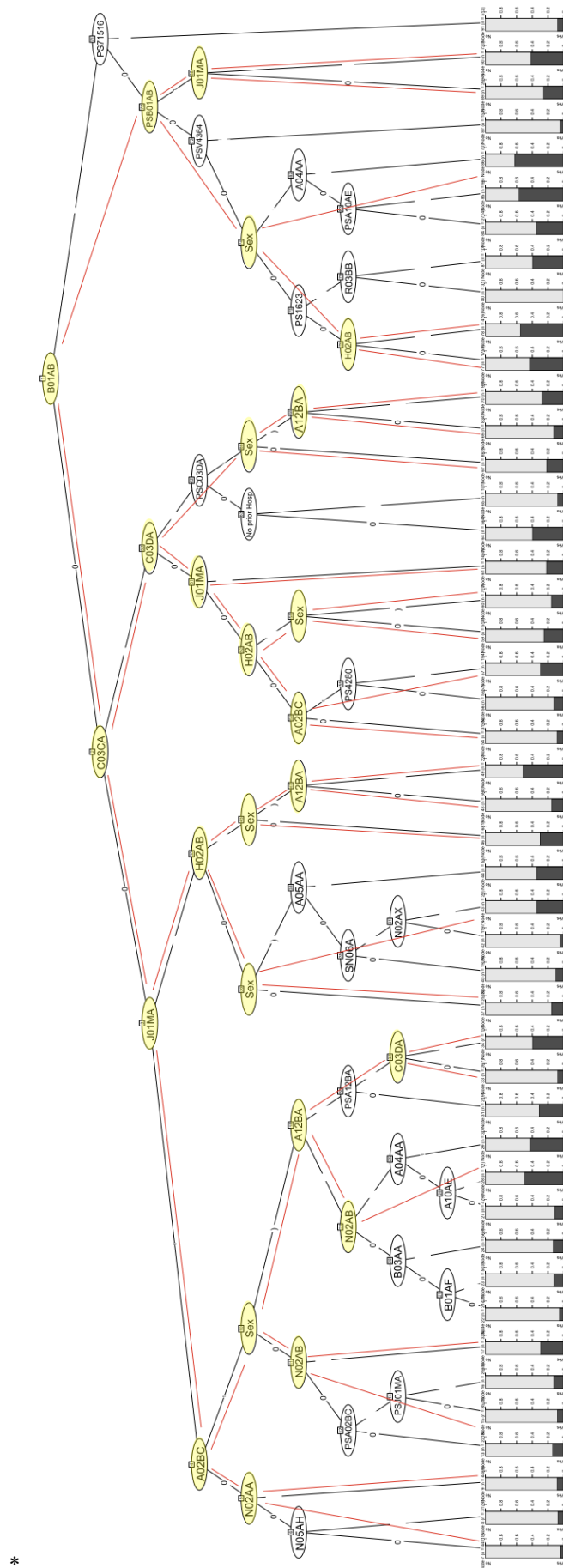


Figure 68 – *sampled CIT for FRIDs*

Among the initial 30 nodes, 11 were retained after iteration: B01AB (heparin group, antithrombotic agents), Sex, PSB01AB (heparin group, antithrombotic agents – prior to the selection date), A02BC (proton pump inhibitors, drugs for peptic ulcer and gastro-oesophageal reflux), A12BA (potassium, a mineral supplement), C03CA (sulphonamides, diuretics). C03DA (aldosterone antagonists, diuretics), H02AB (glucocorticoids), J01MA (fluoroquinolones, antibacterials), N02AA (natural opium alkaloids) and N02AB (phenylpiperidine derivatives).

All the branches to the terminal nodes classified under the refined decision paths are reported in **Appendix 8**.

For each of these subgroups, the risk of hospitalization was quantified and reported in **Table 65** which shows the prioritized high-risk FRIDs-related scenarios, representing patient subgroups that exceed the baseline risk of hospitalization associated with overall FRIDs exposure. The lower bounds of the 95% CI ORs for each selected scenario are greater than or equal to the lower bound of the overall PIMs OR (1.62, 1.51-1.73). These values range from 1.85 (95% CI: 1.66–2.05) to 13.34 (95% CI: 3.85–46.18), confirming that the selected branches represent meaningful high-risk profiles.

Figure 69 presents the final selection algorithm proposed for identifying prioritized PIM-exposed patients, based on these refined decision rules.

This algorithm can be applied to FRIDs-selected patients by verifying their status on the variables used in the retained CIT branches (e.g., current exposure to B01AB and J01MA, prior exposure to B01AB, sex, etc.).

For example, patient with a FRIDs dispensation, currently exposed to B01AB, but not exposed to J01MA, and with no exposure to B01AB prior the PIM selection date, would fall into one of the high-risk branches (OR: 2.79, 2.27-3.43), making the individual a candidate for prioritized clinical intervention. A female patient, currently exposed to H02AB and B01AB, who was already in treatment with B01AB, would fall into one of the high-risk branches (OR: 4.34, 3.25-5.79), making also this individual a candidate.

Table 65 – *Prioritization of at higher risk FRIDs possible scenarios*

Scenario	OR	Lower	Upper
FRIDs	1.62	1.51	1.73
Currently exposed to: A02BC, A12BA and C03DA Currently not exposed to: B01AB, C03CA and J01MA Sex: female	13.34	3.85	46.18
Currently exposed to: B01AB and H02AB Previously not exposed to: B01AB Sex: male	4.34	3.26	5.79
Currently exposed to: B01AB Previously not exposed to: B01AB Sex: female	2.86	2.62	3.13
Currently exposed to: J01MA and H02AB Currently not exposed to: B01AB and C03CA Sex: male	2.80	2.34	3.36
Currently exposed to: B01AB and J01MA Prior exposed to: B01AB	2.79	2.27	3.43
Currently exposed to: C03CA, C03DA and A12BA Currently not exposed to: B01AB Sex: female	2.74	1.75	4.31
Currently exposed to: A02BC, A12BA Currently not exposed to: B01AB, C03CA, J01MA and C03DA Sex: female	2.39	1.87	3.05
Currently exposed to: B01AB Currently not exposed to: J01MA Prior exposed to: B01AB	2.12	1.93	2.34
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB Sex: male	1.95	1.67	2.27
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB and A12BA Sex: female	1.87	1.59	2.20
Currently exposed to: J01MA Currently not exposed to: B01AB, C03CA and H02AB Sex: male	1.85	1.66	2.05

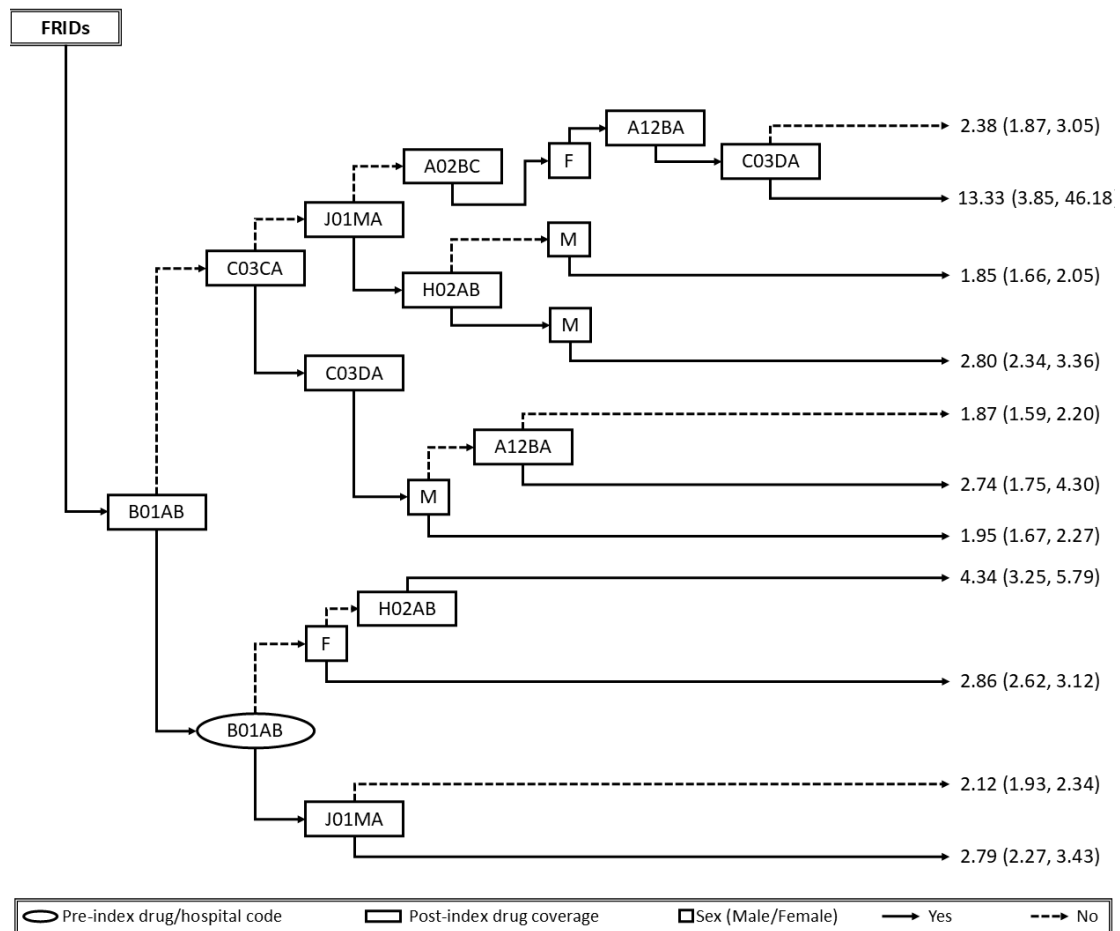


Figure 69 – FRIDs prioritization algorithm illustration.

5.4.4 TDs

Based on the training dataset, **Figure 70** illustrates the full-sample CIT developed for TDs, which includes 39 nodes (variables) that reached statistical significance ($p < 0.05$) and 61 branches (scenarios).

Figure 71 presents the resulting sample CIT developed for FRIDs, where the most consistently selected nodes and branches (i.e., variables and scenarios) are highlighted in red.



Figure 71 – *sampled CIT for TDs*

Among the initial 39 nodes, 14 were retained after iteration: B01AB (heparin group, antithrombotic agents), J01MA (fluoroquinolones, antibacterials), Sex, PSB01AB (heparin group, antithrombotic agents – prior to the selection date), C03DA (aldosterone antagonists, diuretics), C03CA (sulphonamides, diuretics), A02BC (proton pump inhibitors, drugs for peptic ulcer and gastro-oesophageal reflux), the therapeutic duplication SB01AB_B01AB (heparin group, antithrombotic agents) and the therapeutic duplication SB01AC_B01AC (platelet aggregation inhibitors, excluded heparin).

All the branches to the terminal nodes classified under the refined decision paths are reported in **Appendix 8**.

For each of these subgroups, the risk of hospitalization was quantified and reported in **Table 66** which shows the prioritized high-risk TD-related scenarios, representing patient subgroups that exceed the baseline risk of hospitalization associated with overall TD exposure.

The lower bounds of the 95% CI ORs for each selected scenario are greater than or equal to the lower bound of the overall PIMs OR (1.52, 1.46-1.58). These values range from 1.68 (95% CI: 1.49–1.90) to 4.04 (95% CI: 3.35–4.87), confirming that the selected branches represent meaningful high-risk profiles. **Figure 72** presents the final selection algorithm proposed for identifying prioritized PIM-exposed patients, based on these refined decision rules.

This algorithm can be applied to TD-selected patients by verifying their status on the variables used in the retained CIT branches (e.g., current exposure to B01AB and J01MA, prior exposure to B01AB, sex, etc.).

For example, male patient with a TD, currently exposed to B01AB and to J01MA with exposure to B01AB prior the TD selection date would fall into one of the high-risk branches (OR: 2.54, 1.85-3.49), making the individual a candidate for prioritized clinical intervention. A patient, currently exposed to B01AB, but not exposed to J01MA but exposed to C03CA and C03DA, would fall into one of the high-risk branches (OR: 1.68, 1.49-1.90), making also this individual a candidate.

Table 66 – *Prioritization of at higher risk TDs possible scenarios.*

Scenario	OR	Lower	Upper
TDs	1.52	1.46	1.58
Currently exposed to: B01AB Currently not exposed to: TD of B01AB, A02BC Previously not exposed to: B01AB Sex: male	4.04	3.35	4.87
Currently exposed to: B01AB and C03DA Currently not exposed to: J01MA Prior exposed to: B01AB Sex: male	3.96	2.20	7.11
Currently exposed to: B01AB Currently not exposed to: TD of B01AB, A02BC Previously not exposed to: B01AB Sex: female	3.69	2.39	5.69
Currently exposed to: B01AB, A02BC and TD of B01AB Previously not exposed to: B01AB Sex: female	3.61	2.91	4.47
Currently exposed to: J01MA and TD of B01AC Currently not exposed to: B01AB and C03CA	3.51	2.58	4.77
Currently exposed to: B01AB and J01MA Prior exposed to: B01AB Sex: male	2.54	1.85	3.49
Currently exposed to: C02CA and J01MA Currently not exposed to: B01AB, C03DA and A02BC	2.53	1.76	3.63
Currently exposed to: B01AB Currently not exposed to: J01MA and C03DA Prior exposed to: B01AB Sex: male	2.42	1.96	2.99
Currently exposed to: B01AB and A02BC Prior exposed to: B01AB Sex: female	1.99	1.62	2.45
Currently exposed to: J01MA Currently not exposed to: B01AB, C03CA, TD of B01AC Sex: male	1.94	1.73	2.17
Currently exposed to: C03CA and A02BC Currently not exposed to: B01AB and C03DA Sex: male	1.75	1.57	1.95
Currently exposed to: C03CA Currently not exposed to: B01AB and C03DA Sex: male	1.72	1.57	1.89
Currently exposed to: TD of B01AC Currently not exposed to: B01AB, C03CA and J01MA	1.71	1.58	1.86
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB and J01MA	1.68	1.49	1.90



Figure 74 – sampled CIT for ACB score

Among the initial 24 nodes, 4 were retained after iteration: B01AB (heparin group, antithrombotic agents), J01MA (fluoroquinolones, antibacterials), PSB01AB (heparin group, antithrombotic agents – prior to the selection date), C03DA (aldosterone antagonists, diuretics), C03CA (sulphonamides, diuretics) and N02AB (phenylpiperidine derivatives).

All the branches to the terminal nodes classified under the refined decision paths are reported in **Appendix 8**.

For each of these subgroups, the risk of hospitalization was quantified and reported in **Table 67** which shows the prioritized high-risk ACB score-related scenarios, representing patient subgroups that exceed the baseline risk of hospitalization associated with overall ACB score ≥ 3 exposure.

The lower bounds of the 95% CI ORs for each selected scenario are greater than or equal to the lower bound of the overall ACB score OR (1.52, 1.43-1.61). These values range from 1.88 (95% CI: 1.56–2.25) to 3.20 (95% CI: 2.72–3.76), confirming that the selected branches represent meaningful high-risk profiles.

Table 67 – Prioritization of at higher risk ACB score $\geq$ possible scenarios.

Scenario	OR	Lower	Upper
ACB score	1.52	1.43	1.61
Currently exposed to: B01AB Previously not exposed to: B01AB	3.20	2.72	3.76
Currently exposed to: B01AB Previously exposed to: B01AB	2.07	1.72	2.49
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB	2.01	1.69	2.38
Currently exposed to: J01MA Currently not exposed to: B01AB, C03CA and N02AB,	1.88	1.56	2.25

Figure 75 presents the final selection algorithm proposed for identifying prioritized ACB score-exposed patients, based on these refined decision rules.

This algorithm can be applied to ACB score-selected patients by verifying their status on the variables used in the retained CIT branches (e.g., current exposure to B01AB, prior exposure to B01AB, sex, etc.).

For example, patient with a ACB score ≥ 3 occurrence, currently exposed to B01AB and already exposed the same drug class would fall into one of the high-risk branches (OR: 2.07, 1.72-2.49), making the individual a candidate for prioritized clinical intervention. Another patient, currently not exposed to B01AB but exposed to C03CA and C03DA, would fall into one of the high-risk branches (OR: 2.01, 1.69-2.38), making also this individual a candidate.

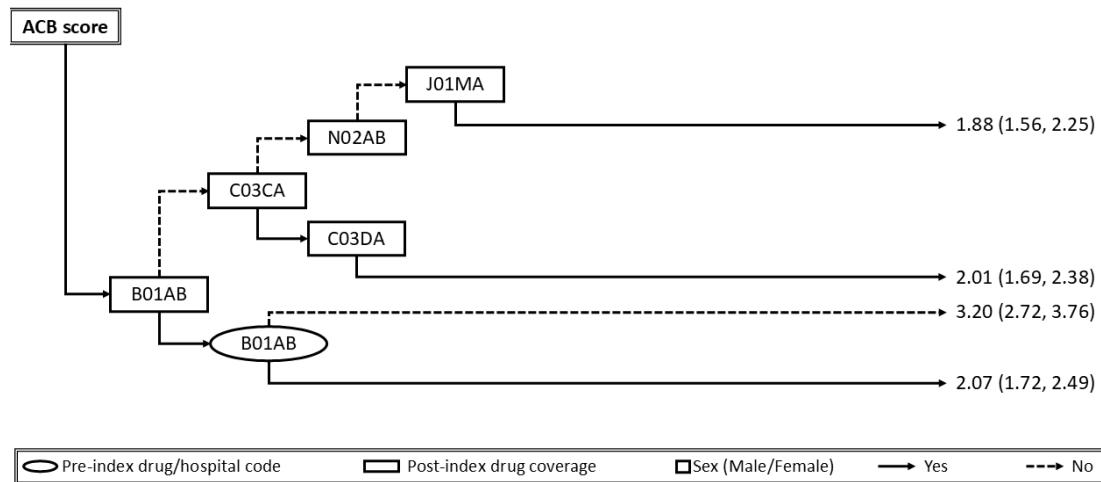
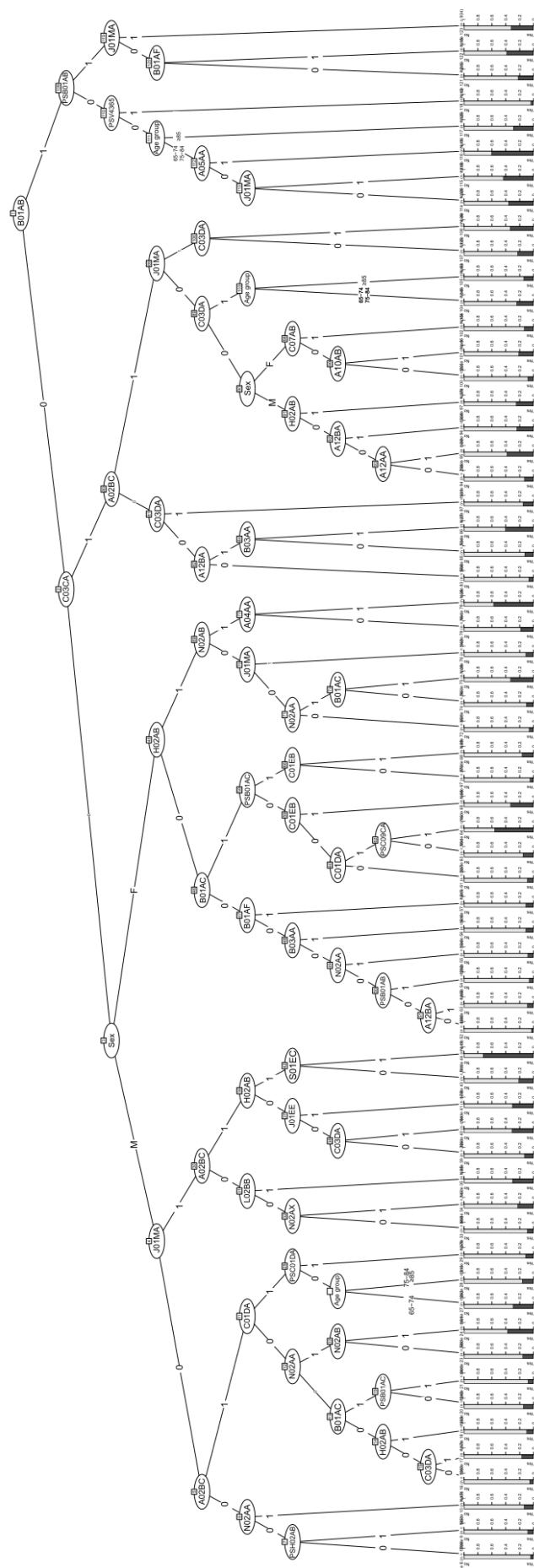


Figure 75 – ACB score prioritization algorithm illustration.

5.4.6 SL score

Based on the training dataset, **Figure 76** illustrates the full-sample CIT developed for SL score, which includes 33 nodes (variables) that reached statistical significance ($p < 0.05$) and 62 branches (scenarios).

Figure 77 presents the resulting sample CIT developed for SL score ≥ 3 , where the most consistently selected nodes and branches (i.e., variables and scenarios) are highlighted in red.



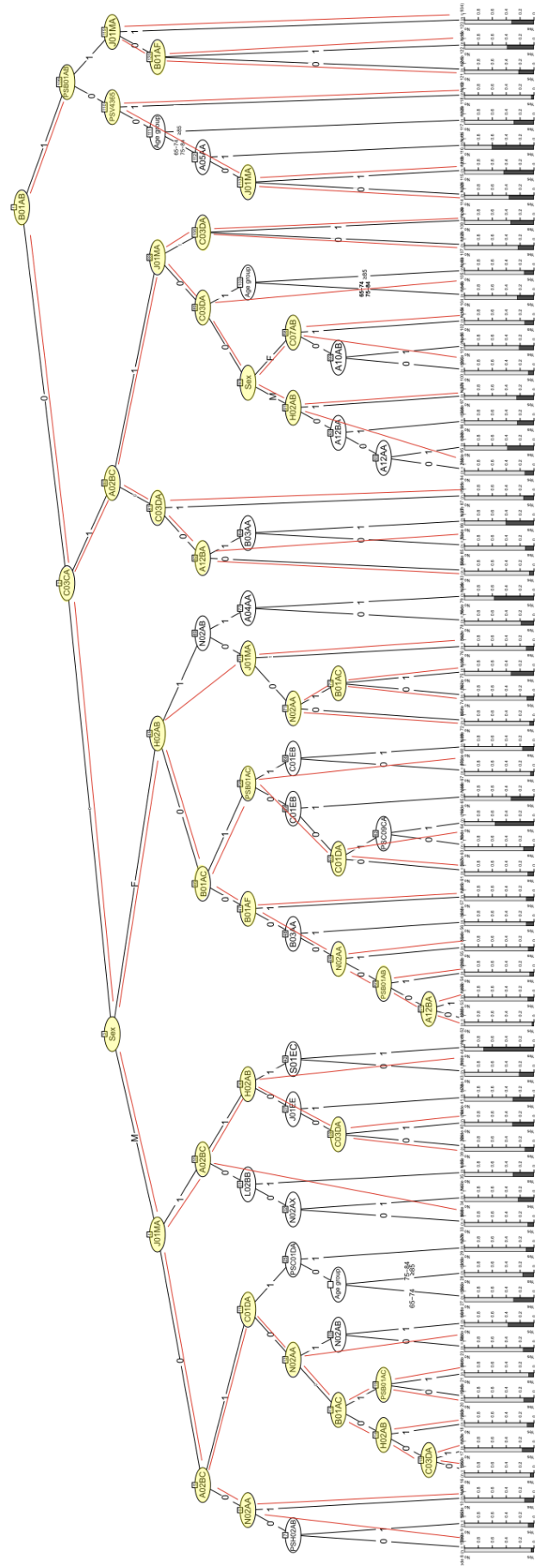


Figure 77 – sampled CIT for SL score

Among the initial 33 nodes, 14 were retained after iteration: B01AB (heparin group, antithrombotic agents), J01MA (fluoroquinolones, antibacterials), Sex, C03DA (aldosterone antagonists, diuretics), C03CA (sulphonamides, diuretics), A12BA (potassium, a mineral supplement), A02BC (proton pump inhibitors, drugs for peptic ulcer and gastro-oesophageal reflux), B01AC (platelet aggregation inhibitors excluded heparin), B01AF (direct factor Xa inhibitors), C01DA (organic nitrates, drugs used as vasodilators in cardiac disease), C07AB (selective beta blocking agents), H02AB (glucocorticoids), N02AA (natural opium alkaloids), PSB01AB ((heparin group, antithrombotic agents – prior to the selection date), PSB01AC (platelet aggregation inhibitors excluded heparin – prior to the selection date) and PSV4365 (knee joint replacement- prior to the selection date).

All the branches to the terminal nodes classified under the refined decision paths are reported in **Appendix 8**.

For each of these subgroups, the risk of hospitalization was quantified and reported in **Table 68** which shows the prioritized high-risk SL score-related scenarios, representing patient subgroups that exceed the baseline risk of hospitalization associated with overall SL score ≥ 3 exposure.

The lower bounds of the 95% CI ORs for each selected scenario are greater than or equal to the lower bound of the overall SL score OR (1.43, 1.31-1.56). These values range from 1.43 (95% CI: 1.34–1.54) to 4.39 (95% CI: 3.79–5.08), confirming that the selected branches represent meaningful high-risk profiles. **Figure 78** presents the final selection algorithm proposed for identifying prioritized PIM-exposed patients, based on these refined decision rules.

This algorithm can be applied to SL score-selected patients by verifying their status on the variables in the retained CIT branches (e.g., current exposure to B01AB and J01MA, prior exposure to B01AB, etc.). For example, a male patient with a SL score ≥ 3 occurrence, currently not exposed to B01AB, but exposed to C03CA, A02BC, H02AB but not exposed to J01MA and C03DA would fall into one of the high-risk branches (OR: 1.78, 1.40-2.27), making the individual a candidate for prioritized clinical intervention.

Table 68 – *Prioritization of at higher risk SL score possible scenarios.*

Scenario	OR	Lower	Upper
SL score	1.43	1.31	1.56
Currently exposed to: B01AB +J01MA Currently not exposed to: Prior exposed to: B01AB Had hospitalizaions: V4365	4.39	3.79	5.08
Currently exposed to: C03CA, A02BC, J01MA and C03DA Currently not exposed to: B01AB	2.71	2.08	3.52
Currently exposed to: B01AB Not prior exposed to: B01AB Currently not exposed to: J01MA Had no hospitalizaions: V4365	2.47	2.27	2.68
Currently exposed to: B01AC and C01DA Currently not exposed to: B01AB, C03CA, H02AB, Not prior exposed to: B01AC Sex: female	2.06	1.45	2.93
Currently exposed to: J01MA, A02BC and H02AB Currently not exposed to: B01AB and C03CA Sex: male	1.94	1.66	2.27
Currently exposed to: A12BA Currently not exposed to: B01AB, C03CA, B01AC, H02AB, B01AF and N02AA Not prior exposed to: B01AB Sex: female	1.82	1.44	2.31
Currently exposed to: C03CA, H02AB andA02BC Currently not exposed to: B01AB, J01MA and C03DA Sex: male	1.78	1.40	2.27
Currently exposed to: A02BC and N02AA Currently not exposed to: B01AB, C03CA, J01MA and C01DA Sex: male	1.78	1.51	2.12
Currently exposed to: B01AB Currently not exposed to: J01AM + B01AF Prior exposed to: B01AB	1.68	1.52	1.86
Currently exposed to: A02BC and C01DA Currently not exposed to: B01AB, C03CA and J01MA Sex: male	1.54	1.32	1.78
Currently exposed to: A02BC and B01AC Currently not exposed to: B01AB, C03CA, J01MA and C01DA Prior not exposed to: B01AC Sex: male	1.54	1.40	1.70
Currently exposed: J01MA and A02BC Currently not exposed to: B01AB, C03CA, H02AB and C03DA Sex: male	1.50	1.38	1.63
Currently exposed to: A02BC and H02AB Currently not exposed to: B01AB, C03CA, J01MA, C01DA and B01AC Sex: male	1.48	1.32	1.66
Currently exposed to: J01MA Currently not exposed to: B01AB, C03CA and A02BC Sex: male	1.43	1.34	1.54

CHAPTER 6

Applying the algorithm to clinical practice

This chapter presents the application of the CIT-derived risk profiles to a real-world, population-level healthcare dataset. This analysis focused on the first semester of 2018, allowing the detectability of prioritized high-risk medication scenarios identified in Chapter 5. Specifically, the aim is to quantify patients exposed to PII and to evaluate their demographic and clinical characteristics, along with prescription records and comorbidities. By applying these CIT-defined algorithms to current data, this chapter bridges the gap between statistical model development and operational clinical utility.

In real-world settings, GPs have access to their patients' pharmaceutical and hospitalization histories, and their aim is to apply the algorithm at a given time point, as to flag those at highest risk, without considering washout periods or follow-up intervals that are not available at that moment. This pragmatic approach reflects how such tools can support targeted interventions within routine clinical workflows, enabling early identification and prioritization of vulnerable patients based on current, actionable data.

6.1 Study cohort

The target population consisted of all individuals aged 65 years and older across the four participating LHUs of Bergamo, Lecco, Monza Brianza, and Mantova, who received at least one pharmaceutical prescription between January 1st and June 30th, 2018 (**Table 69**). The mean age of this population was 75.9 years (SD: 7.5), and 56.3% were female. Most individuals were aged 65–74 years (44.3%), followed by those aged 75–84 years (38.1%) and ≥ 85 years (17.7%).

Table 69 – Study population for the first semester 2018. SD=Standard deviation, yy=years

	First semester of 2018
N	501,785
Female sex, N (%)	282,451 (56.3%)
Age, mean (SD)	75.9 (7.5)
Age group, N (%)	
65-74 yy	236,546 (47.1%)
75-84 yy	190,635 (38.0 %)
≥ 85 yy	74,604 (14.9%)

6.2 Step 1: PII prevalence assessment

Based on the same methodologies described in the previous chapters, the prevalence of each PII was calculated (**Figure 79**).

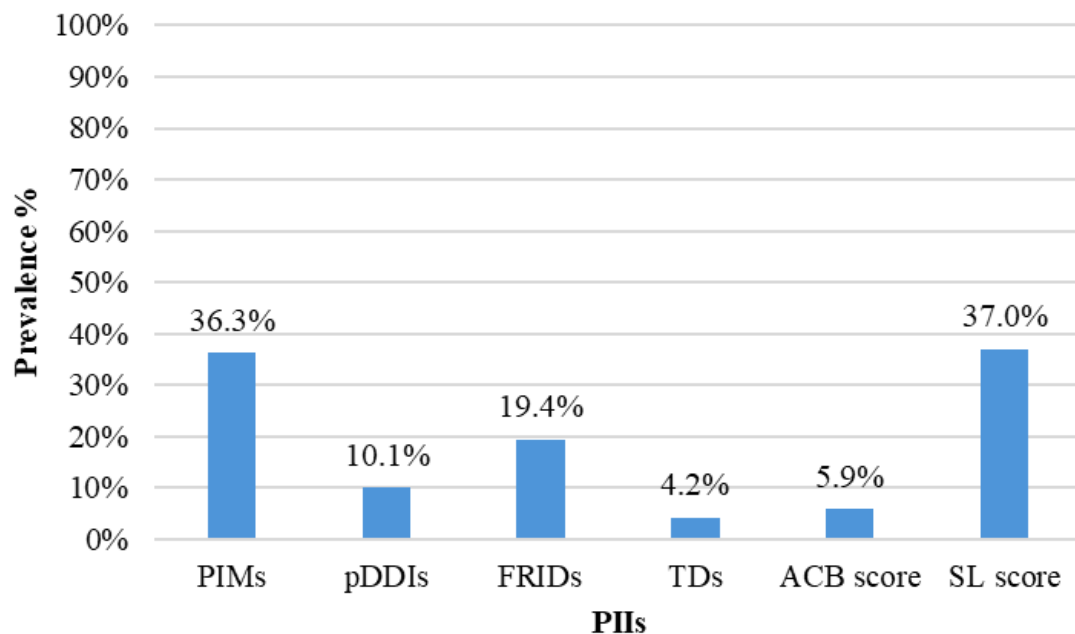


Figure 79- Prevalence (%) of the most common PII in the first semester 2018

Among 501,785 older adults with at least one dispensation during the 6 months period, the most common PII was a high SL score, affecting 37.0% of the population (185,534 individuals), followed by PIMs, with a prevalence of 36.3% (181,952 individuals). FRIDs were also notably frequent, with 19.4% (97,258 individuals) of older adults being exposed to at least one such medication. pDDIs of major or contraindicated severity were identified in 10.1% (50,471 individuals), while ACB scores of ≥ 3 were observed in 5.9% (29,553 individuals). Lastly, TDs were present in 4.2% (20,914 individuals).

6.3 Step 2: multiple concurrent indicators

In clinical practice, simply calculating the prevalence of individual indicators- as done so far for algorithm development- may not be sufficient. It is essential to recognize that a patient at a given moment may simultaneously present multiple indicators. This

condition alone is likely to expose the patient to a higher risk of hospitalization and should be assessed prior to implementing any risk stratification algorithm. Therefore, it was necessary to evaluate the number of concurrent PIIs within the considered time frame to identify patient subgroups where the algorithm's application is most valuable. A portion of the population presenting a high number of simultaneous indicators deserves urgent prioritization and clinical review even before algorithm use, as their risk is already evidently elevated. **Figure 80** illustrates the distribution of the number of PIIs per patient during the first half of 2018.

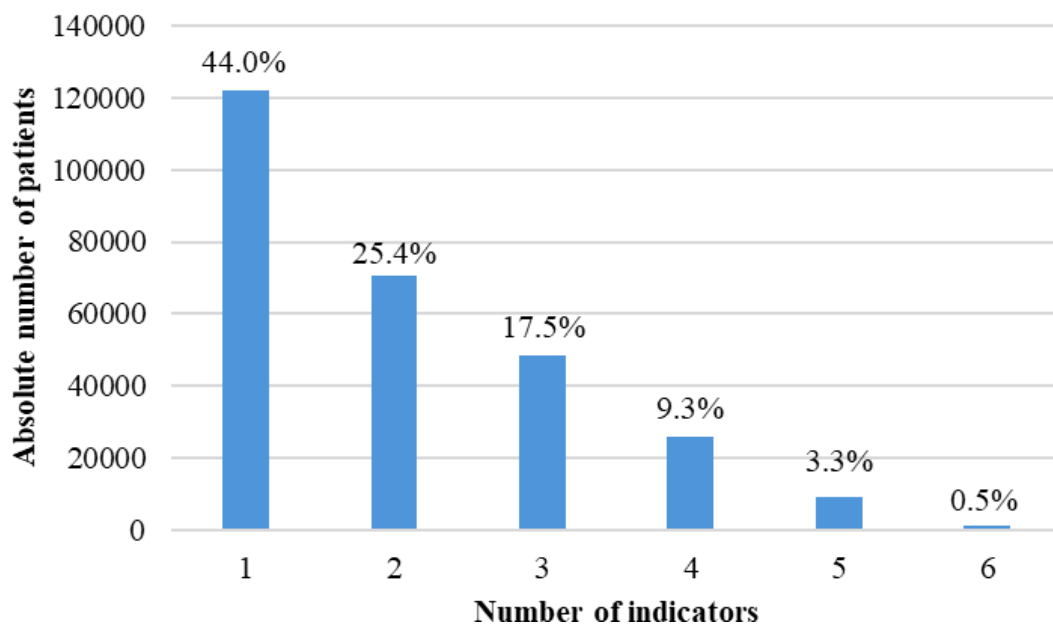


Figure 80- *Distribution of the number of indicators per patient in the first half of 2018*

The majority of exposed individuals had only one PII (44.0%), followed by 25.4% with two PIIs, 17.5% with three PIIs, and progressively smaller proportions with four (9.3%), five (3.3%), or six (0.5%) PIIs. This distribution highlights the presence of a high-risk group characterized by the coexistence of several indicators, underscoring the importance of considering cumulative risk when prioritizing patients for clinical intervention.

6.4 Step 3: identification of high-risk scenarios

Among those exposed to at least one inappropriate prescribing indicator (277,457 individuals, 55.3%), 50,894 fell into at least one high-risk scenario, identified in the previous decision tree analyses, corresponding to 18.4% of all patients with any PII exposure. In **Table 70**, a comparison between subjects prioritized for at least one high-risk scenario and those not prioritized within the PII-exposed cohorts is shown.

Table 70 – Characteristics of the PII-exposed cohorts (N=277,457). The p-value was calculated for the comparison between the Not prioritized and Prioritized subgroups.

Covariates	PII-not exposed	PII-exposed		p-value
		Not prioritized	Prioritized	
N	224,328	226,473	50,984	
Female sex, N (%)	136,811 (61.0)	125,698 (55.5)	19,942 (39.1)	<0.001
Age, mean (SD)	74.4 (7.1)	77.0 (7.4)	78.5 (7.6)	<0.001
Age class, N (%)				
65-74 yy	127,338 (56.8)	92,264 (40.7)	16,944 (33.2)	<0.001
75-84 yy	74,009 (33.0)	94,489 (41.7)	22,137 (43.4)	
≥85 yy	22,981 (10.2)	39,720 (17.5)	11,903 (23.3)	
Politherapy	13,622 (6.1)	130,568 (57.7)	43,883 (86.1)	<0.001
Severe politherapy	17 (0.0)	8,090 (3.6)	9,398 (18.4)	<0.001
Hospitalization, N (%)	12,839 (5.7)	18,808 (8.3)	14,208 (27.9)	<0.001
Age, mean (SD)	74.8 (7.1)	77.5 (7.4)	77.6 (7.4)	0.16
Age class, N (%)				
65-74 yy	6,931 (5.4)	7,169 (7.8)	5,294 (31.2)	0.18
75-84 yy	4,501 (6.1)	8,056 (8.5)	6,225 (28.1)	
≥85 yy	1,407 (6.1)	3,583 (9.0)	2,689 (22.6)	

* Polytherapy: 5 or more 4th level ATC codes during the first semester 2018; Severe polytherapy: 10 or more 4th level ATC codes during the first semester 2018

The distribution of prioritization rates varied across indicators (**Table 71**). The pDDIs and TDs indicators showed the highest prioritization rates, with 35.6% and 36.4% of exposed individuals falling within high-risk scenarios, respectively. Conversely, indicators such as SL score and PIMs had lower prioritization rates, at 11.2% and 9.6%, respectively. ACB score had an intermediate prioritization rate of 17.8%. Despite some indicators (e.g., SL score and PIMs) identified a large proportion of exposed individuals (37.0% and 36.3%, respectively), only a smaller fraction of these were flagged as high-risk through the decision tree approach (4.2% and 3.5%,

respectively), highlighting the algorithm's ability to selectively identify more clinically vulnerable subgroups. On the other hand, indicators with lower overall prevalence such as TDs and pDDIs retained relatively high prioritization efficiency, with more than one-third of exposed patients falling into high-risk scenarios.

Table 71 – *Distribution of prioritization rate across PIIs*

	Individuals with PII / target population		Prioritized individuals / target population		Prioritization Rate (Prioritized individuals / Individuals with PII)
	N	%	N	%	%
PIMs	181,952	36.3%	17,492	3.5%	9.6%
pDDIs	50,471	10.1%	17,965	3.6%	35.6%
FRIDs	97,258	19.4%	7,604	1.5%	7.8%
TDs	20,914	4.2%	7,608	1.5%	36.4%
ACB score	29,553	5.9%	5,250	1.0%	17.8%
SL score	185,534	37.0%	20,851	4.2%	11.2%

Patients with only one PII may either be prioritized for that single indicator or not flagged at all- meaning that despite the exposure, they do not fall into any high-risk scenario defined by the decision tree approach. Conversely, patients with two or more PIIs might be prioritized for the same number of indicators, or for fewer, depending on whether their specific combinations correspond to any high-risk profiles. In fact, a substantial portion of patients with multiple PIIs did not meet the criteria for high-risk scenarios. **Table 72** shows the distribution of number of PIIs by exposed patients, along with distribution of number of PIIs by prioritized patients.

Table 72 – *Distribution of number of PIIs*

PIIs [N]	Exposed [N]	Prioritized [N]	Prioritization rate
1	122,061	34,698	28.4%
2	70,543	9,628	13.6%
3	48,564	4,345	8.9%
4	25,876	1,816	7.0%
5	9,135	465	5.1%
6	1,278	32	2.5%

Figure 81 illustrates the number of patients within the prioritization process. The figure shows the proportion of prioritized patients among those exposed to a given number of PIs.

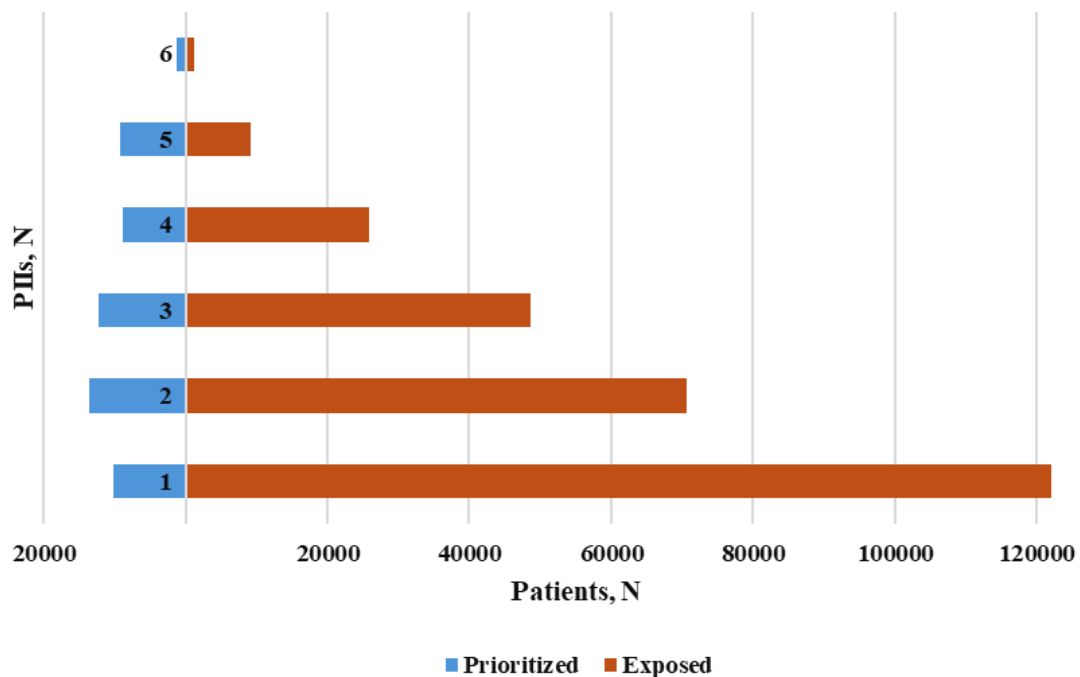


Figure 81 – Reduction of number of patients or each PPIs exposure within the prioritization

6.4.1 Selection assumptions

Assuming that the concurrent presence of more than one indicator increases the risk of hospitalization in itself, we can posit a scenario in which individuals with at least *four* indicators are automatically considered as prioritized. In our study cohort, 36,289 subjects (7.2% of the target population) fell in this scenario. The 241,168 subjects with one, two, or three indicators were then prioritized according to the presence of at least one high-risk prescribing scenario, leading to the selection of 35,827 individuals, (7.1% of the target population). This approach would identify 72,116 subjects as potentially requiring closer monitoring or intervention- either due to a high burden of inappropriate prescriptions or increased vulnerability linked to specific clinical contexts, with an overall prioritization rate of 14.3% of the target population.

Otherwise, we can propose that all individuals with at least *three* indicators be considered eligible for prioritization. Similarly, as done previously, we can initially select individuals with three or more indicators (84,853 individuals, 16.9% of the target population) and those with two or less indicators who also meet one of the higher-risk scenarios (23,665 individuals, 4.7% of the target population). Overall, this approach would identify 108,518 individuals to be prioritized, corresponding to 21.6% of the target population as potentially requiring closer monitoring or intervention.

Finally, we can adopt a more conservative approach and propose that all individuals with *five* or *six* indicators be considered eligible for prioritization. We can initially select individuals with at least *five* indicators (10,413 individuals, 2.1% of the target population) and those with *four or less* indicators who also meet one of the higher-risk scenarios (44,555 individuals, 8.9% of the target population). Overall, this approach would identify 54,968 individuals to be prioritized, corresponding to 11.0% of the target population as potentially requiring closer monitoring or intervention.

6.4.2 Clinical impact estimate for general practitioners

To illustrate the practical implications of applying the algorithm in routine clinical practice, we can consider a GP with a patient panel of 1,500 individuals, of whom approximately 24% (i.e., 360 patients) are aged 65 years or older³⁰ and that 97.2% of the over 65 years old population received at least one prescription, according to AIFA OSMED estimates¹²¹. Applying the algorithm, approximately from 11.0% to 21.6% of these older adults could be flagged for potential medication review, due to the presence of inappropriate prescribing indicators, combined with high-risk prescribing scenarios. This would correspond to an estimated from 38 to 76 patients per GP requiring prioritized assessment.

Sensitivity analysis is reported in **Figure 82**, which considers variations in the proportion of older adults across GP panels (ranging from 19% to 29%), assuming that from 94.4 to 100% of these patients actively receive prescriptions and adopts the 14.3% prioritization rate as the central reference point (50 patients per GP considering 97.2%¹²¹ of older patients access the dispensations system and considering 24% of

older patients per GP). We adopted the central estimate-based on a 14.3% prioritization rate, assuming 24.0% of older patients per GP and considering 97.2% of the older population accesses the dispensation system- as a reference point (base case), leading to an estimated number of 50 patients per GP to be prioritized.

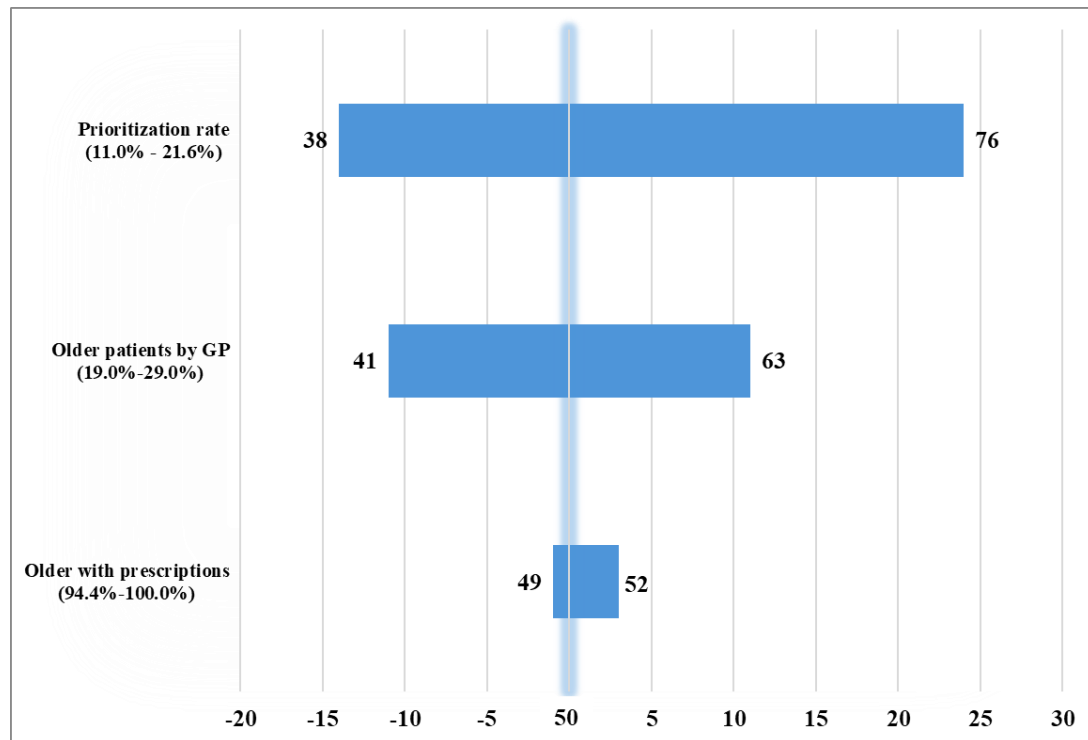


Figure 82 – Sensitivity analysis on the expected number of prioritized patients per GP under different assumptions.

The upper bar shows how the estimated number of patients per GP varies based on different prioritization rates (ranging from 11.0% to 21.6%), resulting in an estimate between 38 and 76 patients. The second bar reflects variation in the proportion of older adults in a GP's patient panel (from 19.0% to 29.0%), while the third bar incorporates the assumption that 95% of older patients are active users of the regional prescription system.

6.4.3 Examples of prioritized patients

Three patients among those exposed to 2 or 3 PIIIs and with at least one at risk scenario have been randomly selected across the different age groups.

Patient A

The first patient, patient A, was a 66-year-old man. Between 2014 and 2018, he was hospitalized for:

- other specified gastritis without mention of haemorrhage – 2015;
- iron deficiency anaemia secondary to blood loss (chronic) – 2017;
- closed fracture of lumbar vertebrae without mention of spinal cord injury – 2018;
- acute gastritis with haemorrhage – 2018;
- hepatic coma – 2018.

During the first semester of 2018, the dispensed drugs were:

- A02BC02 pantoprazole;
- A07AA11 rifaximin;
- A12BA01 potassium chloride;
- B01AB05 enoxaparin;
- B03AA07 ferrous sulphate;
- B03BB01 folic acid;
- C03DA03 canrenone;
- C07AB03 atenolol;
- C09AA05 ramipril;
- C10AA05 atorvastatin;
- J01DC02 cefuroxime.

The patient A has a complex multisystem profile, including cardiovascular disease (hypertension, hyperlipidemia, possible heart failure). Gastrointestinal disorders, including chronic and hemorrhagic gastritis, treated with pantoprazole and rifaximin, have possibly contributed to iron deficiency anemia. A hepatic coma in 2018 indicates

significant liver dysfunction, while a prior lumbar vertebra fracture may have increased thrombotic risk.

The patient A was exposed to PMI and SL score and prioritized according to two high risk scenarios, that appeared partially overlapped (**Table 73**). Specifically, the patient is currently treated with a low-molecular-weight heparin (B01AB) and an aldosterone antagonist (C03DA), without current exposure to fluoroquinolone antibiotics (J01MA).

Table 73– *High risk scenarios of Patient A*

Scenario	OR	Lower	Upper
PIMs	1.55	1.48	1.62
Currently exposed to: B01AB and C03DA Currently not exposed to: J01MA Prior exposed to: B01AB	3.32	2.27	4.86
SL score	1.43	1.31	1.56
Currently exposed to: B01AB Currently not exposed to: J01AM + B01AF Prior exposed to: B01AB	1.68	1.52	1.86

The patient's current pharmacological profile suggests an increased vulnerability to adverse events. Exposure to low-molecular-weight heparins (B01AB) carries a well-recognized risk of bleeding, which may be particularly concerning in older or comorbid individuals. Concomitant treatment with aldosterone antagonists (C03DA) further contributes to clinical fragility, as these agents can lead to hyperkalemia and electrolyte imbalance, especially in patients with impaired renal function, which may be relevant given the patient's outcome on 2018. Enoxaparin and cefuroxime may have been initiated in response to acute events (e.g., fracture or infection), but their continued use should be reconsidered. Finally, due the most recent hospitalization, hepatic coma, concern involves atorvastatin, given the patient's history of hepatic impairment.

To optimise the patient's pharmacotherapy and reduce the risk of adverse events, a number of interventions may be considered:

- laboratory monitoring should be prioritised, focusing on:

- serum potassium and creatinine to evaluate the risk and presence of hyperkalemia or renal impairment;
- liver function tests and CPK levels, particularly in the context of ongoing atorvastatin therapy and a background of hepatic dysfunction.
- deprescribing should be actively considered where appropriate. Specifically, this applies to pantoprazole, even it did not meet PII-exposure criteria for chronic use, potassium supplements and revaluations of ferrous sulphate supplement.

Patient B

The second patient, the patient B, randomly selected was a 77-year-old woman with no recorded hospitalizations between 2014 and 2018. During the first semester of 2018, the dispensed drugs were:

- A02BC03 lansoprazole;
- A11CC05 colecalciferol;
- C03CA01 furosemide;
- C07AB12 nebivolol;
- C09AA03 lisinopril;
- C09BX02 perindopril and bisoprolol;
- N06AB05 paroxetine.

The patient has a condition of polypharmacy (5 or more 4th level ATC codes during the first semester 2018) and was treated with multiple antihypertensive and cardioprotective agents, suggesting a history of hypertension and likely heart failure. Lansoprazole was prescribed for gastrointestinal protection, while colecalciferol indicated prevention or treatment of osteoporosis. The use of paroxetine pointed to a coexisting depressive disorder, consistent with a complex profile of multimorbidity in advanced age.

The patient was exposed to PIMs, pDDIs, FRIDs, ACB score and SL score prioritized according to one pDDIs high risk scenario (**Table 74**). The dual exposure C03CA (loop diuretics, e.g. furosemide) and C03DA (potassium-sparing agents, e.g. spironolactone, canrenone) increases the risk of serious adverse events such as

electrolyte disturbances, renal dysfunction, hypotension, and arrhythmias, particularly in elderly, multimorbid patients.

Table 74– High risk scenarios of Patient B

Scenario	OR	Lower	Upper
pDDIs	1.50	1.43	1.57
Currently exposed to: C03CA and C03DA Currently not exposed to: B01AB and J01MA	2.16	1.94	2.42

The concomitant use of a loop diuretic (C03CA) and a potassium-sparing diuretic (C03DA) suggests treatment for heart failure or resistant hypertension. While this combination may be clinically justified to optimize volume control and maintain potassium balance, it carries a heightened risk of electrolyte disturbances- particularly hyperkalemia and renal impairment- especially in the elderly. Careful monitoring of serum potassium, sodium, and renal function is therefore essential, alongside regular assessment of blood pressure, hydration status, and overall tolerability. If the clinical indication is not compelling, dose adjustment or discontinuation of one agent should be considered to minimize adverse outcomes. Moreover, the concurrent use of paroxetine with diuretics may further elevate the risk of hyponatremia. Long-term PPI therapy carries potential adverse effects on magnesium and vitamin B12 status, and bone health. Given the extent of polypharmacy, careful monitoring of renal function, electrolytes, blood pressure, and heart rate is warranted, alongside periodic reassessment of ongoing therapy to optimize safety and efficacy.

To optimise the patient’s pharmacotherapy and reduce the risk of adverse events, a number of interventions are advised:

- assess the lansoprazole indications, if any;
- consider switch from paroxetine to safer SSRI (Selective Serotonin Reuptake Inhibitors) in the older subject ;
- review dual antiplatelet therapy (acetylsalicylic acid and clopidogrel): beyond 12 months in older patients should be carefully reassessed unless stented;
- assess the potential duplication effect of lisinopril, premdinopril, bisoprolol, nebivolol, in combo or not, considering the clinical condition of the patient;

- evaluate mental status and falls risk after assessment of SSRI, ACE-inhibitors and beta-blockers.

Patient C

The third patient, the patient C, was 86-year-old man. Between 2014 and 2018, he was hospitalized for:

- broncopneumonia, unspecified– 2014;
- congestive heart failure, unspecified (heart failure, unspecified) – 2015;
- chronic respiratory failure – in 2015, 2016, 2017 and 2018.

During the first semester of 2018, the dispensed drugs were:

- A02BC02 pantoprazole;
- A07AA02 nystatin;
- A11CC05 colecalciferol;
- B01AC06 acetylsalicylic acid;
- B03BB01 folic acid;
- C03CA01 furosemide;
- C08CA01 amlodipine;
- C10AA05 atorvastatin;
- J01MA12 levofloxacin;
- J01MA17 prulifloxacin;
- M01AE01 ibuprofen;
- M04AA03 febuxostat;
- R03AL03 vilanterol and umeclidinium bromide.

The patient has a condition of severe polypharmacy (10 or more 4th level ATC codes during the first semester 2018) and was treated with antihypertensive and cardioprotective agents, suggesting a history of hypertension, and as shown by hospitalization in 2015 (congestive heart failure, unspecified), likely heart failure. Pantoprazole was prescribed for gastrointestinal protection, while colecalciferol indicated prevention or treatment of osteoporosis. The use of febuxostat pointed to a coexisting gout, consistent with a complex profile of multimorbidity in advanced age.

Two diverse fluoroquinolones were also prescribed, in line with the recurrent chronic respiratory failure.

The patient was exposed to pDDs and SL score and prioritized according to two pDDIs high risk scenarios (**Table 75**). The exposure to C03CA (loop diuretics, e.g. furosemide), to A02BC (PPI) and to J01MA (fluoroquinolones) increases the risk of serious adverse events such as electrolyte disturbances, renal dysfunction, hypotension, and arrhythmias, particularly in elderly, multimorbid patients.

Table 75– *High risk scenarios of Patient C*

Scenario	OR	Lower	Upper
pDDIs	1.50	1.43	1.57
Currently exposed to: C03CA, A02BC and J01MA Currently not exposed to: B01AB and C03DA	2.12	1.80	2.49
Currently exposed to: C03CA Currently not exposed to: B01AB and C03DA	1.61	1.52	1.71

Co-exposure to C03CA (furosemide), A02BC (pantoprazole) and J01MA (fluoroquinolones) carries significant risks of electrolyte imbalance, arrhythmias and drug–drug interactions. The use of two fluoroquinolones in close sequence, with only a short interval between them, further increases the risk of serious adverse events (QT prolongation, tendinopathy, neurotoxicity). Long-term pantoprazole therapy, if not periodically reassessed, may lead to an increased risk of fractures, intestinal and respiratory infections, hypomagnesemia and vitamin B12 deficiency. The absence of exposure to B01AB and C03DA respectively prevents hemorrhagic risk and hyperkalemia.

To optimise the patient’s pharmacotherapy and reduce the risk of adverse events, a number of interventions are advised:

- assess the pantoprazole long-term indication and duration, considering the co-exposure to acetylsalicylic acid;
- reconsider febuxostat use (gout management) in a patient with heart failure, given the increased cardiovascular risk;
- evaluate the clinical benefit of atorvastatin in an 86-year-old subject, especially if only for primary prevention;

- review the concomitant prescriptions of acetylsalicylic acid and ibuprofen: in the elderly, this combination significantly increases bleeding and renal risk, despite PPI co-therapy;
- assess the use of fluoroquinolones (levofloxacin and prulifloxacin): although prescribed for chronic respiratory failure, fluoroquinolones are generally discouraged in older patients due to increased risk of tendinopathy, QT prolongation, and neuropsychiatric effects;
- laboratory tests:
 - monitor renal and liver function, electrolytes (Na^+ , K^+) and uric acid;
 - complete blood count for anemia and infection monitoring;
 - clinical follow-up: blood pressure, fluid status, falls risk, signs of bleeding or myopathy.

CHAPTER 7

Discussion and conclusion

In recent decades, national healthcare systems have encountered a range of common challenges. These include rising healthcare costs, together with an aging population accompanied by an increase in chronic diseases and multiple health conditions, which drive higher demand for medical services. These issues have also led to a rise in serious medication-related problems, such as misuse, underuse, overuse of drugs, unnecessary prescriptions, and polypharmacy particularly among elderly patients ³⁸. While awareness of these problems is reportedly increasing ^{74 100}, Italy still lacks formal policy frameworks or regulatory guidelines to address medications review. This study offers novel and practical insights into how real-world healthcare administrative data can be leveraged to identify patient subgroups most likely to benefit from further clinical attention- critical aspects for enhancing patient outcomes and optimizing healthcare resources within the health system. Rather than providing direct guidance on deprescribing or defining standardized medication review procedures, the approach focuses on supporting clinicians by highlighting those patients whose pharmacological profiles indicate greater vulnerability and therefore merit more in-depth evaluation. By doing so, the provided approach addresses a central challenge of contemporary healthcare: prioritizing limited time and resources toward patients at higher risk, thus creating the conditions for more targeted, equitable, and effective interventions.

7.1 Inappropriateness measurement

Our findings reveal a widespread prevalence of potentially harmful prescribing among older subjects, representing a significant challenge for clinicians and policymakers alike. The application of explicit criteria to large administrative databases allowed not only to assess prescribing quality, but also served as a foundation for developing a practical tool for patient prioritization to be applied in clinical practice.

7.1.1 Prevalence of PIIIs

Our findings firmly place the level of PIM exposure in the older population of Lombardy within the range reported across Italy and Europe, confirming it as a significant and common public health issue. In our cohort, the annual prevalence of

PIMs ranged from 34.1% to 40.0%. This finding is highly consistent with the international landscape, as a recent comprehensive meta-analysis by Tian et al., 2023 reported a pooled global prevalence of PIM use among older outpatients of 36.7%¹²² or Drusch et al., 2023, found that 39.6% of older adults were exposed to at least one PIM¹²³. Our results are also in close alignment with other large-scale studies conducted using Italian administrative data. For instance, Galimberti et al., 2022 reported a PIM prevalence in the Piedmont region (north-west Italy) of 33.2% in 2018¹²⁴. Other epidemiological findings in older adults in different settings of care show wide range, up to 84.5% in acute care¹²⁵, up to 62.4% in non institutionalized seniors in the community¹²⁶, or up to 70% in older residents in nursing homes¹²⁷. According to two systematic reviews, the weighted prevalence of the use of PIMs in Europe was 22.6% in community-dwelling older adults and 49.0% in institutionalized older people, with substantial variations across study sites and countries^{128 129}. Two larger studies using claims databases examined the trends of the use of PIMs in the outpatient setting in Ireland and in the USA (1997–2012), and showed that the prevalence of PIMs slightly increased in Ireland from 32.6% to 37.3% and decreased in the USA from 64.9% to 56.6%¹³⁰. Further context can be drawn from studies using different methodologies within the same northern geographical area. A cross-sectional study by Piccoliori et al., 2021¹³¹ in northern Italy found a higher PIM prevalence of 45.9%, likely attributable both to the older age cut-off (≥ 75 years) of their study population and to the application of the 2012 Beers criteria, as demonstrated by Pasina et al., 2014 finding that the prevalence of PIMs in the same cohort of hospitalized elderly patients was higher with the updated 2012 version compare to the 2003 version of Beers criteria¹³². This highlights that the constant updating and revision of these tools is another critical factor influencing prevalence estimates.

Our study highlights the substantial burden of pDDIs. In our cohort, the annual prevalence of patients exposed to at least one clinically significant pDDI (major or contraindicated) ranged from 23.7% to 24.6%. This finding positions pDDIs exposure as a common clinical issue, though comparing prevalence rates across the literature is complex due to methodological heterogeneity. A recent systematic review and meta-analysis of 31 studies involving more than 17 million community-dwelling individuals aged ≥ 65 years reports a pooled DDI prevalence of 28.8% (95% CI 19.3, 40.7), with

significant heterogeneity ($p < 0.10$; $I^2 = 100\%$; $\tau^2 = 2.13$) largely explained by the different DDI identification methods used across studies¹³³. Goretn et al, 2017 found that 33% of older populations prescriptions have DDIs¹³⁴. Therefore, despite the challenges in making direct comparisons, our results confirm that a substantial portion of older adults in Italy is exposed to potentially harmful drug combinations linked to DDIs, reinforcing the need for clinical vigilance and medication review.

Similarly, FRIDs exposure affected 22.2% to 24.2% of patients. However, for this PII we only considered drugs with effects on the CNS. This approach limited the application of the full FRIDs list, which also includes blood pressure-lowering medications known to be highly prevalent in older adults, with some studies reporting exposure rates of up to 60-70%¹³⁵. Focusing specifically on CNS-active drug classes in the FRIDs list (Appendix 3), our findings are consistent with the literature. The risk of fracture has been specifically linked to opioids, dopaminergic agents, anxiolytics, antidepressants, and hypnotics/sedatives, for which a study in a cohort of adults aged 75 and older reported prevalences of 20%, 2%, 16%, 16%, and 25%, respectively¹³⁶. These rates are comparable to those observed in our analysis, where antidepressants (13.0% to 14.0%) and opioids (9.3% to 10.1%, most of them not in the reimbursement process of the Italian healthcare system) were the most prevalent FRIDs in the matched cohort. Another important consideration for this PII is the clinical outcome. Many studies in the literature link FRIDs exposure to specific endpoints such as fall-related hospital admissions (e.g. hip fractures) that are indeed common causes of injury and hospitalization in the older population^{137 138}. In the general population, however, hospitalizations for falls remain relatively infrequent, even though around 30% of adults over 65 experience at least one fall each year, and not every fall leads to a fracture or to a hospital admission coded as fall-related^{139 140}. As a result, the high FRIDs prevalence rates reported in the literature—often between 20% and over 60%—mostly come from studies conducted in cohorts of patients already hospitalized for falls, where the risk is inherently higher¹⁴¹. This focus on high-risk populations, while informative, likely underestimates the broader clinical impact of FRIDs exposure in the general older population.

The annual prevalence of TDs in our cohort was consistent, ranging from 8.8% to 9.1%. This finding is remarkably similar to that of the Italian REPOSI study, which

reported a TD prevalence of 7.8% among hospitalized elderly patients, also defining duplication at the 4th ATC level ⁷⁴. The consistency of these figures, despite the different care settings (community-dwelling vs. hospitalized), suggests that TDs represent a persistent prescribing issue in the Italian older population. Prevalence rates in the literature vary based on the population and definition used. For instance, Erhan et al, 2024, found among Swedish older adults with ordinary prescriptions that the prevalence of potential duplications increased from 5.2% to 10.6% in 65- to 79-year-olds and from 7.0% to 11.7% in those aged ≥ 80 years ⁷⁵. It is methodologically relevant to note that this study defined duplications using the 5th level of the ATC classification, a more specific approach than the one adopted in our analysis. Numerous studies have evaluated the prevalence and predictors of therapeutic duplications across a variety of healthcare settings and populations. These include large, nationwide register-based studies of community-dwelling older adults ⁷⁵, multi-center analyses of hospitalized patient cohorts ⁷⁴, and cross-sectional studies in high-risk populations such as nursing home residents ¹⁴². This body of research confirms that therapeutic duplications are a common and measurable indicator of prescribing quality, although prevalence estimates vary depending on the methodology and population studied. The approach for identifying TDs varies significantly across studies, which directly impacts reported prevalence rates. A recent systematic review highlights this heterogeneity, showing that definitions range from the concurrent use of two identical active substances to the co-prescription of two different drugs belonging to the same therapeutic or pharmacological class ¹⁴³.

Regarding the cumulative burden indicators, the annual prevalence of ACB score ≥ 3 (7.0% to 7.9%) was substantially lower than SL score ≥ 3 (36.5% to 38.4%). Focusing on the Anticholinergic Burden, our prevalence for a high ACB score was consistent with Grossi et al. that found from other large-scale studies on older populations a prevalence of potent anticholinergic of 9.9% in 2008-11 ¹⁴⁴; accordingly Jazbar et al., 2024, proportion of individuals with a clinically ACB score ≥ 3 remained relatively stable over a decade (10.9 % in 2009 and 10.9 % in 2019) ¹⁴⁵. As expected, our estimate is considerably lower than those reported from specific, higher-risk clinical cohorts. Higher-risk cohorts, such as hospitalized patients or those with cancer, are characterized by a greater burden of disease, multimorbidity, and frailty compared to

the general community-dwelling population analyzed in our study. Symptoms that are common in these vulnerable groups - such as nausea, insomnia, urinary incontinence, or behavioral disturbances - are frequently managed with medications that carry a significant anticholinergic load. For example, while in a general hospitalized geriatric population the prevalence of ACB score ≥ 3 is 13.98%¹⁴⁶, the prevalence escalates to 25.8% in patients hospitalized for falls¹⁴⁷, and becomes even more pronounced in patients with cancer, where reaches 46.2%^{148 149}. The choice of measurement tool and the definition of exposure are critical determinants of prevalence estimates. One study comparing various scales highlighted that the prevalence of any anticholinergic use could be as high as 51% when using the ACB scale, underscoring the difference between measuring any exposure versus a clinically significant threshold¹⁵⁰. The importance of using context-specific tools is also noted in the literature; for example, a study employing a Japanese ACB scale reported a prevalence of over 4.0% for a score ≥ 3 ¹⁴⁹. These comparisons demonstrate that our findings are well-situated within the existing evidence when the nature of our population and the specific operational definitions used are taken into account.

Conversely, the prevalence of SL score in our cohort ranged 36.5% to 38.4% underscores the widespread use of medications with sedative properties. Our findings indicate a higher prevalence than that reported in several other European studies on older populations. For instance, Jazbar et al. found rates of 14.5 % in 2009 and 13.2 % in 2019¹⁴⁵ while Taipale et al. found 23% of participants total sedative load of ≥ 2 ¹⁵¹ and 8% among community-dwelling people aged 75 years or older with sedative load of 3 or greater¹⁵². The prevalence of a high sedative burden appears to increase in specific, more vulnerable clinical populations. For example, in a cohort of patients with mild-to-moderate Alzheimer's Disease, 22.2% had an SL score of ≥ 3 ¹⁵³. Similarly, in care homes for people with dementia, the prevalence of a high sedative burden ranged from 12.2% to 14.3%¹⁵⁴. Considering the Drug Burden Index (DBI), which combines both sedative and anticholinergic effects; one study found that 8.7% of older adults had a DBI greater than 1¹⁵⁵, or Drusch et al., 2023 found that 7.3% of the older population had concomitant use of three or more central nervous system-active drugs, moreover Peklar et al. found among community-dwelling population aged ≥ 65 years that only the 19% of the participants took sedative drugs¹⁵⁶.

7.1.2 Key medications

A detailed analysis across the study reveals that a specific subset of medications and therapeutic classes is disproportionately involved in PII selection among older adults. These recurring drugs not only have a high prevalence, but also frequently act as significant risk modifiers in the prioritization algorithm, highlighting key areas for clinical vigilance.

Psychotropic medications represent a major category of concern. Antidepressants, particularly SSRIs (ATC class N06AB) and other agents (N06AX), were consistent among the most frequent PIM, they were the main culprits behind FRIDs and ranked first among the drugs that conferred a high ACB score. In line with our results, the cross-sectional study by Piccoliori et al., 2021, in northern Italy identified benzodiazepines/hypnotics (19.7%) as the most common ¹³¹.

It has been reported that older adults are 7 to 18 times more likely to use psychotropic drugs than their middle-aged counterparts and more than 50% of older patients on antidepressant were also prescribed a concurrent psychotropic drug ¹⁵⁷. The most common combinations observed were an antidepressant with either a benzodiazepine or an antipsychotic and this pattern of high use and co-prescribing is not an isolated phenomenon but a recognized international trend, with similar findings reported in both the United States and various European countries ¹⁵⁷. This highlights a major clinical challenge: balancing the need to treat depression and anxiety against the well-documented risks associated with these agents. In Italy, antidepressants accounted for approximately 3.4% of the total drug consumption in 2023, with selective serotonin reuptake inhibitors (SSRIs) representing around 70% of that usage. The prevalence of antidepressant use was estimated at 7% of the population, increasing with age and more common among women ¹²¹. The use of these drugs in older adults is often considered inappropriate due to their unfavorable risk–benefit profile in this population. Elderly patients are particularly vulnerable to adverse drug reactions, including hyponatremia, falls, fractures, cardiac arrhythmias, and cognitive impairment, which may outweigh the potential benefits of treatment ¹⁵⁸. Age-related pharmacokinetic and pharmacodynamic changes, polypharmacy, and multimorbidity further increase the likelihood of harmful interactions and reduced tolerability ¹⁵⁹.

Moreover, evidence suggests that the efficacy of antidepressants in late-life depression may be modest, while non-pharmacological interventions such as psychotherapy and psychosocial support can be equally or more effective with fewer risks. Therefore, antidepressant use in the elderly should be carefully evaluated, regularly reassessed, and often limited to specific clinical situations where safer alternatives are not viable.

It is also noteworthy that there was a high prevalence of PPIs among inappropriate medications, a finding widely reported in the literature and often linked to prolonged, unreviewed prescriptions. In our study, PPIs were among the primary medications involved in PIMs, pDDIs, TDs, and those that conferred a high SL score. PPIs are among the most frequently prescribed drugs all over the world, as well as in Italy, and their use is particularly widespread in the elderly. They represent the first therapeutic category in class A purchased by citizens, with the highest expenditure, with a prevalence of use of about 30% among subjects aged 65 years or more, reaching 60% among older patients ¹²¹. While these medications are highly effective and generally safe when employed for short-term therapy, their long-term use raises significant concerns. Data from both hospitals and long-term care facilities show that a large proportion of older adults receive PPIs without a clear clinical indication ^{121 160}. Several factors explain this trend. In clinical practice, once PPIs are started- often during hospitalization for stress ulcer prophylaxis or to reduce gastrointestinal risk in polytreated patients- they tend to be continued indefinitely without systematic reassessment. The combination of multiple comorbidities, frequent polypharmacy, and the perceived safety of these drugs reinforces prescribing inertia. Clinicians may underestimate the potential harms of long-term PPI therapy, while patients often regard them as harmless pills for “digestion,” leading to chronic, unchecked use ¹⁶¹. Although geriatricians are increasingly aware of the risks, prescription behaviors remain variable and the lack of consistent deprescribing strategies contributes to the persistence of inappropriate use ¹⁶². The consequences of such prescribing patterns are far from trivial. In older adults, chronic PPI therapy has been associated with micronutrient deficiencies, including vitamin B12, magnesium, calcium, and iron. These deficiencies may contribute to anemia, neuromuscular symptoms, and bone fragility, thereby increasing the risk of falls and fractures. In addition, prolonged use has been linked to a higher incidence of *Clostridioides difficile* infections, community-acquired

pneumonia, kidney dysfunction, and possibly even increased mortality in frail patients after hospital discharge ¹⁶³. These outcomes highlight the importance of careful patient selection and regular reevaluation of therapy, especially since in most cases PPIs should not be continued beyond eight weeks unless strongly indicated. The interaction between pantoprazole (A02BC02) and levothyroxine (H03AA01) was also a key combination among pDDIs in our study. It is often problematic because it can compromise the effectiveness of thyroid replacement therapy. Levothyroxine needs an acidic gastric environment to dissolve properly and be absorbed in the intestine. When pantoprazole is prescribed, it raises gastric pH by suppressing acid production, and this change makes levothyroxine less available to the body. As a result, patients who take both drugs may experience a reduction in the therapeutic effect of levothyroxine, with fluctuations in thyroid hormone levels and even a return of hypothyroid symptoms despite being on a stable dose ¹⁶⁴. This interaction is particularly relevant in older adults, since even small alterations in absorption can have meaningful clinical consequences.

7.1.3 Significance of PIIIs

The six PIIIs reflect the distinct clinical rationale underpinning each selection. A key feature of this multi-indicator approach is the intentional and clinically meaningful overlap between the lists, which should not be interpreted as redundancy. For instance, certain antidepressants and opioids are included in the PIMs and FRIDs lists and also contribute to the ACB and SL scores. The reason for flagging a patient, however, is conceptually different for each indicator. In the case of PIMs and FRIDs, the risk is considered inherent to the drug itself in an older adult where a single dispensation is sufficient to flag a patient because the medication's use should be generally discouraged or carefully administered in this population. This is distinct from the rationale for the ACB and SL scores, where the risk arises from the cumulative pharmacological burden. A patient is only flagged as high-risk if the total score from all concurrently prescribed medications exceeds a validated clinical threshold (a score ≥ 3 for at least three consecutive days in our study). Therefore, a patient prescribed a single low-dose antidepressant might be flagged for a PIM but not for a high ACB or

SL score if their total burden remains below the threshold. Furthermore, a drug with both sedative and anticholinergic properties does not necessarily contribute equally to both scores, reflecting the different pharmacodynamic effects being measured.

ACB and SL scores assess dimension of prescribing quality, but unlike indicators based on drug risk, also pDDIs and TDs assess the management of multiple medication regimen. These indicators, therefore, can capture risks arising from a lack of review and coordination in a patient's overall therapeutic plan.

The SL model encompasses a much broader array of medications whose primary or secondary effect is sedation, including many common cardiovascular drugs, whereas the ACB list is more focused on agents with specific anticholinergic receptor activity. This also explains the different frequency patterns observed at the patient level. These burdens translate into a range of specific and often debilitating adverse clinical outcomes that lead to the non-specific endpoint of all-cause hospitalization. A high ACB, for instance, is robustly linked to adverse central nervous system effects, including an increased risk of delirium, accelerated cognitive decline, and even a higher long-term incidence of dementia. It also causes a variety of peripheral effects such as dry mouth, constipation, and urinary retention, which can severely impact a patient's quality of life and lead to further complications. Similarly, a high SL directly impairs psychomotor function, translating into a significantly increased risk of dizziness, falls, and subsequent fracture.

7.2 Risk associated with inappropriate prescription

7.2.1 Comparison in literature

A core objective of this thesis was not only to identify patterns of inappropriate prescribing but also to validate their association with all-cause hospitalization. This outcome was selected as the primary outcome (within 90 days from the index date) due to its clinical relevance, reliability of measurement, and suitability for use in administrative healthcare databases. With this approach, we showed that patients with inappropriate medications have a 40-60% higher risk to be hospitalized. The magnitude of these associations is clinically significant and aligns with existing

evidence in the literature, which links inappropriate prescribing to increased hospitalizations and morbidity in the older population.

For example, Endres et al, 2016, found PIM use as a significant risk factor for hospitalization, with an OR of 1.378 (95% CI 1.349–1.407) compared to use of PIM alternatives¹⁶⁵. Moreover, the systematic review and meta analysis of Mekonnen et al, 2021, found that potentially inappropriate prescriptions were associated with 91%, 60% and 26% increased risk of adverse drug event-related hospital admissions (OR 1.91, 95% CI 1.21-3.01), functional decline (OR 1.60, 95% CI 1.28-2.01), and adverse drug reactions and adverse drug events (OR 1.26, 95% CI 1.11-1.43)¹⁶⁶. Another study using the PRISCUS list, showed that PIM use compared to PIM alternatives was associated with an increased risk of all-cause hospitalization in the 180 days following individual index date (OR = 1.38; 95% CI: 1.35–1.41)¹⁶⁵.

7.2.2 Role of age and sex

A particularly noteworthy finding from the stratified analyses was the modulation of risk by age. For nearly all indicators, the association with hospitalization risk was strongest in the "younger-old" population (65–74 years) and progressively attenuated in the older age groups (≥ 85 years). A study by Francisco et al., 2019, found that younger adults (45-64 years) with 3 or more conditions had more hospitalized days compared to patients the ≥ 75 age group with 3 or more conditions¹⁶⁷. Hoffmann et al, 2016, confirmed differences among ages in nursing home residents' hospitalizations. In this systematic review 18 studies assessed the influence of age and found an increasing proportion of admissions with increasing age, but several studies also found decreasing hospitalisations above the age of about 80-85 years¹⁶⁸. Moreover, three studies addressed the influence of age in their discussion and concluded that lower hospitalisation rates in older age reflect a less aggressive treatment approach^{169 170 171}. This apparent decrease in risk among the "oldest-old" should not be misinterpreted as a sign that these medications are safer in this group. Rather, it likely reflects a "competing risk" phenomenon: in very elderly individuals, the baseline risk of hospitalization due to frailty, multimorbidity, and functional decline is so high that it can mask the additional impact of a single inappropriate prescription. In other words,

hospitalization in this age bracket is a complex, multifactorial event where the contribution of a single PII becomes harder to isolate from the "background noise" of other clinical conditions. This is compounded by a potential "survivor bias," whereby individuals who reach a very advanced age may possess greater biological resilience, making them less susceptible to adverse drug events. This phenomenon in the oldest-old could be also partly explained by concepts such as "successful aging"¹⁷² and "healthy ageing"¹⁷³, which describe a subgroup of individuals who maintain high functional and cognitive capacity despite their advanced age. Nevertheless, it is crucial to acknowledge that there is a recognized lack of research exploring the harms of polypharmacy specifically in the "very old"¹⁷⁴.

Significant differences between sexes also emerged for certain indicators. For example, the risk associated with FRIDs, pDDIs, TDs, ACB score and SL score was found to be higher in males, whereas for PIMs, it was slightly higher in females. In general, the risk of receiving a potential inappropriate medications has been described as higher in female older patients^{175 176 177 178 179}, but the evidence across studies is not always consistent. Bradley et al, 2012¹⁸⁰, found that men are at increased odds of receiving a potentially inappropriate prescription in the UK. Other studies have found that women's increased odds of receiving a potentially inappropriate prescription is moderated when patient age, health status or income are taken into account^{181 176 182}. Moreover, Barè et al, 2023, found that the risk of frailty in older women may be between 34% and 144% higher than in older men and older women have a different multimorbidity profile (when considering chronic conditions and geriatric syndromes) from older men and more frailty dependence in all age strata¹⁸³. The systematic review and meta-analysis by Rodrigues et al, 2022, found that positive association between multimorbidity and hospitalization regardless of gender and without significant variation between men and women¹⁸⁴. They observed that, despite the prevalence of multimorbidity in older adults was higher in women^{185,186}, the occurrence of hospitalization due to multimorbidity was not different between genders. Moreover, a previous systematic review on the association between use and costs of health services among older people with multiple chronic conditions did not find an association between gender and hospitalization¹⁸⁷. On the other hand, Hoffmann et al, 2016, confirmed differences among sex in hospitalizations. In this systematic review of 20

studies, hospitalisations were more often in male (OR between 1.22 and 1.67) ¹⁶⁸. Despite the fact that females had a higher PIM prevalence, also Haerig et al, 2023, found that male patients had a higher risk of hospitalization than female patients ¹⁸⁸.

7.2.3 Inappropriate prescriptions and other outcomes

Unlike our study, which focused on all-cause hospitalizations, other investigations have explored the association between inappropriate prescribing and different clinical outcomes. In particular, prior research has examined endpoints such as disease-specific hospital admissions, adverse drug events, functional decline, or mortality, thereby providing complementary perspectives on the potential consequences of inappropriate medication use.

Some studies evaluated the risk of hospital readmission associated with inappropriate prescription, but this association has not always been confirmed as significant. As an example, a systematic review of eighteen studies found that only five studies demonstrated a positive association between inappropriate prescribing and hospital readmissions. This was reinforced by the results of a meta-analysis, where the pooled, adjusted estimates showed no statistically significant increase in the risk of readmission for patients with inappropriate prescriptions (adjusted OR 1.11, 95% CI 0.76–1.63). Interestingly, the same meta-analysis did find a modest but significant association in the crude, unadjusted data. The disappearance of this effect after adjusting for confounders suggests that the apparent risk of readmission may be more attributable to the underlying clinical complexity of the patients rather than the inappropriate prescription itself ¹⁸⁹.

Beyond hospitalization, mortality represents another critical clinical outcome often investigated in relation to inappropriate prescribing. However, again, the evidence for this association is less consistent than for other outcomes. For instance, a systematic review that analyzed nineteen studies found that only four reported a significantly increased risk of mortality linked to potentially inappropriate prescriptions ¹⁸⁹. The overall pooled results from this meta-analysis confirmed this ambiguity, showing no

statistically significant association between general inappropriate prescribing exposure and mortality (OR 1.10, 95% CI 0.90–1.36).

Another critical outcome directly linked to inappropriate prescribing is the occurrence of ADEs and medication-related hospitalizations. Prescription of PIMs was not associated with a higher risk of adverse clinical events, re-hospitalization and all-cause mortality at 3-month follow-up ¹³². Conversely, the meta-analysis of Bloomfield et al, 2020, demonstrated that older adults with inappropriate prescriptions have 26% higher odds of experiencing an ADR or ADE ¹⁸⁹. Furthermore, this risk appears to follow a dose-response relationship, with the same review finding that each additional inappropriate prescription was associated with a 73% increase in the odds of an adverse event, although this finding was associated with significant statistical heterogeneity. In more severe cases, these events led to medication-related hospitalizations. Pooled analyses estimated that potentially inappropriate prescriptions are a causal or contributory factor in approximately 11% of such admissions. The statistical association is also strong, with one meta-analysis showing that inappropriate prescription use was linked to 91% increased odds of an ADE-related hospitalization. However, it is worth noting that this association may be sensitive to the specific studies included in the analysis. Collectively, this body of evidence confirms that the PIIIs used in our thesis are strongly linked to a measurable burden of patient harm, ranging from general adverse reactions to severe events requiring hospital care ¹⁸⁹. However, it is important to note the methodological sensitivity of these findings. The same meta-analysis showed that the significant association between inappropriate prescriptions and ADE-related admissions could be lost in a sensitivity analysis, depending on which specific potentially inappropriate tools were included in the pooled estimate. This suggests that while there is a clear and strong link between inappropriate prescribing and adverse events, the magnitude of this association can vary based on the specific criteria used to define inappropriateness ¹⁸⁹.

Outcomes related to falls are far more extensively documented in the literature, with studies consistently demonstrating an increased risk associated with several indicators of inappropriate prescribing. Specifically, criteria such as the Beers list (referring to specific medications), high anticholinergic and sedative burden, and the use of FRIDs have all been robustly linked to a heightened risk of falls. This link is further supported

by evidence showing a dose-response relationship, where the risk of falling increases with the number of inappropriate medications. For example, one study found that patients taking two EU(7)-PIM listed drugs had a significantly higher risk of falling (AOR, 95% CI 1.01–1.88), which increased further for those taking three PIMs (AOR, 1.64, 95% CI 1.20–2.24) compared to patients taking none ¹⁹⁰. Furthermore, the risk is not uniform across all types of PIMs but is particularly associated with specific drug classes. Research has confirmed that the use of PIMs acting on the central nervous system is a significant predictor of falls (OR 1.81, 95% CI 1.05–3.10) ¹⁹¹.

7.3 The prioritization and the clinical impact

While the risk assessment phase confirmed that PIIIs are associated with adverse clinical outcomes, it also highlighted a crucial challenge: the high prevalence of these indicators in the older population. A primary care physician is faced with a number of patients exposed to potentially inappropriate prescriptions that is simply too large to allow for a thorough medication review for each individual, given the constraints of time and resources. This realization underscores the need for tools that enable a targeted selection of the highest-risk patients.

Addressing this issue is the central goal of this thesis, pursued through the development of a data-driven prioritization algorithm. By leveraging machine learning techniques, specifically CITs, we moved beyond simply estimating the average risk associated with a PII. The objective was to identify specific high-risk "scenarios" or patient profiles- that is, combinations of demographic and clinical characteristics (such as comorbidities or co-treatments) that significantly amplify the danger associated with PII exposure.

7.3.1 Key scenarios

This approach led to the identification of 59 distinct risk scenarios across the six PIIIs. By combining this scenario-based stratification with an approach based on cumulative burden (prioritizing patients with multiple concurrent PIIIs), the algorithm proved

capable of isolating a smaller, manageable, and significantly higher-risk fraction of patients who warrant priority clinical attention.

A deeper analysis of the 59 high-risk scenarios reveals that the algorithm consistently identified clinically coherent patient profiles where the risk of hospitalization is amplified by plausible pharmacological and pathophysiological interactions. Certain medications and conditions frequently appeared as nodes in the decision trees, acting as consistent risk modifiers. For instance, exposure to anticoagulants/antithrombotics (B01AB), diuretics (especially loop diuretics, C03CA, and aldosterone antagonists, C03DA), and fluoroquinolone antibiotics (J01MA) were recurrent predictors of high risk. The presence of anticoagulants often signals a patient with significant underlying cardiovascular morbidity (e.g., atrial fibrillation, post-myocardial infarction), who is inherently more vulnerable. When such a patient is exposed to a PII, their limited physiological reserve makes them more susceptible to destabilization. Similarly, the use of multiple diuretics may indicate complex conditions like heart failure or resistant hypertension, where fluid and electrolyte balance can be impaired by an additional pharmacological insult.

Furthermore, the scenarios frequently captured the hazardous intersection of chronic vulnerability and acute events. A common high-risk profile involved a patient with a stable but complex chronic regimen who then receives a short-term prescription for an acute issue, such as a course of fluoroquinolones for an infection (J01MA) or glucocorticoids (H02AB) for an inflammatory exacerbation. For example, one of the highest-risk scenarios for PIMs (OR 3.32 95% CI: 2.27–4.86) involved patients with prior and current exposure to heparin-group drugs (B01AB) and aldosterone antagonists (C03DA), but no concurrent fluoroquinolones. This profile suggests a patient with severe cardiovascular and possibly renal disease, for whom any additional inappropriate medication can easily tip the balance toward hospitalization. This demonstrates the algorithm's ability to learn and flag situations where an acute prescription, layered on top of a complex chronic therapy regimen, acts as the "final straw" that leads to an adverse outcome. By identifying these specific, clinically plausible scenarios, the algorithm provides a far more nuanced and actionable assessment of risk than a simple list-based alert system could ever achieve.

Furthermore, our model flagged the dangerous combination of corticosteroids (H02AB) and fluoroquinolones (J01MA), known to synergistically increase the risk of tendon rupture, especially in older adults. These examples confirm that our pDDI indicator effectively identifies patients exposed to tangible, preventable harm.

Cardiovascular and related Medications emerged as a critical theme, not just as standalone issues but as powerful "risk amplifiers". Diuretics, especially loop diuretics (C03CA) and aldosterone antagonists (C03DA), and anticoagulants/antithrombotics from the heparin group (B01AB) were consistently identified by the decision tree models as key predictors that significantly increase the risk of hospitalization across nearly all PII categories.

Collectively, the frequent appearance of these specific drug classes underscores the intersection between the management of common geriatric syndromes- such as cardiovascular disease, depression, and pain- and the heightened potential for iatrogenic harm.

7.3.2 Similar tools

While clinical decision support tools have been developed to aid prescribing specialists, their overall effectiveness in improving care for older people remains uncertain, as highlighted in a recent systematic review ¹⁹².

A significant portion of these existing tools focuses on flagging the presence of explicit indicators, but fewer are designed specifically for risk-based patient prioritization. Indeed, explicit criteria themselves can be seen as a primary tool for patient selection (and they can lead to 40-60% of selected patients), and a growing part of research is moving toward promoting their large-scale application using electronic health data. This is an evolving field, with a number of studies demonstrating the feasibility of using electronic health data to build more sophisticated prediction models. For instance, Tang et al. developed a machine learning model to predict the risk of potentially inappropriate medications, though it was implemented in a selected cohort of older stroke patients ¹⁹³. Their study evaluated PIM use, as defined by the 2023 American Geriatrics Society Beers Criteria, in a cohort of 1,252 discharged stroke

patients. The resulting prediction model was then tested on an independent external validation cohort of 240 patients, where it demonstrated good accuracy and generalizability, offering a solid basis for guiding clinical treatment in this specific high-risk population. Similarly, another predictive tool used machine learning to identify important risk factors, including the drug burden index (DBI), for predicting 30-day emergency hospitalization in older adults¹⁹⁴. This study, conducted on a large cohort of 86,670 older adults from the UK Biobank, validated the DBI, mobility, history of fractures and falls, hazardous alcohol drinking, and smoking as important variables for predicting 30-day emergency hospitalization in older adults.

A particularly relevant example is the work of Abdo et al¹⁹⁵, who recently developed a machine learning-based tool to prioritize patients at high risk of medication errors upon hospital admission, with the aim of directing medication reconciliation efforts¹⁹⁶. Much like our project, their approach leverages data from electronic health records and uses ML models to identify the patients most in need of clinical intervention. To achieve this, data were collected from the electronic health records of patients at Reims University Hospital who underwent medication reconciliation between 2017 and 2023. Using this information, data from 7200 patients and 52 variables were used to train four machine learning-based models, which were then used to prioritize admitted patients according to their likelihood of being exposed to a medication error.

However, the successful implementation of such tools is not without its challenges, as highlighted by a study from Korup et al.¹⁹⁶. They compared two risk prioritization algorithms, Medicine Risk Score (MERIS), developed in Denmark, consists of three items: reduced renal function, number of drugs, and number of drugs with different categories of risk of harm and risk of interaction; and modified Assessment of Risk Tool (mART), developed in New Zealand, consists of 38 items divided into five categories: patient profile, patient encounter, clinical profile - patients with chronic diseases, high-risk medications and laboratory values. with the real-world 1,133 admitted patient selection process carried out by clinical pharmacists in an emergency department. The study found a significant disagreement between the risk stratification provided by the algorithms and the pharmacists' choices, which were often guided by "non-clinical ground rules" such as the length of stay or administrative needs. This demonstrates that even clinically algorithms can fail to align with established

workflows, underscoring the critical need for tools that are not only statistically robust but also pragmatically designed to integrate into and support clinical judgment. This is precisely the gap our project aims to fill, by providing a tool that serves as a support to, rather than a replacement for, the clinician's expertise.

7.4 Practical implications

The ultimate goal of this research was to develop a tool with tangible utility in a real-world primary care setting, where time and resources are limited. For GPs in Italy, who are responsible for the care of large patient panels (about 1,500), the challenge of managing polypharmacy in an aging population (estimate 24% of the patient panels) is a daily reality. Faced with hundreds of older patients on multiple medications, the task of conducting systematic medication reviews for everyone is daunting and impractical. Our algorithm addresses this barrier by translating a population-level problem into a manageable clinical workload. The key practical output of this work is a focused, prioritized list of patients. By applying our proposed strategy- which combines automatically flagging patients with a cumulative burden of three or more PIIIs with the scenario-based stratification for those with fewer PIIIs- a GP with a typical panel of 1,500 patients would be prompted to review an estimated 49-52 older individuals. This figure, derived from applying the algorithm to a large cohort, transforms an overwhelming requirement into a focused, achievable clinical quality improvement activity. Clinicians are provided with a much smaller number of individuals most likely to have potential harm.

Crucially, the algorithm is designed to function as a clinical decision support tool, not a clinical replacement. Its purpose is not to automate deprescribing but to maximise the efficiency of the clinician's judgment by flagging patients who warrant a closer look. The final decision to modify, continue, or deprescribe a therapy remains firmly in the hands of the clinician, who can integrate the alert with their comprehensive knowledge of the patient's history, preferences, and clinical status.

This approach is situated within a broader movement in healthcare toward using data-driven and machine learning models to develop predictive tools for patient

prioritization. Similar tools have demonstrated considerable success in other clinical areas. For instance, a clinical decision support tool for prioritizing patients on surgical waiting lists showed a high level of accuracy in predicting post-operative mortality and complications, demonstrating its value in optimizing the use of limited resources¹⁹⁷. In a context more similar to our own, Peterson et al. developed ML models to predict the risk of acute care use (e.g., emergency visits and hospitalizations) for patients starting chemotherapy. Their models also showed promising accuracy, reinforcing the potential for these approaches to enable targeted, preventative interventions that can improve outcomes and reduce costs¹⁹⁸.

However, the development and implementation of these tools also highlight significant challenges and future directions. The same study by Peterson et al, 2021, revealed that their model had limitations in its predictive accuracy for black and medicaid patients, underscoring the critical need to address potential inequities and biases in AI-driven healthcare¹⁹⁸. Furthermore, as discussed in a recent narrative review, the future of clinical decision support lies in integrating diverse data sources, including administrative data like ours, electronic health records (EHRs), and even patient-generated health data (PGHD). While AI can help manage and interpret these vast and heterogeneous datasets, significant challenges remain concerning data standards, interoperability, and security¹⁹⁹.

Therefore, while our algorithm represents a robust and practical step forward using readily available administrative data, it also serves as a foundation for future work. The long-term vision is the development of more sophisticated, integrated systems that can provide an even more holistic assessment of patient risk, ultimately transforming the delivery of clinical care.

The principles underpinning our algorithm are reflective of this broader trend toward AI-driven triage and patient prioritization. A recent comprehensive review on this topic by Da Costa et al, 2025, identified substantial benefits of such systems, including improved patient prioritization, reduced wait times, and optimized resource allocation, all of which align with the objectives of our tool²⁰⁰.

However, the same review also highlights the significant challenges that must be addressed for successful real-world implementation. Key barriers include clinician

trust in the algorithm's recommendations, the risk of algorithmic bias perpetuating health disparities, and the need for clear ethical frameworks regarding data privacy and accountability²⁰⁰. Crucially, the review emphasizes the importance of a "Human-in-the-Loop" framework, where the AI serves as a decision-support tool rather than an autonomous decision-maker. This aligns perfectly with the design philosophy of our algorithm, which is intended to augment, not replace, the clinician's expertise by providing a focused, data-driven starting point for their holistic patient evaluation. While the review by Da Costa et al focuses on the Emergency Department, these core principles - leveraging AI for efficiency while ensuring clinician oversight and addressing ethical challenges - are directly translatable to the primary care context of our work.

7.5 Strengths and limitations

This thesis introduces a pragmatic, data-driven algorithm specifically designed to prioritize older adults for medication review, addressing a real and urgent gap in clinical practice. Like any study based on real-world data, this thesis project has both significant strengths and inherent limitations that are crucial to acknowledge for a proper interpretation of the findings.

Among the primary strengths, is the use of large administrative health databases, which allowed for the analysis of a population cohort of over 640,000 older adults in the Lombardy Region. This approach ensures high statistical power and, importantly, considerable external validity, as the data reflect daily clinical practice in an unselected setting, unlike in controlled clinical trials. Another key methodological strength lies in the process of selecting and adapting the PIs. Rather than rigidly applying international criteria, a systematic effort was made to integrate and, above all, contextualize them. Six prescribing inappropriateness indicators (PIMs, pDDIs, FRIDs, TDs, ACB, SL) were selected, covering a broad spectrum of inappropriate prescribing patterns validated internationally capturing different dimensions of harm from intrinsic drug risk to cumulative burden and regimen complexity. From a statistical perspective, the rigor of the analysis is supported by the adoption of a matched-set cohort design and the use of HDPS for adjustment, a technique that

controls for a vast number of potential confounders. Finally, the use of CITs for developing the algorithm represents an innovative and statistically robust machine learning approach that overcomes the selection bias of traditional methods and enhances the interpretability of the results.

The most significant strength, however, lies in the study's practical relevance: the project does not merely identify a problem but proposes a pragmatic solution, translating the results into a manageable workload and offering a tool that fills a recognized gap in the Italian healthcare context making the model interpretable and clinically actionable. The algorithm can be applied to large populations, and its rules can be integrated into clinical decision support systems, enhancing feasibility in real-world healthcare settings. The model is simple enough to support general practitioners, who often face time constraints, by highlighting a manageable number of high-priority patients (≈ 49 –52 per GP).

Nevertheless, it is essential to consider the limitations. The main constraint stems from the nature of the administrative data used. While complete and accurate for reimbursed services, these databases lack granular clinical information such as diagnoses, laboratory results, vital signs clinical notes, or patient preferences. Consequently, a medication flagged as potentially inappropriate might have a valid clinical justification that is not visible in the data. Furthermore, the data record drugs that were dispensed, not necessarily consumed by the patient. Another gap is the absence of data on OTC or non-reimbursed drugs, the use of which could lead to an underestimation of the risk. Moreover, although the study is large, the data originate from four LHUs in a single Italian region, Lombardy; therefore, the generalizability of the findings to other regions with different healthcare organizations or to international contexts should be approached with caution.

From a methodological perspective, the reliance on explicit criteria is inherently rigid and cannot capture the complexity of every individual clinical case, potentially leading to false positives, as some medications deemed inappropriate may still be necessary or optimal in individual cases. The chosen outcome, all-cause hospitalization, while robust, is non-specific and does not allow for the establishment of a direct causal link between the prescription and the event. Finally, it must be highlighted that the

algorithm has not yet been tested prospectively in clinical practice, so its real-world performance and clinician acceptance remain uncertain. Although adapted to the Italian healthcare system, some findings may not translate directly to countries with different drug markets, healthcare structures, or prescribing patterns.

Despite these limitations, this study provides a solid and innovative framework for improving medication safety in the older population, laying the groundwork for future prospective validation and the integration of similar tools into clinical practice.

7.6 Conclusions and future perspectives

This thesis has addressed one of the most pressing challenges facing modern healthcare systems: the management of polypharmacy and prescribing in a growing older population. Stemming from the observation that, within the Italian context, GPs lack practical tools to systematically identify patients at the highest risk of adverse drug events, this project has developed and validated an innovative prioritization algorithm based on real-world data. By leveraging the richness of administrative health databases, our work demonstrates that it is possible to move from a general awareness of the problem to targeted, sustainable clinical action.

The main contribution of this research lies in the creation of a pragmatic framework that, starting from validated inappropriateness indicators, does not merely estimate an average hospitalization risk but stratifies this risk through the identification of specific high-vulnerability clinical scenarios. The algorithm proved capable of effective discrimination, reducing a large population of exposed patients to a smaller and significantly higher-risk subgroup. This allows for the transformation of a huge task for the individual clinician into a manageable activity, quantifiable as approximately 48-52 patients warranting a priority medication review assessment per GP. In this way, the proposed tool is designed to support, not replace, clinical judgment, optimizing the allocation of limited primary care resources toward interventions with the greatest potential impact.

Looking ahead, this work opens up several important future perspectives. The most immediate and crucial next step is the prospective validation of the algorithm. It will

be essential to conduct field studies to assess whether the application of this tool in daily clinical practice actually translates into a reduction of adverse outcomes, such as hospitalizations, and to test its usability and acceptability among physicians. In the long term, the true potential of this framework can be realized through its integration into digital clinical decision support systems, such as the electronic health record software used by general practitioners. An integrated system could provide real-time alerts, flagging high-risk patients at the point of prescribing or during a routine visit, thereby facilitating timely intervention.

Furthermore, the algorithm itself could be refined. Future iterations could include other clinically relevant outcomes beyond all-cause hospitalization, such as specific adverse events, falls, or mortality, and could be enriched with more granular data should they become available. Finally, this study also has implications at the health policy level, highlighting the strategic value of administrative data not just for reimbursement purposes, but as a fundamental resource for monitoring the quality of care and for implementing continuous improvement programs in primary care. In summary, this thesis lays the foundation for a more proactive and evidence-based approach to medication safety, with the ultimate goal of improving the quality of life and health of the older population.

Beyond prospective validation within the initial study setting, a significant future direction involves assessing the generalizability and adaptability of this prioritization framework to different healthcare contexts, both nationally and internationally. Within Italy, the standardized nature of administrative data collection across regions offers a prime opportunity to validate the algorithm's performance and transportability. Applying the same methodology to data from other Italian regions would provide invaluable insights into the consistency of the identified high-risk scenarios and could help tailor the tool to account for regional variations in prescribing cultures and population health profiles.

On an international level, testing this methodological framework in countries with similarly robust, population-wide health registries, such as Denmark, represents a particularly compelling avenue for future research. This endeavor would require more than a direct application of the Lombardy-derived algorithm; it would necessitate a

careful adaptation of the PII lists to the local drug formulary and a potential recalibration of the model to account for differences in the healthcare system, clinical guidelines, and patient characteristics. However, such comparative research would not only test the robustness of our data-driven approach but could also lead to the development of country-specific prioritization tools, advancing a more tailored and evidence-based approach to medication safety on a global scale.

CHAPTER 8

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APPENDIX

Appendix 1 – PIMs list

Pharmacological subgroups		ATC code or class selected		Inappropriateness selection
A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	A02BC	Proton pump inhibitors	Use for > 8 weeks with no concomitant use B01AC56, B01AC06, M01A, N02BA, H02.
		A02BD	Combinations for eradication of <i>Helicobacter pylori</i>	Use for > 14 days
A03B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	A03BA01	Belladonna alkaloids, tertiary amines	Dispensation
		A03BA03	Belladonna alkaloids, tertiary amines	Dispensation
A03C	ANTISPASMODICS IN COMBINATION WITH PSYCHOLEPTICS	A03CB03	Belladonna derivatives in combination with psycholeptics	Dispensation
		A03CB31	Belladonna derivatives in combination with psycholeptics	Dispensation
A03F	PROPULSIVES	A03FA01	Propulsives	Dispensation
A04A	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	A04AD01	Other antiemetics	Dispensation
		A04AD51	Other antiemetics	Dispensation
A10A	INSULINS AND ANALOGUES	A10AB	Insulins and analogues for injection, fast-acting	Regimens containing only short- or rapid-acting insulin
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BB01	Sulfonylureas	Dispensation
		A10BB02	Sulfonylureas	Dispensation
		A10BB03	Sulfonylureas	Dispensation
		A10BB04	Sulfonylureas	Dispensation
		A10BB05	Sulfonylureas	Dispensation
		A10BB06	Sulfonylureas	Dispensation
		A10BB07	Sulfonylureas	Dispensation
		A10BB08	Sulfonylureas	Dispensation
		A10BB09	Sulfonylureas	Dispensation
		A10BB10	Sulfonylureas	Dispensation
		A10BB11	Sulfonylureas	Dispensation
		A10BB12	Sulfonylureas	Dispensation
		A10BB31	Sulfonylureas	Dispensation
		A10BD05	Combinations of oral blood glucose lowering drugs	Dispensation

		A10BD09	Combinations of oral blood glucose lowering drugs	Dispensation
		A10BD12	Combinations of oral blood glucose lowering drugs	Dispensation
		A10BD17	Combinations of oral blood glucose lowering drugs	Dispensation
		A10BF01	Alpha glucosidase inhibitors	Dispensation
		A10BG03	Thiazolidinediones	Dispensation
B01A	ANTITHROMBOTIC AGENTS	B01AA07	Vitamin K antagonists	Dispensation
		B01AC05	Platelet aggregation inhibitors excl. Heparin	Dispensation
		B01AC22	Platelet aggregation inhibitors excl. Heparin	Dispensation
B03A	IRON PREPARATIONS	B03AA07	Iron bivalent, oral preparations	Dispensation
C01A	CARDIAC GLYCOSIDES	C01AA05	Digitalis glycosides	Dispensation
C01B	ANTIARRHYTHMICS, CLASS I AND III	C01BA01	Antiarrhythmics, class Ia	Dispensation
		C01BA03	Antiarrhythmics, class Ia	Dispensation
		C01BA51	Antiarrhythmics, class Ia	Dispensation
		C01BA71	Antiarrhythmics, class Ia	Dispensation
		C01BC03	Antiarrhythmics, class Ic	Dispensation
		C01BC04	Antiarrhythmics, class Ic	Dispensation
		C01BD01	Antiarrhythmics, class III	Dispensation
		C01BD07	Antiarrhythmics, class III	Dispensation
C01E	OTHER CARDIAC PREPARATIONS	C01EB16	Other cardiac preparations	Dispensation
C02A	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	C02AB01	Methyldopa	Dispensation
		C02AB02	Methyldopa	Dispensation
		C02AC05	Imidazoline receptor agonists	Dispensation
C02L	ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LB01	Methyldopa and diuretics in combination	Dispensation
		C02LC01	Imidazoline receptor agonists in combination with diuretics	Dispensation
		C02LC05	Imidazoline receptor agonists in combination with diuretics	Dispensation
		C02LC51	Imidazoline receptor agonists in combination with diuretics	Dispensation
C03C	HIGH-CEILING DIURETICS	C03CA	Sulfonamides, plain	Dispensation
C07A	BETA BLOCKING AGENTS	C07AA07	Beta blocking agents, non-selective	Dispensation
		C07AG01	Alpha and beta blocking agents	Dispensation

C07B	BETA BLOCKING AGENTS AND THIAZIDES	C07BA07	Beta blocking agents, non-selective, and thiazides	Dispensation
		C07BG01	Alpha and beta blocking agents and thiazides	Dispensation
C07C	BETA BLOCKING AGENTS AND OTHER DIURETICS	C07CG01	Alpha and beta blocking agents and other diuretics	Dispensation
C08C	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	C08CA04	Dihydropyridine derivatives	Dispensation
	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	C08CA05	Dihydropyridine derivatives	Dispensation
G02C	OTHER GYNECOLOGICALS	G02CB03	Prolactine inhibitors	Dispensation
G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	G03AA	Progestogens and estrogens, fixed combinations	Dispensation
		G03AA04	Progestogens and estrogens, fixed combinations	Dispensation
		G03AB	Progestogens and estrogens, sequential preparations	Dispensation
		G03AB01	Progestogens and estrogens, sequential preparations	Dispensation
		G03AC	Progestogens	Dispensation
		G03AC05	Progestogens	Dispensation
G03B	ANDROGENS	G03B	Androgens	Dispensation
		G03BA02	3-oxoandrostens (4) derivatives	Dispensation
		G03BA03	3-oxoandrostens (4) derivatives	Dispensation
G03C	ESTROGENS	G03C	Estrogens	Dispensation
G03D	PROGESTOGENS	G03DB02	Pregnadien derivatives	Dispensation
G03E	ANDROGENS AND FEMALE SEX HORMONES IN COMBINATION	G03EK01	Androgens and female sex hormones in combination with other drugs	Dispensation
G03F	PROGESTOGENS AND ESTROGENS IN COMBINATION	G03F	Androgens and female sex hormones in combination	Dispensation
		G03FA08	Progestogens and estrogens, fixed combinations	Dispensation
		G03FB04	Progestogens and estrogens, sequential preparations	Dispensation

G04B	UROLOGICALS	G04BD04	Drugs for urinary and frequency incontinence	Dispensation
		G04BD07	Drugs for urinary and frequency incontinence	Dispensation
		G04BD08	Drugs for urinary and frequency incontinence	Dispensation
G04C	DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	G04CA	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA01	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA02	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA03	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA04	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA51	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA52	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA53	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA54	Alpha-adrenoreceptor antagonists	Dispensation
		G04CA55	Alpha-adrenoreceptor antagonists	Dispensation
H01A	ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES	H01AC01	Somatropin and somatropin agonists	Dispensation
H01B	POSTERIOR PITUITARY LOBE HORMONES	H01BA02	Vasopressin and analogues	Dispensation
J01X	OTHER ANTIBACTERIALS	J01XE01	Nitrofurantoin derivatives	Dispensation
		J01XE51	Nitrofurantoin derivatives	Dispensation
L02A	HORMONES AND RELATED AGENTS	L02AB01	Progestogens	Dispensation
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STERIODS	M01A	Antiinflammatory and antirheumatic products, non-steroids	Use for > 3 months
M03B	MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	M03BA02	Carbamic acid esters	Dispensation
		M03BA03	Carbamic acid esters	Dispensation
		M03BA52	Carbamic acid esters	Dispensation
		M03BA53	Carbamic acid esters	Dispensation

		M03BA72	Carbamic acid esters	Dispensation
		M03BA73	Carbamic acid esters	Dispensation
		M03BB03	Oxazol, thiazine, and triazine derivatives	Dispensation
		M03BB53	Oxazol, thiazine, and triazine derivatives	Dispensation
		M03BB73	Oxazol, thiazine, and triazine derivatives	Dispensation
		M03BC01	Ethers, chemically close to antihistamines	Dispensation
		M03BC51	Ethers, chemically close to antihistamines	Dispensation
		M03BX01	Other centrally acting agents	Dispensation
		M03BX08	Other centrally acting agents	Dispensation
N02A	OPIOIDS	N02AD01	Benzomorphan derivatives	Dispensation
		N02AD51	Benzomorphan derivatives	Dispensation
		N02AJ02	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ07	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ08	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ13	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ14	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ15	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ16	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ18	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ19	Opioids in combination with non-opioid analgesics	Dispensation
		N02AJ23	Opioids in combination with non-opioid analgesics	Dispensation
		N02AX02	Other opioids	Dispensation

N02B	OTHER ANALGESICS AND ANTIPYRETICS	N02BA01	Salicylic acid and derivatives	Dispensation
		N02BA11	Salicylic acid and derivatives	Dispensation
		N02BA51	Salicylic acid and derivatives	Dispensation
		N02BA71	Salicylic acid and derivatives	Dispensation
N02C	ANTIMIGRAINE PREPARATIONS	N02CC51	Selective serotonin (5HT1) agonists	Dispensation
N03A	ANTIEPILEPTICS	N03AA02	Barbiturates and derivatives	Dispensation
		N03AB02	Hydantoin derivatives	Dispensation
		N03AB52	Hydantoin derivatives	Dispensation
		N03AE	Benzodiazepine derivatives	Dispensation
		N03AE01	Benzodiazepine derivatives	Dispensation
		N03AX11	Other antiepileptics	Dispensation
N04A	ANTI-PARKINSON DRUGS	N04AA01	Tertiary amines	Dispensation
		N04AA02	Tertiary amines	Dispensation
		N04AB02	Ethers chemically close to antihistamines	Dispensation
N04B	DOPAMINERGIC AGENTS	N04BC01	Dopamine agonists	Dispensation
		N04BC06	Dopamine agonists	Dispensation
N05A	ANTIPSYCHOTICS	N05AA01	Phenothiazines with aliphatic side-chain	Dispensation
		N05AA02	Phenothiazines with aliphatic side-chain	Dispensation
		N05AB02	Phenothiazines with piperazine structure	Dispensation
		N05AB06	Phenothiazines with piperazine structure	Dispensation
		N05AC01	Phenothiazines with piperidine structure	Dispensation
		N05AD01	Butyrophenone derivatives	Dispensation
		N05AE04	Indole derivatives	Dispensation
		N05AE05	Indole derivatives	Dispensation
		N05AF05	Thioxanthene derivatives	Dispensation
		N05AG02	Diphenylbutylpiperidine derivatives	Dispensation
		N05AH02	Diazepines, oxazepines, thiazepines and oxepines	Dispensation
		N05AH03	Diazepines, oxazepines, thiazepines and oxepines	Dispensation
		N05AH04	Diazepines, oxazepines, thiazepines and oxepines	Dispensation
		N05AH05	Diazepines, oxazepines, thiazepines and oxepines	Dispensation

		N05AH06	Diazepines, oxazepines, thiazepines and oxepines	Dispensation
		N05AH53	Diazepines, oxazepines, thiazepines and oxepines	Dispensation
		N05AX08	Other antipsychotics	Dispensation
		N05AX12	Other antipsychotics	Dispensation
		N05AX13	Other antipsychotics	Dispensation
		N05AX15	Other antipsychotics	Dispensation
		N05AX16	Other antipsychotics	Dispensation
N05B	ANXIOLYTICS	N05BA	Benzodiazepine derivatives	Dispensation
		N05BB01	Diphenylmethane derivatives	Dispensation
		N05BB51	Diphenylmethane derivatives	Dispensation
N05C	HYPNOTICS AND SEDATIVES	N05C	Hypnotics and sedatives	Dispensation
		N05CM05	Other hypnotics and sedatives	Dispensation
N06A	ANTIDEPRESSANTS	N06AA01	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA02	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA04	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA06	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA09	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA10	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA12	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AA17	Non-selective monoamine reuptake inhibitors	Dispensation
		N06AB	Selective serotonin reuptake inhibitors	Dispensation
		N06AB03	Selective serotonin reuptake inhibitors	Dispensation
		N06AB05	Selective serotonin reuptake inhibitors	Dispensation
		N06AB08	Selective serotonin reuptake inhibitors	Dispensation
		N06AF	Monoamine oxidase inhibitors, non-selective	Dispensation
		N06AG	Monoamine oxidase A inhibitors	Dispensation
		N06AX	Other antidepressants	Dispensation

		N06AX62	Other antidepressants	Dispensation
N06B	SYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS	N06BA04	Centrally acting sympathomimetics	Dispensation
N06C	PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION	N06CA01	Antidepressants in combination with psycholeptics	Dispensation
		N06CA03	Antidepressants in combination with psycholeptics	Dispensation
N07X	OTHER NERVOUS SYSTEM DRUGS	N07XX59	Other nervous system drugs	Dispensation
R05D	COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS	R05DA09	Opium alkaloids and derivatives	Dispensation
R06A	ANTIHISTAMINES FOR SYSTEMIC USE	R06AA02	Opium alkaloids and derivatives	Dispensation
		R06AA09	Opium alkaloids and derivatives	Dispensation
		R06AA11	Opium alkaloids and derivatives	Dispensation
		R06AA59	Opium alkaloids and derivatives	Dispensation
		R06AA61	Opium alkaloids and derivatives	Dispensation
		R06AB01	Substituted alkylamines	Dispensation
		R06AB02	Substituted alkylamines	Dispensation
		R06AB51	Substituted alkylamines	Dispensation
		R06AB52	Substituted alkylamines	Dispensation
		R06AD02	Phenothiazine derivatives	Dispensation
		R06AD07	Phenothiazine derivatives	Dispensation
		R06AD52	Phenothiazine derivatives	Dispensation
		R06AE06	Piperazine derivatives	Dispensation
		R06AX02	Other antihistamines for systemic use	Dispensation

		R06AX07	Other antihistamines for systemic use	Dispensation
		R06AX17	Other antihistamines for systemic use	Dispensation
		R06AX25	Other antihistamines for systemic use	Dispensation

Appendix 2 – pDDIs list

Clinical significance: C - Level of documentation: 1				
Clinical significance: C Level of documentation: 1	A02BC01-J02AC04,	A02BC05-L04AD02,	A02BX02-M05BA02,	A02BX02-M05BA04,
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	A05AA02-A02BX13,	A05AA02-V03AE04,	A10AB04-A10BG03,	A10AB05-A10BG03,
	A10AB06-A10BD09,	A10AD01-A10BD05,	A10AE04-A10BG03,	A10AE05-A10BG03,
	A10AE06-A10BD05,	A10BB01-L04AD01,	A10BB01-S01ED51,	A10BF01-N03AG01,
	B01AB01-N06AB03,	B01AF01-B01AC05,	B03AA07-N04BX02,	C01BA03-C07AB02,
	C01BD01-C10AA05,	C01BD01-L04AD02,	C02AC01-C07AB05,	C02AC01-C07AB07,
	C02AC01-N06AA06,	C02AC01-N06AA09,	C02AC01-N06AA10,	C03CA01-N05AN01,
	C03DA01-C09CA07,	C03DA01-C09DA04,	C07AA03-C02AC01,	C07AA05-N06AB03,
	C07AB02-C02AC01,	C08CA05-L02BA01,	C08DB01-C10AA05,	C08DB01-N02AB03,
	C09CA04-C03DA03,	C09CA07-C03DA03,	C10AC01-H03AA02,	D05BB02-G03FB12,
	G02CB03-J02AC02,	G03AA09-L04AD01,	G03DC02-L04AD01,	G03FA01-D05BB02,
	G03FA11-L04AD01,	H02AB02-B01AA03,	H02AB04-L04AD01,	H03BB02-N06AX12,
	J01EE01-A10BB12,	J01EE01-L04AD01,	J01FA01-L02BA01,	J01FA01-N02AB03,
	J01FA01-N06AX18,	J01FA09-J02AC02,	J01FA09-L04AA18,	J01FA15-N06DA02,
	J01MA02-N05AH03,	J01MA12-N06AB03,	J02AC01-N06AA10,	J02AC01-R03AK11,
	J02AC02-A02BC02,	J02AC02-A02BC03,	J02AC02-G04BE08,	J02AC02-N06DA02,
	J04AB02-N06AB04,	J04AB02-N06AB06,	J04AB02-N06AX11,	J04AM05-B01AA03,
	J04AM05-N03AG01,	L01BA01-J01AA02,	L04AD01-C01BC03,	L04AD01-D01BA01,
	L04AD01-J04AB04,	L04AD01-L02BA01,	L04AD02-J01FA07,	L04AX03-A02BD08,
	M01AB16-B01AC05,	M01AE03-L04AD01,	M04AA01-A02BX13,	N02AX02-N06AA02,
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	N02AX02-N06AB08,	N02AX02-N06AB10,	N02AX02-N06AX16,	N02BA01-C09CA01,
	N03AA02-A10BX02,	N03AA02-N06AX11,	N03AA02-N06AX18,	N03AA03-A11CC03,
	N03AB02-A04AA01,	N03AB02-A10BX02,	N03AB02-B01AA07,	N03AB02-C08DA01,
	N03AB02-C10AA01,	N03AB02-N03AX18,	N03AB02-N06AX05,	N03AB02-P01AB01,
	N03AB02-R03DC01,	N03AF01-A04AA01,	N03AF01-A10BX02,	N03AF01-B01AE07,
	N03AF01-C10AA05,	N03AF01-G04BD04,	N03AF01-N03AX18,	N03AF01-N06AX18,
	N03AF01-N07BC02,	N03AF01-P01AB01,	N03AF02-L04AD01,	N03AF02-N03AX18,
	N03AF02-N05AH04,	N03AX09-N03AX18,	N04BA02-N05AE04,	N04BC04-B01AA03,
	N05AH02-G03AA10,	N05AN01-C03BA11,	N05AN01-M01AE03,	N05AN01-N06AA10,

Clinical significance: C Level of documentation: 2	N05AN01-S01AD03,	N05AX08-N06AX12,	N06AA06-N06AB08,	N06AB03-N06AA06,
	N06AB05-N06AA06,	N06AX12-N06AA06,	N06AX12-N06AB03,	N06AX16-N06AA04,
	N06AX18-J01FA09,	N06AX18-J02AC02,	P01AB01-C01BD01,	R03AK07-J01FA09,
	R03DA04-C01BD01,	S01ED05-C02AC01,	V03AE02-L04AD01,	V03AE02-L04AD02.
	Clinical significance: C - Level of documentation: 2			
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	A03FA01-N06AB06,	A03FA01-N06AB08,	A03FA01-N06AX16,	A07EC02-B01AA03,
	A12AX -J01DD04,	B01AA03-D01BA01,	B01AA03-G03AA09,	B01AA03-N06AX21,
	B01AF01-B01AC06,	C01AA05-A12AX ,	C01AA05-P01BA02,	C01AA08-C10AC01,
	C01BA03-J01FA10,	C02AB01-N05AN01,	C02AC01-L04AD01,	C02AC01-S01ED01,
	C03CA01-A02BD08,	C03CA01-M01AC01,	C03CA01-N06AB03,	C03CA01-N06AB04,
	C03CA01-N06AB05,	C03CA01-N06AB06,	C03CA01-N06AB08,	C03CA01-N06AB10,
	C03CA01-V03AE02,	C03CA04-A02BD08,	C03CA04-B01AA03,	C07AB02-N06AB03,
	C08CA05-J02AC02,	C08CA05-L04AD02,	C08DA01-G04CB02,	C08DB01-L04AD02,
	C09DA03-N03AX11,	C09DA04-N06AB03,	C09DA06-N06AB05,	C09DA07-A02BD08,
	C09DA07-N06AB06,	C09DA08-N06AB08,	C09DX04-C10AA05,	C10AA01-M04AC01,
	C10AA03-M04AC01,	C10AA04-B01AA03,	C10AA04-M04AC01,	C10AA05-M04AC01,
	C10AB02-B01AA03,	C10AB02-M04AC01,	C10AB04-M04AC01,	C10AB05-L04AA18,
	D01BA02-C07AB02,	D01BA02-N05AX08,	D01BA02-N06AA09,	D01BA02-N06AA10,
	D06AX01-C10AA07,	D06AX01-C10BA02,	D07AC14-J04AB02,	G03CX01-D11AH01,
	G03XA01-A11CC03,	G03XA01-B01AA03,	G03XA01-L04AD01,	G04BE09-C02CA04,
	H02AB02-J04AB02,	H02AB02-N02BA01,	H02AB02-N03AA02,	H02AB07-J04AM02,
	H02AB09-J04AB02,	H03BB02-B01AA03,	J01CF05-B01AA03,	J01EE01-A10BB07,
	J01FA01-C10AA02,	J01FA01-L04AD02,	J01FA09-C10AA02,	J01FA09-L04AD02,
	J01FA09-N05AH04,	J01GB01-L04AD01,	J01MA02-N05AH05,	J01MA12-B01AA07,
	J01MA14-B01AA03,	J02AC01-C10AA05,	J02AC01-M01AH01,	J02AC01-N06AA09,
	J04AB02-N03AG01,	J04AB02-N06AA09,	J04AB02-N06AA10,	J04AB02-P01BA02,
	J04AM05-N03AF01,	J05AB01-J01DD04,	L01BB02-B01AA03,	L01BB02-B01AA07,
	L01CB01-B01AA03,	L02BA01-B01AA03,	L02BA01-B01AA07,	L02BB01-B01AA03,
	L04AA06-A02BC05,	L04AA06-N03AG01,	L04AA10-J02AC01,	L04AA13-B01AA03,
	L04AD01-A07AA02,	L04AD01-C01BD01,	L04AD01-C10BA02,	L04AD01-G03AA10,
	L04AD01-H01CB02,	L04AD01-J01GB06,	L04AD01-P01BA01,	L04AD02-C01EB18,
	L04AX01-B01AA03,	L04AX01-B01AA07,	L04AX03-J01CR02,	L04AX03-J01CR05,
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	M04AA01-L04AD01,	N01BB02-C07AA05,	N02BA01-H02AB08,	N02CC01-N02CA52,
	N03AA02-A11CC03,	N03AA02-A11CC04,	N03AA02-C01BC03,	N03AA02-H05BX02,
	N03AA02-J02AC02,	N03AA02-L04AD01,	N03AA02-L04AD02,	N03AA03-A11CC04,
	N03AB02-A11CC03,	N03AB02-A11CC04,	N03AB02-B01AA03,	N03AB02-B01AE07,
	N03AB02-C08DB01,	N03AB02-C10AA05,	N03AB02-H05BX02,	N03AB02-M04AA01,
	N03AB02-N03AD01,	N03AB02-N05AH02,	N03AB02-N06AB03,	N03AF01-A11CC03,
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Clinical significance: C Level of documentation: 3	N03AF01-H05BX02,	N03AF01-J01FA07,	N03AF01-J01FA09,	N03AF01-J02AC01,
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	N03AG01-N06AA04,	N03AG01-S01EC01,	N03AX09-N05AH04,	N04AA01-N03AG01,
	N05AA02-N06AA04,	N05AD01-N06AB08,	N05AH02-J04AB02,	N05AH02-N05AA02,
	N05AN01-C09CA06,	N05AN01-C09CA07,	N05AN01-C09DA01,	N05AN01-J01MA14,
	N05AN01-M01AC01,	N05AN01-N06AA09,	N05AN01-N06AB08,	N05AX12-N03AF02,
	N06AA02-C01BC03,	N06AB03-B01AC24,	N06AB03-C03EA14,	N06AB03-N06AA04,
	N06AB03-N06AA10,	N06AB04-B01AC24,	N06AB04-N05AL07,	N06AB05-B01AA03,
	N06AB05-B01AC24,	N06AB05-C03EA14,	N06AB05-N06AA04,	N06AB06-B01AA03,
	N06AB06-B01AC24,	N06AB06-C03EA14,	N06AB06-N03AX09,	N06AB08-C03EA14,
	N06AB10-B01AC24,	N06AX12-N06AA04,	N06DA02-N06AB03,	N06DA04-N06AB05,
	P01AB01-L04AD02,	R03AK07-C01BD01,	R03DA04-C01BC03,	R03DA04-J01FA09,
	R03DA04-J01MA12,	V03AE04-H03AA01.		
	Clinical significance: C - Level of documentation: 3			
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	A02BC02-J02AC04,	A02BC03-H03AA01,	A02BC03-L04AA06,	A02BC03-L04AD02,
	A02BC05-H03AA01,	A02BC05-J02AC04,	A02BX02-C10AA07,	A02BX02-H03AA01,
	A02BX02-L04AA06,	A02BX02-N03AX12,	A02BX02-N05AL07,	A02BX13-N05AL07,
	A02BX13-R06AX26,	A03FA01-N06AB03,	A05AA02-C08CA08,	A10BA02-C01EB18,
	A10BB01-C07AA05,	A10BB01-C07AG02,	A10BG03-B01AC04,	A10BX02-J01FA15,
	A12AA04-H03AA01,	A12AA20-B03AA07,	A12AX -J01AA02,	A12AX -J01MA12,
	A12AX -L04AA06,	A12AX -M05BA04,	B01AA03-B01AC04,	B01AA03-C01BC03,
	B01AA03-C01BD07,	B01AA03-H03AA01,	B01AA03-N03AF04,	B01AA03-R03DC01,
	B01AB04-M01AB15,	B01AC04-N02BA01,	B01AC06-B01AF02,	B01AC22-B01AA03,
	B01AC30-A02BC03,	B01AC30-R03DA04,	B01AE07-B01AC24,	B01AF01-B01AC04,
	B01AF01-C08DA01,	B01AF02-B01AC04,	B01AF03-C01BD01,	B01AF03-C01BD07,
	B01AF03-C08DA01,	B01AF03-L04AD01,	B01AF03-M01AE02,	B01AF03-N02BA01,
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	B03XA01-C09BA12,	C01AA05-A10BF01,	C01AA05-B01AC24,	C01AA05-C01BD01,
	C01AA05-C01BD07,	C01AA05-C01EB18,	C01AA05-C03DA01,	C01AA05-C03DA03,
	C01AA05-C08CA07,	C01AA05-C08DB01,	C01AA05-C09BB02,	C01AA05-J01FA15,
	C01AA05-J01GB03,	C01AA05-J02AC02,	C01AA05-J04AB02,	C01AA05-L04AD01,
	C01AA05-M01AB01,	C01AA08-C08DA01,	C01BA03-C07AB03,	C01CA24-C07AA05,
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	C02KX01-B01AA03,	C02KX01-G04BE03,	C03CA01-J01GB03,	C03CA01-M01AB15,
	C03CA01-M01AE03,	C03DA01-M01AB01,	C03EB01-M01AC05,	C07AA03-N06AB03,
	C07AA05-C02AC01,	C07AA05-N06AB08,	C07AA07-A02BX02,	C07AA07-A02BX13,
	C07AA07-C02AC01,	C07AA07-V03AE04,	C07AB02-C01BC03,	C07AB02-C01BD07,
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	C08DA01-C09XA52,	C08DA01-C10AA01,	C08DA01-L04AA10,	C08DA01-L04AA18,
	C08DA01-L04AD01,	C08DA01-N03AF01,	C08DA01-N05AX08,	C08DA01-N06AA02,

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C08DB01-C01BD07,	C08DB01-C01EB18,	C08DB01-C09DB02,	C08DB01-C10AA02,
C08DB01-G04CA01,	C08DB01-L04AA10,	C09AA01-B03XA01,	C09AA02-B03XA01,
C09AA03-B03XA01,	C09AA04-B03XA01,	C09AA05-B03XA01,	C09AA06-B03XA01,
C09AA09-B03XA01,	C09BA07-B03XA01,	C09BA08-B03XA01,	C09DA01-N06AB04,
C09DA04-C10AC01,	C09DA07-N06AB10,	C09DA08-N05AN01,	C10AA01-C01BD01,
C10AA01-N03AF04,	C10AA04-C08CA13,	C10AA07-A02BX13,	C10AA07-B01AA03,
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Clinical significance: D - Level of documentation: 4				
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	N02BA01-B01AA07,	N03AF01-G03AB06,	N03AF01-G03DB04,	N03AF01-G03FA11,
	N03AF01-N05AH04,	N03AF01-N05AX08,	N04BA02-A03FA01,	N06AB08-B01AA07,
	N06AB08-N06AA04,	N06AX16-N06AB05,	P01AB01-B01AA03.	

Appendix 3 – FRIDs list, Drugs that may increase the risk of falls

ATC	Drug Class
N02A	Opioids
N05A excl. Lito (N05AN01)	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A	Antidepressants

Appendix 4 – ACB score list

ATC	Substance	ACB score
A03BA01	atropine	3
A03CB03	atropine and psycholeptics	3
A04AD01	scopolamine (hyoscine/ hyoscamine)	3
A04AD51	scopolamine, combinations	3
D04AA10	promethazine	3
G04BD04	oxybutynin	3
G04BD07	tolterodine	3
G04BD08	solifenacin	3
G04CA53	tamsulosin and solifenacin	3
M03BC01	orphenadrine (citrate)	3
M03BC51	orphenadrine, combinations	3
N05AA01	chlorpromazine	3
N05AB06	trifluoperazine	3
N05AH02	clozapine	3
N05CM05	scopolamine	3
N06AA06	trimipramine	3
N06AA09	amitriptyline	3
N06AA10	nortriptyline	3
N06CA01	amitriptyline and psycholeptics	3
R06AD02	promethazine	3
R06AD52	promethazine, combinations	3
S01FA01	atropine	3
S01FA02	scopolamine	3
A08AA62	bupropion and naltrexone	2
C01BA03	disopyramide	2
N02AC04	dextropropoxyphene	2
N02AC52	methadone, combinations excl. psycholeptics	2
N02AC54	dextropropoxyphene, combinations excl. psycholeptics	2

N02AC74	dextropropoxyphene, combinations with psycholeptics	2
N02AE01	buprenorphine	2
N02AJ13	tramadol and paracetamol	2
N02AJ15	tramadol and other non-opioid analgesics	2
N02AJ16	tramadol and celecoxib	2
N02AX02	tramadol	2
N03AF02	oxcarbazepine	2
N03AX16	pregabalin	2
N05AG02	pimozide	2
N05AH03	olanzapine	2
N05AH04	quetiapine	2
N05AH53	olanzapine and samidorphan	2
N06AB05	paroxetine	2
N06AX12	bupropion	2
N06AX23	desvenlafaxine	2
N07BC01	buprenorphine	2
N07BC02	methadone	2
N07BC51	buprenorphine, combinations	2
R06AE07	cetirizine	2
R06AX26	fexofenadine	2
S01GX12	cetirizine	2
A01AC03	hydrocortisone	1
A02BA03	famotidine	1
A02BA53	famotidine, combinations	1
A02BC03	lansoprazole	1
A02BC53	lansoprazole, combinations	1
A02BD02	lansoprazole, tetracycline and metronidazole	1
A02BD03	lansoprazole, amoxicillin and metronidazole	1
A02BD07	lansoprazole, amoxicillin and clarithromycin	1
A02BD09	lansoprazole, clarithromycin and tinidazole	1
A02BD10	lansoprazole, amoxicillin and levofloxacin	1
A07AA09	vancomycin	1
A07DA52	morphine, combinations	1
A07EA02	hydrocortisone	1
A07EA03	prednisone	1
B01AA03	warfarin	1
C01AA05	digoxin	1
C01DA08	isosorbide mononitrate	1
C01DA14	isosorbide	1
C01DA58	isosorbide dinitrate	1
C03BA04	chlorthalidone/ chlortalidone	1

ATC	Substance	ACB score
C03BB04	chlortalidone and potassium	1
C03CA01	furosemide	1
C03CB01	furosemide and potassium	1
C03EA06	chlortalidone and potassium-sparing agents	1
C03EB01	furosemide and potassium-sparing agents	1
C05AA01	hydrocortisone	1
C05AE02	isosorbide dinitrate	1
C05AE03	diltiazem	1
C07AB02	metoprolol	1
C07AB03	atenolol	1
C07AB05	betaxolol	1
C07AB11	s-atenolol	1
C07BB02	metoprolol and thiazides	1
C07BB03	atenolol and thiazides	1
C07BB52	metoprolol and thiazides, combinations	1
C07CB02	metoprolol and other diuretics	1
C07CB03	atenolol and other diuretics	1
C07CB53	atenolol and other diuretics, combinations	1
C07DB01	atenolol, thiazides and other diuretics	1
C07FB02	metoprolol and felodipine	1
C07FB03	atenolol and nifedipine	1
C07FX03	metoprolol and acetylsalicylic acid	1
C07FX05	metoprolol and ivabradine	1
C08CA05	nifedipine	1
C08CA55	nifedipine, combinations	1
C08DB01	diltiazem	1
C08GA01	nifedipine and diuretics	1
C09AA01	captopril	1
C09AA10	trandolapril	1
C09BA01	captopril and diuretics	1
C09BB10	trandolapril and verapamil	1
C09DB02	metoprolol and amlodipine	1
C10BX03	amlodipine and celecoxib	1
D07AA01	methylprednisolone	1
D07AA02	hydrocortisone	1
D07AB02	hydrocortisone butyrate	1
D07AB11	hydrocortisone buteprate	1
D07AC14	methylprednisolone aceponate	1
D07AC16	hydrocortisone aceponate	1
D07BA04	hydrocortisone and antiseptics	1

ATC	Substance	ACB score
D07BB04	hydrocortisone butyrate and antiseptics	1
D07CA01	hydrocortisone and antibiotics	1
D07CA02	methylprednisolone and antibiotics	1
D07XA01	hydrocortisone	1
D10AA02	methylprednisolone	1
D10AF01	clindamycin	1
D10AF51	clindamycin, combinations	1
D11AX04	lithium succinate	1
G01AA10	clindamycin	1
G02CB01	bromocriptine	1
H02AB04	methylprednisolone	1
H02AB09	hydrocortisone	1
H02BX01	methylprednisolone, combinations	1
H05AB07	prednisone	1
J01CA01	ampicillin	1
J01CA51	ampicillin, combinations	1
J01CR01	ampicillin and beta-lactamase inhibitor	1
J01FF01	clindamycin	1
J01XA01	vancomycin	1
L01BC06	capecitabine	1
L01XX33	celecoxib	1
L04AD01	cyclosporine	1
L04AX01	azathioprine	1
M01AB15	ketorolac	1
M01AH01	celecoxib	1
M04AC01	colchicine	1
N01AH01	fentanyl	1
N01AH51	fentanyl, combinations	1
N02AA01	morphine	1
N02AA05	oxycodone	1
N02AA51	morphine, combinations	1
N02AA55	oxycodone and naloxone	1
N02AA56	oxycodone and naltrexone	1
N02AA59	codeine, combinations excl. psycholeptics	1
N02AA79	codeine, combinations with psycholeptics	1
N02AB03	fentanyl	1
N02AG01	morphine and antispasmodics	1
N02AJ06	codeine and paracetamol	1
N02AJ07	codeine and acetylsalicylic acid / aspirin	1
N02AJ08	codeine and ibuprofen	1

ATC	Substance	ACB score
N02AJ09	codeine and other non-opioid analgesics	1
N02AJ14	oxycodone and paracetamol	1
N02AJ17	oxycodone and paracetamol	1
N02AJ18	oxycodone and acetylsalicylic acid	1
N02AJ19	oxycodone and ibuprofen	1
N02CC01	sumatriptan	1
N02CC05	almotriptan	1
N03AA02	phenobarbital	1
N03AF01	carbamazepine	1
N03AF04	eslicarbazepine	1
N03AG01	valproic acid	1
N03AX15	zonisamide	1
N04BC01	bromocriptine	1
N04BC05	pramipexole	1
N04BD01	selegiline	1
N04BX02	entacapone	1
N05AE04	ziprasidone	1
N05AF05	zuclopenthixol	1
N05AH05	asenapine	1
N05AN01	lithium	1
N05AX08	risperidone	1
N05AX12	aripiprazole	1
N05CD08	midazolam	1
N06AB03	fluoxetine	1
N06AB06	sertraline	1
N06AB08	fluvoxamine	1
N06AB10	escitalopram	1
N06AX11	mirtazapine	1
N06AX16	venlafaxine	1
N06CA03	fluoxetine and psycholeptics	1
N07BB04	naltrexone	1
P01BC02	mefloquine	1
P01BF02	artesunate and mefloquine	1
R01AD60	hydrocortisone, combinations	1
R05DA04	codeine	1
R05DA05	opium alkaloids with morphine	1
R06AE09	levocetirizine	1
R06AX27	desloratadine	1
S01AA19	ampicillin	1
S01AA28	vancomycin	1

S01BA02	hydrocortisone	1
S01BB01	hydrocortisone and mydriatics	1
S01BC05	ketorolac	1
S01CA03	hydrocortisone and antiinfectives	1
S01CA08	methylprednisolone and antiinfectives	1
S01CB03	hydrocortisone	1
S01ED02	betaxolol	1
S01ED52	betaxolol, combinations	1
S01FB51	phenylephrine and ketorolac	1
S01XA18	cyclosporine	1
S02BA01	hydrocortisone	1
S03CA04	hydrocortisone and antiinfectives	1
S03CA07	methylprednisolone and antiinfectives	1

Appendix 5 – SL score list

ATC	Substance	SL score
A01AB17	metronidazole	1
A02BA03	famotidine	1
A02BA53	famotidine, combinations	1
A02BB01	misoprostol	1
A02BC01	omeprazole	1
A02BC02	pantoprazole	1
A02BC03	lansoprazole	1
A02BC04	rabeprazole	1
A02BC05	esomeprazole	1
A02BC53	lansoprazole, combinations	1
A02BC54	rabeprazole, combinations	1
A02BD01	omeprazole, amoxicillin and metronidazole	1
A02BD02	lansoprazole, tetracycline and metronidazole	1
A02BD03	lansoprazole, amoxicillin and metronidazole	1
A02BD04	pantoprazole, amoxicillin and clarithromycin	1
A02BD05	omeprazole, amoxicillin and clarithromycin	1
A02BD06	esomeprazole, amoxicillin and clarithromycin	1
A02BD07	lansoprazole, amoxicillin and clarithromycin	1
A02BD08	bismuth subcitrate, tetracycline and metronidazole	1
A02BD09	lansoprazole, clarithromycin and tinidazole	1
A02BD10	lansoprazole, amoxicillin and levofloxacin	1
A02BD11	pantoprazole, amoxicillin, clarithromycin and metronidazole	1
A02BD12	rabeprazole, amoxicillin and clarithromycin	1
A02BD13	rabeprazole, amoxicillin and metronidazole	1

ATC	Substance	SL score
A02BD15	vonoprazan, amoxicillin and metronidazole	1
A02BD16	omeprazole, amoxicillin and rifabutin	1
A03BA01	atropine	2
A03CB03	atropine and psycholeptics	2
A03FA01	metoclopramide	2
A04AD01	scopolamine (hyoscine/ hyoscamine)	2
A04AD51	scopolamine, combinations	2
A07DA52	morphine, combinations	2
A08AA51	phentermine and topiramate	2
A08AA62	bupropion and naltrexone	2
A10BB07	glipizide	1
A10BB12	glimepiride	1
A10BD04	glimepiride and rosiglitazone	1
A10BD06	glimepiride and pioglitazone	1
A10BH51	sitagliptin and simvastatin	1
A10BH52	gemigliptin and rosuvastatin	1
A11CC04	calcitriol	1
C01EB03	indomethacin	2
C01EB16	ibuprofen	1
C02AB	methyldopa	1
C02AB01	methyldopa (levorotatory)	1
C02AB02	methyldopa (racemic)	1
C02AC01	clonidine	1
C02CA04	doxazosin	1
C02LB	Methyldopa and diuretics in combination	1
C02LB01	methyldopa (levorotatory) and diuretics	1
C02LC01	clonidine and diuretics	1
C02LC51	clonidine and diuretics, combinations with other drugs	1
C03AA03	hydrochlorothiazide	1
C03AB03	hydrochlorothiazide and potassium	1
C03AX01	hydrochlorothiazide, combinations	1
C03BA08	metolazone	1
C03BA11	indapamide	1
C03CA01	furosemide	1
C03CA03	estradiol	1
C03CB01	furosemide and potassium	1
C03DA01	spironolactone	1
C03DA04	eplerenone	1
C03DB01	amiloride	1
C03EA01	hydrochlorothiazide and potassium-sparing agents	1
C03EA12	metolazone and potassium-sparing agents	1
C03EB01	furosemide and potassium-sparing agents	1

ATC	Substance	SL score
C05AE03	diltiazem	1
C07AA03	pindolol	1
C07AA07	sotalol	1
C07AB02	metoprolol	1
C07AB03	atenolol	1
C07AB05	betaxolol	1
C07AB07	bisoprolol	1
C07AB11	s-atenolol	1
C07AG01	labetalol	1
C07BA07	sotalol and thiazides	1
C07BB02	metoprolol and thiazides	1
C07BB03	atenolol and thiazides	1
C07BB07	bisoprolol and thiazides	1
C07BB52	metoprolol and thiazides, combinations	1
C07BG01	labetalol and thiazides	1
C07CA03	pindolol and other diuretics	1
C07CB02	metoprolol and other diuretics	1
C07CB03	atenolol and other diuretics	1
C07CB53	atenolol and other diuretics, combinations	1
C07CG01	labetalol and other diuretics	1
C07DB01	atenolol, thiazides and other diuretics	1
C07FB02	metoprolol and felodipine	1
C07FB03	atenolol and nifedipine	1
C07FB07	atorvastatin, amlodipine and ramipril	1
C07FB12	losartan and amlodipine	1
C07FB13	lisinopril and amlodipine	1
C07FX05	metoprolol and ivabradine	1
C08CA01	amlodipine	1
C08CA02	felodipine	1
C08CA03	isradipine	1
C08CA04	nicardipine	1
C08CA05	nifedipine	1
C08CA51	aliskiren and amlodipine	1
C08CA55	nifedipine, combinations	1
C08DA01	verapamil	1
C08DA51	verapamil, combinations	1
C08DB01	diltiazem	1
C08GA01	nifedipine and diuretics	1
C08GA02	aliskiren, amlodipine and hydrochlorothiazide	1
C09AA01	captopril	1
C09AA02	enalapril	1
C09AA04	perindopril	1

ATC	Substance	SL score
C09AA05	ramipril	1
C09AA06	quinapril	1
C09AA07	benazepril	1
C09AA09	fosinopril	1
C09AA10	trandolapril	1
C09AA13	moexipril	1
C09BA01	captopril and diuretics	1
C09BA02	enalapril and diuretics	1
C09BA03	lisinopril and diuretics	1
C09BA04	perindopril and diuretics	1
C09BA05	ramipril and diuretics	1
C09BA06	quinapril and diuretics	1
C09BA07	benazepril and diuretics	1
C09BA09	fosinopril and diuretics	1
C09BA13	moexipril and diuretics	1
C09BB02	enalapril and lercanidipine	1
C09BB03	irbesartan and amlodipine	1
C09BB04	olmesartan medoxomil and amlodipine	1
C09BB05	ramipril and felodipine	1
C09BB06	enalapril and nitrendipine	1
C09BB07	perindopril, amlodipine and indapamide	1
C09BB10	trandolapril and verapamil	1
C09BB13	atorvastatin, amlodipine and perindopril	1
C09BX01	olmesartan medoxomil, amlodipine and hydrochlorothiazide	1
C09BX02	perindopril and bisoprolol	1
C09BX03	perindopril, bisoprolol and amlodipine	1
C09BX04	perindopril and amlodipine	1
C09BX05	ramipril and bisoprolol	1
C09CA02	eprosartan	1
C09CA03	valsartan	1
C09CA04	irbesartan	1
C09CA07	telmisartan	1
C09CA08	olmesartan medoxomil	1
C09DA02	eprosartan and diuretics	1
C09DA03	valsartan and diuretics	1
C09DA04	irbesartan and diuretics	1
C09DA07	telmisartan and diuretics	1
C09DA08	olmesartan medoxomil and diuretics	1
C09DB01	telmisartan and amlodipine	1
C09DB02	metoprolol and amlodipine	1
C09DB04	rosuvastatin, amlodipine and lisinopril	1
C09DB05	candesartan, amlodipine and hydrochlorothiazide	1

ATC	Substance	SL score
C09DB06	irbesartan, amlodipine and hydrochlorothiazide	1
C09DB07	benazepril and amlodipine	1
C09DB08	valsartan and lercanidipine	1
C09DB09	candesartan and amlodipine	1
C09DX01	telmisartan, amlodipine and hydrochlorothiazide	1
C09DX02	valsartan and aliskiren	1
C09DX03	nebivolol and amlodipine	1
C09DX04	valsartan and sacubitril	1
C09DX05	valsartan and nebivolol	1
C09DX06	bisoprolol and amlodipine	1
C09DX07	fimasartan and amlodipine	1
C09DX08	rosuvastatin, amlodipine and perindopril	1
C09XA52	aliskiren and hydrochlorothiazide	1
C09XA54	aliskiren, amlodipine and hydrochlorothiazide	1
C10AA01	simvastatin	1
C10AA03	pravastatin	1
C10AA04	fluvastatin	1
C10AA05	atorvastatin	1
C10AA07	rosuvastatin	1
C10AB05	fenofibrate	1
C10AB11	choline fenofibrate	1
C10BA02	simvastatin and ezetimibe	1
C10BA03	pravastatin and fenofibrate	1
C10BA04	simvastatin and fenofibrate	1
C10BA05	atorvastatin and ezetimibe	1
C10BA06	rosuvastatin and ezetimibe	1
C10BA07	rosuvastatin and omega-3 fatty acids	1
C10BA08	atorvastatin and omega-3 fatty acids	1
C10BA09	rosuvastatin and fenofibrate	1
C10BA11	pravastatin and ezetimibe	1
C10BA12	pravastatin, ezetimibe and fenofibrate	1
C10BX03	amlodipine and celecoxib	1
C10BX07	ramipril, amlodipine and hydrochlorothiazide	1
C10BX09	ramipril and amlodipine	1
C10BX10	rosuvastatin and valsartan	1
C10BX11	atorvastatin and amlodipine	1
C10BX13	rosuvastatin, perindopril and indapamide	1
C10BX14	rosuvastatin and amlodipine	1
C10BX15	atorvastatin and perindopril	1
C10BX16	rosuvastatin and fimasartan	1
C10BX17	rosuvastatin and ramipril	1
C10BX18	atorvastatin, amlodipine and candesartan	1

ATC	Substance	SL score
C10BX19	amlodipine and diuretics	1
D04AA10	promethazine	2
D05AX03	calcitriol	1
D06BX01	metronidazole	1
D11AX04	lithium succinate	3
D11AX18	diclofenac	1
G01AF01	metronidazole	1
G02AD06	misoprostol	1
G02CB01	bromocriptine	1
G02CB03	cabergoline	1
G02CC01	ibuprofen	1
G02CC02	naproxen	1
G03AA04	megestrol and ethinylestradiol	1
G03AA05	norethisterone and ethinylestradiol	1
G03AA08	medroxyprogesterone and ethinylestradiol	1
G03AA14	nomegestrol and estradiol	1
G03AA17	medroxyprogesterone and estradiol	1
G03AB01	megestrol and ethinylestradiol	1
G03AB04	norethisterone and ethinylestradiol	1
G03AB08	dienogest and estradiol	1
G03AC01	norethisterone	1
G03AC05	megestrol	1
G03AC06	medroxyprogesterone	1
G03CA53	estradiol, combinations	1
G03DA02	medroxyprogesterone	1
G03DA04	progesterone	1
G03DB02	megestrol	1
G03DB04	nomegestrol	1
G03DC02	norethisterone	1
G03FA01	norethisterone and estrogen	1
G03FA04	progesterone and estrogen	1
G03FA08	megestrol and estrogen	1
G03FA12	medroxyprogesterone and estrogen	1
G03FB04	megestrol and estrogen	1
G03FB05	norethisterone and estrogen	1
G03FB06	medroxyprogesterone and estrogen	1
G03FB12	nomegestrol and estrogen	1
G04BD04	oxybutynin	1
G04BD07	tolterodine	1
G04BD08	solifenacin	1
G04BE09	varденаfil	1
G04CA03	terazosin	1

ATC	Substance	SL score
G04CA53	tamsulosin and solifenacin	1
G04CA55	doxazosin and finasteride	1
H01BA02	desmopressin	1
H01CC53	elagolix, estradiol and norethisterone	1
H01CC54	relugolix, estradiol and norethisterone	1
J01DC02	cefuroxime	1
J01DC04	cefaclor	1
J01DD04	ceftriaxone	1
J01DD08	cefixime	1
J01DD14	ceftibuten	1
J01DD54	ceftriaxone, combinations	1
J01DD63	ceftriaxone and beta-lactamase inhibitor	1
J01MA02	ciprofloxacin	1
J01MA06	norfloxacin	1
J01MA12	levofloxacin	1
J01MA14	moxifloxacin	1
J01RA03	cefuroxime and metronidazole	1
J01RA04	spiramycin and metronidazole	1
J01RA05	levofloxacin and ornidazole	1
J01RA10	ciprofloxacin and metronidazole	1
J01RA11	ciprofloxacin and tinidazole	1
J01RA12	ciprofloxacin and ornidazole	1
J01RA13	norfloxacin and tinidazole	1
J01RA14	norfloxacin and metronidazole	1
J01RA15	cefixime and ornidazole	1
J01RA16	cefixime and azithromycin	1
J01XD01	metronidazole	1
J04AB02	rifampin / rifampicin	1
J04AM02	rifampicin and isoniazid	1
J04AM05	rifampicin, pyrazinamide and isoniazid	1
J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid	1
J04AM07	rifampicin, ethambutol and isoniazid	1
J04BA50	dapsone and rifampicin	1
J04BA51	dapsone, rifampicin and clofazimine	1
L01AA01	cyclophosphamide	1
L01AX03	temozolomide	1
L01BB02	mercaptopurine	1
L01BB05	fludarabine	1
L01BC06	capecitabine	1
L01EA01	imatinib	1
L01EG02	everolimus	1
L01EX05	regorafenib	1

ATC	Substance	SL score
L01XF03	bexarotene	1
L01XX11	estramustine	1
L01XX23	mitotane	1
L01XX33	celecoxib	1
L01XX35	anagrelide	1
L02AB01	megestrol	1
L02AB02	medroxyprogesterone	1
L02BA01	tamoxifen	1
L04AA18	everolimus	1
M01AB01	indometacin	2
M01AB05	diclofenac	1
M01AB15	ketorolac	1
M01AB51	indometacin, combinations	2
M01AB55	diclofenac, combinations	1
M01AC06	meloxicam	1
M01AC56	meloxicam, combinations	1
M01AE01	ibuprofen	1
M01AE02	naproxen	1
M01AE03	ketoprofen	1
M01AE09	flurbiprofen	1
M01AE51	ibuprofen, combinations	1
M01AE52	naproxen and esomeprazole	1
M01AE53	ketoprofen, combinations	1
M01AE56	naproxen and misoprostol	1
M01AH01	celecoxib	1
M01AX01	nabumetone	1
M02AA10	ketoprofen	1
M02AA12	naproxen	1
M02AA13	ibuprofen	1
M02AA15	diclofenac	1
M02AA19	flurbiprofen	1
M02AA23	indometacin	2
M03BC01	orphenadrine (citrate)	2
M03BC51	orphenadrine, combinations	2
M04AA01	allopurinol	1
M04AA51	allopurinol, combinations	1
N01AH01	fentanyl	2
N01AH51	fentanyl, combinations	2
N01BB59	bupivacaine and meloxicam	1
N02AA01	morphine	2
N02AA05	oxycodone	2
N02AA08	dihydrocodeine	2

ATC	Substance	SL score
N02AA51	morphine, combinations	2
N02AA55	oxycodone and naloxone	2
N02AA56	oxycodone and naltrexone	2
N02AA58	dihydrocodeine, combinations	2
N02AA59	codeine, combinations excl. psycholeptics	2
N02AA79	codeine, combinations with psycholeptics	2
N02AB03	fentanyl	2
N02AC04	propoxyphene chloride (dextro-propoxyphene)	2
N02AC52	methadone, combinations excl. psycholeptics	2
N02AC54	dextropropoxyphene, combinations excl. psycholeptics	2
N02AC74	dextropropoxyphene, combinations with psycholeptics	2
N02AE01	buprenorphine	2
N02AG01	morphine and antispasmodics	2
N02AJ01	dihydrocodeine and paracetamol	2
N02AJ03	dihydrocodeine and other non-opioid analgesics	2
N02AJ06	codeine and paracetamol	2
N02AJ08	codeine and ibuprofen	2
N02AJ09	codeine and other non-opioid analgesics	2
N02AJ13	tramadol and paracetamol	2
N02AJ14	oxycodone and paracetamol	2
N02AJ15	tramadol and other non-opioid analgesics	2
N02AJ16	tramadol and celecoxib	2
N02AJ17	oxycodone and paracetamol	2
N02AJ19	oxycodone and ibuprofen	2
N02AX02	tramadol	2
N02AX06	tapentadol	2
N02BF01	gabapentin	2
N02CC01	sumatriptan	2
N02CC03	zolmitriptan	2
N02CC05	almotriptan	2
N02CC07	frovatriptan	2
N02CX02	clonidine	1
N03AA02	phenobarbital	2
N03AA03	primidone	2
N03AB02	phenytoin	2
N03AB52	phenytoin, combinations	2
N03AF01	carbamazepine	2
N03AF02	oxcarbazepine	2
N03AF03	rufinamide	2
N03AF04	eslicarbazepine	2
N03AG01	valproic acid	2
N03AG04	vigabatrin	2

ATC	Substance	SL score
N03AX09	lamotrigine	2
N03AX10	felbamate	2
N03AX11	topiramate	2
N03AX14	levetiracetam	2
N03AX15	zonisamide	2
N03AX16	pregabalin	2
N03AX18	lacosamide	2
N03AX22	perampanel	2
N03AX23	brivaracetam	2
N03AX24	cannabidiol	2
N04BA01	levodopa	1
N04BA02	levodopa and decarboxylase inhibitor	1
N04BA03	levodopa, decarboxylase inhibitor and COMT inhibitor	1
N04BC01	bromocriptine	1
N04BC04	ropinirole	1
N04BC05	pramipexole	1
N04BC06	cabergoline	1
N04BD01	selegiline	1
N04BD02	rasagiline	1
N04BD03	safinamide	1
N04BX01	tolcapone	1
N04BX02	entacapone	1
N05AA01	chlorpromazine	2
N05AB06	trifluoperazine	3
N05AE04	ziprasidone	3
N05AF05	zuclopenthixol	3
N05AG02	pimozide	2
N05AH02	clozapine	2
N05AH03	olanzapine	2
N05AH04	quetiapine	2
N05AH05	asenapine	2
N05AH53	olanzapine and samidorphan	2
N05AN01	lithium	3
N05AX08	risperidone	2
N05AX12	aripiprazole	2
N05AX15	cariprazine	2
N05CD08	midazolam	3
N05CM05	scopolamine	2
N06AA06	trimipramine	3
N06AA09	amitriptyline	3
N06AA10	nortriptyline	3
N06AB03	fluoxetine	2

ATC	Substance	SL score
N06AB05	paroxetine	2
N06AB06	sertraline	2
N06AB08	fluvoxamine	2
N06AB10	escitalopram	2
N06AX11	mirtazapine	2
N06AX12	bupropion	2
N06AX16	venlafaxine	2
N06AX21	duloxetine	2
N06AX23	desvenlafaxine	2
N06AX26	vortioxetine	2
N06CA01	amitriptyline and psycholeptics	3
N06CA03	fluoxetine and psycholeptics	2
N06DA02	donepezil	1
N06DA03	rivastigmine	1
N06DA04	galantamine	1
N06DA52	donepezil and memantine	1
N06DA53	donepezil, memantine and Ginkgo folium	1
N06DX01	memantine	1
N07BB01	disulfiram	1
N07BB03	acamprosate	1
N07BB04	naltrexone	1
N07BC01	buprenorphine	2
N07BC02	methadone	2
N07BC51	buprenorphine, combinations	2
NA	olmesartan	1
P01AB01	metronidazole	1
P01AB51	metronidazole and furazolidone	1
P01AB52	metronidazole and diloxanide	1
P01BA02	hydroxychloroquine	1
P01BB51	proguanil and atovaquone	1
P01BC02	mefloquine	1
P01BF02	artesunate and mefloquine	1
P03AA04	disulfiram	1
P03AA54	disulfiram, combinations	1
R02AX01	flurbiprofen	1
R02AX02	ibuprofen	1
R03DA04	theophylline	2
R03DA54	theophylline, combinations excl. psycholeptics	2
R03DA74	theophylline, combinations with psycholeptics	2
R03DB04	theophylline and adrenergics	2
R03DC03	montelukast	1
R03DC53	montelukast, combinations	1

ATC	Substance	SL score
R05DA04	codeine	2
R05DA05	opium alkaloids with morphine	2
R06AD02	promethazine	2
R06AD52	promethazine, combinations	2
R06AE06	oxatomide	2
R06AE07	cetirizine	1
R06AE09	levocetirizine	1
R06AX26	fexofenadine	1
R06AX27	desloratadine	1
S01AA27	cefuroxime	1
S01AE02	norfloxacin	1
S01AE03	ciprofloxacin	1
S01AE05	levofloxacin	1
S01AE07	moxifloxacin	1
S01BC01	indometacin	2
S01BC03	diclofenac	1
S01BC04	flurbiprofen	1
S01BC05	ketorolac	1
S01CC01	diclofenac and antiinfectives	1
S01CC02	indometacin and antiinfectives	2
S01EA04	clonidine	1
S01EC01	acetazolamide	1
S01ED02	betaxolol	1
S01ED52	betaxolol, combinations	1
S01FA01	atropine	2
S01FA02	scopolamine	2
S01FB51	phenylephrine and ketorolac	1
S01GX12	cetirizine	1
S02AA15	ciprofloxacin	1
S03AA07	ciprofloxacin	1

Appendix 6 – Overview of all R packages used in the analysis, and description of the information required by the main functions and specific scripts developed for the study.

All statistical analyses were conducted using R version 4.4.1.

For this study, to support data manipulation, matched cohort construction, propensity score modelling, and regression analysis we employed the following packages: *readr*, *AdhereR*, *dplyr*, *writexl*, *lubridate*, *readxl*, *foreign*, *stringr*, *ggplot2*, *haven*, *caret*, *plyr*, *MatchIt*, *survival*, *ranger*, *ggfortify*, *ggsurvfit*, *casebase*, *etm*, *cobalt*, *Publish*, *visreg*, *splines*, *xfuntdyr*, *Epi*, *xlsx*.

In the following sections, only the packages directly involved in the main analytical phases- matching strategy, dimensionality reduction, propensity score estimation, and risk assessment- are specifically described and discussed, as they represent the core methodological steps of the study.

Appendix 6.1- Matching

To construct the matched cohort, the function *ccwc()* from the *Epi package* was used. This function implements risk-set matching by pairing each exposed individual with an unexposed control who was still at risk at the same time point. Matching was performed on age and sex, ensuring temporal alignment and comparability of baseline characteristics between groups. The function parameters specified the entry time (start of follow-up- when observation period begins), index date (exposure – the first day when selection criteria have been met), event status (if selection criteria have been met), and matching variables (sex, age). A 1:1 matching ratio was applied. The matched dataset included only the necessary variables for subsequent analyses, preserving essential demographic, exposure, and outcome information (**Figure Appendix 6.1**).

```

dietcc <- cwc(entry = Data_origine, # First date of data availability (01-01-2014) - from when patients can be followed
             exit = Data_indice, # Start, the min inappropriateness date
             fail = Outcome, # Inappropriate 1, not inappropriate 0
             origin = Data_origine, # First date of data availability (01-01-2014)
             controls = 1, # match 1-1
             data = DS_Final_RSM, # The dataset with the study populations and selected patients
             match = list(Sesso_pz, Eta_pz), # Sex and Age
             include = list(Cod_pz,
                           Stato_pz, Date_exit, Data_indice,
                           Outcome, TTI, Classi_Unite, Num_Classi_Diversi, Classe_gruppo_final ), # variables to keep
             silent = TRUE
)

```

Figure 6.1. Matching code with variables and explanation of the main variables

In **Figure Appendix 6.2** are reported key variables as example of the resulting dataset.

Patient_ID	Set	Fail	Time	Date_exit	Index_date
2F1FD079-F216-45B5-B570-84AF9C9690CB	327	Inappropriate	2016-01-08	2018-12-31	2016-01-08
2F577256-CE9B-47FE-B523-C4431703D1B8	328	Inappropriate	2018-01-29	2018-12-31	2018-01-29
3540B9B9-22C6-4B69-800D-CD53F91783DF	327	Inappropriate	2016-01-08	2018-12-31	2016-01-08
5C0BF8EF-BD77-4F06-97A8-B6220CF773F1	327	Not_inappropriate	2016-01-08	2018-12-31	2016-11-11
9C1D5544-C8A1-45E1-8B8F-90EB684547BA	327	Not_inappropriate	2016-01-08	2018-12-31	2018-12-31
BD6187BC-64BB-4DF8-BB4D-593C90AD0131	328	Inappropriate	2018-01-29	2018-12-31	2018-01-29
D5470091-5363-4306-841B-8F2D1E20C7A1	328	Not_inappropriate	2018-01-29	2018-12-31	2018-12-31
D56F20EE-9C0C-47DE-883D-9DA9023AF5E1	327	Not_inappropriate	2016-01-08	2018-12-31	2018-12-31
DC119E29-3E73-4B66-BA37-EBD8C14D0749	328	Not_inappropriate	2018-01-29	2018-12-31	2018-12-31
EF2259AB-0AD7-44B7-822A-A3580132D3F1	327	Inappropriate	2016-01-08	2018-12-31	2016-01-08

Figure Appendix 6.2. Matched dataset

Specifically:

- Set: denotes the matched stratum, identifying each matched pair (1:1 matching) and allowing the conditional logistic regression to compare individuals within the same matched group;
- Fail: the failure status, a binary indicator of the exposure status at the index date (1 = exposed; 0 = unexposed), used as the primary explanatory variable in the model;
- Time: failure time of the case in a specific set. It represents a mirror of the index date, used to align timing in the dataset for analysis so that up to this time point, the patient contributes as a control; from this time onward, the patient is considered selected for PII (case);
- Date_exit: indicates the end of the observation period for each subject (e.g., due to censoring, death, or event);

- `Index_date`: the moment of exposure and serves as the temporal anchor for follow-up and outcome assessment. After this date, the patients cannot be a control.

These variables form the backbone of the statistical analysis, allowing for within-pair comparisons that preserve the integrity of the matching process.

Appendix 6.2- NZV

As described in section 4.4.2, we used the high-dimensional propensity score (HDPS) which involves an overwhelming number of variables. Therefore, a Near Zero Variance-like strategy was adopted to reduce dimensionality and retain only the most informative covariates. This method involved calculating the prevalence of each binary predictor (e.g., diagnosis or medication code) across all subjects, then excluding variables with extreme prevalence values. Specifically, the frequency of each variable was computed as the percentage of patients for whom the variable was present. Variables were retained only if their prevalence fell between 0.5% and 99.5%. This cut-off-based selection effectively excludes variables that are either almost universally present or extremely rare, thereby mimicking the intended effect of NZV filtering:

- Variables present in less than 0.5% of cases are considered "near-zero" (almost absent);
- Variables present in more than 99.5% of cases are considered "near-constant" (almost always present).

For instance, a diagnosis code that appears in only 0.5% of patients- or in 99.5% of them- would be excluded. This is because such variables have either too little variation (almost always present or almost always absent) and are unlikely to contribute meaningfully to the model.

By applying this tailored prevalence-based filtering, the study ensured a stable and parsimonious set of covariates for propensity score estimation while maintaining computational efficiency. This approach, shown in **Figure Appendix 6.3**, preserved

meaningful variability and improved model interpretability without sacrificing the robustness of confounding adjustment.

```
1 sum_row = colSums(df_final[,-1])
2 sum_row <- as.data.frame(sum_row)
3 sum_row$SDO = rownames(sum_row)
4 rownames(sum_row) <- NULL
5 sum_row$Tot = nrow(df_final)
6 sum_row$Perc = sum_row$sum_row/sum_row$Tot*100
7 sum_row <- sum_row[which(sum_row$Perc>0.5 & sum_row$Perc<99.5),]
8 cols_keep = sum_row$SDO
9 cols_keep <- c("Cod_pz",cols_keep)
10 df_final_filt = df_final[,cols_keep]
```

Figure Appendix 6.3. *NZV-like code*

From line 1 to line 4, we calculated how many individuals have a value of 1 for each binary variable. In lines 5 and 6 we computed the prevalence (in percentage) of each variable keeping only the variables with a prevalence between 0.5% and 99.5% in line 7. Finally, from line 8 to 10, we selected only the retained variables for each patient identifier (Cod_pz).

Appendix 6.3- High Dimension Propensity Score computation

The propensity score was estimated through logistic regression using the generalized linear model function *glm*, a function used to fit generalized linear models, specified by giving a symbolic description of the linear predictor and a description of the error distribution. The model, which code is reported in **Appendix Figure 6.4**, was specified with a binomial family and *logit link function*, appropriate for modelling a binary outcome.

```
1 fit <- glm(Fail ~ . -Fail, data = total, family = binomial) # Fail means be inappropriate ad a certain date Time
2 propensity_score = predict(fit, data=ds_per_propensity, type="response")
```

Figure Appendix 6.4. *Propensity score computation code*

Fit is the logistic regression model estimated on the dataset “*total*”. The binary outcome variable (*Fail*), indicating exposure status (e.g., receipt of a potentially inappropriate medication) at a specific index date (*Time*- failure time of the case in a specific set). *Propensity_score* represents the PS for each individual, computed by

predict function. The incorporated covariates (*ds_per_propensity*) encompassed a comprehensive set of baseline variables, including demographic characteristics (e.g., age, sex), and the NZV-like reduced sets of chronic medication dispensations coded via Anatomical Therapeutic Chemical (ATC) classification, and prior hospitalizations and ICD-9. These variables capture patients' underlying health status, comorbidities, and healthcare utilization patterns, which are crucial confounders influencing both medication exposure and risk of hospitalization.

Appendix 7- Overview of R package used for Conditional Inference Trees (CITs) development

The CITs development was conducted using R version 4.4.1. We employed the *ctree()* function from the *partykit* package in R to construct CITs which applies permutation-based significance tests at each node to determine the most appropriate variable for splitting (Figure 7.1)

```
citd.ctree <- partykit::ctree(Hospitalization ~ ., data = ds_allLHUs)
```

Figure Appendix 7.1. CITs code

In this line of code, *citd.ctree* is the final object name, *partykit::ctree* indicates the use of the *ctree* function from *partykit* package. *Hospitalization* is the model dependent variable and *~ .* indicates that all the variable in the *ds_allLHUs* dataset are used (Sex, age groups, ATC codes, ICD-9 codes).

Appendix 8- Subgroups of patients exposed to inappropriate dispensations for whom the risk of hospitalization is elevated.

I D	PIMs								
1	B01AB	J01MA							
2	B01AB	J01MA _{no}	PSB01AB	C03DA					
3	B01AB	J01MA _{no}	PSB01AB	C03DA _{no}	M				
4	B01AB	J01MA _{no}	PSB01AB	C03DA _{no}	F				
5	B01AB	J01MA _{no}	PSB01AB _{no}						
6	B01AB _{no}	C03CA	C03DA						
7	B01AB _{no}	C03CA	C03DA _{no}	A12BA					
8	B01AB _{no}	C03CA	C03DA _{no}	A12BA _{no}					
9	B01AB _{no}	C03CA _{no}	J01MA	F	A02BC				
10	B01AB _{no}	C03CA _{no}	J01MA	F	A02BC _{no}				
11	B01AB _{no}	C03CA _{no}	J01MA	M	A02BC				
12	B01AB _{no}	C03CA _{no}	J01MA	M	A02BC _{no}				
13	B01AB _{no}	C03CA _{no}	J01MA _{no}	A02BC _{no}	C01BD				
14	B01AB _{no}	C03CA _{no}	J01MA _{no}	A02BC _{no}	C01BD _{no}				
15	B01AB _{no}	C03CA _{no}	J01MA _{no}	A02BC	A12BA				
16	B01AB _{no}	C03CA _{no}	J01MA _{no}	A02BC	A12BA _{no}	M			
17	B01AB _{no}	C03CA _{no}	J01MA _{no}	A02BC	A12BA _{no}	F	C01BD		
18	B01AB _{no}	C03CA _{no}	J01MA _{no}	A02BC	A12BA _{no}	F	C01BD _{no}		
I D	DDIs								
1	B01AB	C03DA							
2	B01AB	C03DA _{no}							
3	B01AB	C03DA	J01MA						
4	B01AB	C03DA	J01MA _{no}						
5	B01AB _{no}	C03CA	C03DA	J01MA					
6	B01AB _{no}	C03CA	C03DA	J01MA _{no}					
7	B01AB _{no}	C03CA	C03DA _{no}						
8	B01AB _{no}	C03CA	C03DA _{no}	A02BC	J01MA				
9	B01AB _{no}	C03CA	C03DA _{no}	A02BC	J01MA _{no}	B03AA			
10	B01AB _{no}	C03CA	C03DA _{no}	A02BC	J01MA _{no}	B03AA _{no}	A12BA		
11	B01AB _{no}	C03CA	C03DA _{no}	A02BC	J01MA _{no}	B03AA _{no}	A12BA _{no}		
12	B01AB _{no}	C03CA	C03DA _{no}	A02BC _{no}	C01BD				

13	B01AB no	C03CA	C03DA _{no}	A02BC no	C01BD no	M			
14	B01AB no	C03CA	C03DA _{no}	A02BC no	C01BD no	F			
15	B01AB no	C03CA _{no}	F	B03AA					
16	B01AB no	C03CA _{no}	F	B03AA no					
17	B01AB no	C03CA _{no}	M	J01MA	A02BC				
18	B01AB no	C03CA _{no}	M	J01MA	A02BC no				
19	B01AB no	C03CA _{no}	M	J01MA no	C01BD				
20	B01AB no	C03CA _{no}	M	J01MA no	C01BD no	A02BC			
21	B01AB no	C03CA _{no}	M	J01MA no	C01BD no	A02BC _{no}			
22	B01AB no	C03CA _{no}	M	J01MA no	C01BD no	C03DA			
23	B01AB no	C03CA _{no}	M	J01MA no	C01BD no	C03DA _{no}			
1D	FRIDs								
1	B01AB	PSB01AB	J01MA						
2	B01AB	PSB01AB	J01MA _{no}						
3	B01AB	PSB01AB no	M	H02AB					
4	B01AB	PSB01AB no	F						
5	B01BA no	C03CA	C03DA	F	A12BA				
6	B01BA no	C03CA	C03DA	F	A12BA no				
7	B01BA no	C03CA	C03DA	M					
8	B01BA no	C03CA	C03DA _{no}	J01MA					
9	B01BA no	C03CA	C03DA _{no}	J01MA no	H02AB	F			
10	B01BA no	C03CA	C03DA _{no}	J01MA no	H02AB	M			
11	B01BA no	C03CA	C03DA _{no}	J01MA no	H02AB no	A02BC			
12	B01BA no	C03CA	C03DA _{no}	J01MA no	H02AB no	A02BC _{no}			
13	B01BA no	C03CA	C03DA _{no}	J01MA no					
14	B01BA no	C03CA _{no}	J01MA	H02AB	F	A12BA			
15	B01BA no	C03CA _{no}	J01MA	H02AB	F	A12BA _{no}			
16	B01BA no	C03CA _{no}	J01MA	H02AB	M				
17	B01BA no	C03CA _{no}	J01MA	H02AB no	F				
18	B01BA no	C03CA _{no}	J01MA	H02AB no	M				
19	B01BA no	C03CA _{no}	J01MA _{no}	A02BC	F	A12BA	C03DA		
20	B01BA no	C03CA _{no}	J01MA _{no}	A02BC	F	A12BA	C03DA no		
21	B01BA no	C03CA _{no}	J01MA _{no}	A02BC	F	A12BA _{no}	N02AB		
22	B01BA no	C03CA _{no}	J01MA _{no}	A02BC	F	A12BA _{no}	N02AB no		
23	B01BA no	C03CA _{no}	J01MA _{no}	A02BC	M	N02AB			

24	B01BA no	C03CAno	J01MAno	A02BC	M	N02ABno			
25	B01BA no	C03CAno	J01MAno	A02BC no	N02AA				
26	B01BA no	C03CAno	J01MAno	A02BC no	N02AA no				
ID	TDs								
1	B01AB	PSB01AB	F	A02BC					
2	B01AB	PSB01AB	F	A02BC no					
3	B01AB	PSB01AB	M	J01MA					
4	B01AB	PSB01AB	M	J01MA no	C03DA				
5	B01AB	PSB01AB	M	J01MA no	C03DA no				
6	B01AB	PSB01AB no	SB01AB_B01A B						
7	B01AB	PSB01AB no	SB01AB_B01A Bno	F	A02BC				
8	B01AB	PSB01AB no	SB01AB_B01A Bno	F	A02BC no				
9	B01AB	PSB01AB no	SB01AB_B01A Bno	M					
10	B01AB no	C03CA	C03DA	J01MA					
11	B01AB no	C03CA	C03DA	J01MA no					
12	B01AB no	C03CA	C03DAno	F					
13	B01AB no	C03CA	C03DAno	M					
14	B01AB no	C03CA	C03DAno	A02BC	F				
15	B01AB no	C03CA	C03DAno	A02BC	M				
16	B01AB no	C03CA	C03DAno	A02BC no	J01MA				
17	B01AB no	C03CA	C03DAno	A02BC no	J01MA no				
18	B01AB no	C03CAno	SB01AC_B01A C	J01MA					
19	B01AB no	C03CAno	SB01AC_B01A C	J01MA no					
20	B01AB no	C03CAno	SB01AC_B01A Cno	J01MA	F	A02BC			
21	B01AB no	C03CAno	SB01AC_B01A Cno	J01MA	F	A02BCno			
22	B01AB no	C03CAno	SB01AC_B01A Cno	J01MA	M				
23	B01AB no	C03CAno	SB01AC_B01A Cno	J01MA no	A02BC	F			
24	B01AB no	C03CAno	SB01AC_B01A Cno	J01MA no	A02BC	M			
25	B01AB no	C03CAno	SB01AC_B01A Cno	J01MA no	A02BC no				
ID	ACB score								
1	B01AB	PSB01AB							
2	B01AB	PSB01AB no							
3	B01AB no	C03CA	C03DA						
4	B01AB no	C03CA	C03DAno	J01MA					
5	B01AB no	C03CA	C03DAno	J01MA no					

6	B01AB no	C03CAno	N02AB						
7	B01AB no	C03CAno	N02ABno	J01MA					
8	B01AB no	C03CAno	N02ABno	J01MA no					
I D	SL score								
1	B01AB	PSB01AB	J01MA						
2	B01AB	PSB01AB	J01MAno	B01AF					
3	B01AB	PSB01AB	J01MAno	B01AF no					
4	B01AB	PSB01AB no	PSV4365						
5	B01AB	PSB01AB no	PSV4365no	J01MA					
6	B01AB	PSB01AB no	PSV4365no	J01MA no					
7	B01AB no	C03CA	A02BC	J01MA	C03DA				
8	B01AB no	C03CA	A02BC	J01MA	C03DA no				
9	B01AB no	C03CA	A02BC	J01MA no	C03DA				
1 0	B01AB no	C03CA	A02BC	J01MA no	C03DA no	F	C07AB		
1 1	B01AB no	C03CA	A02BC	J01MA no	C03DA no	F	C07AB no		
1 2	B01AB no	C03CA	A02BC	J01MA no	C03DA no	M	H02AB		
1 3	B01AB no	C03CA	A02BC	J01MA no	C03DA no	M	H02AB no		
1 4	B01AB no	C03CA	A02BCno	C03DA					
1 5	B01AB no	C03CA	A02BCno	C03DA no	A12AB				
1 6	B01AB no	C03CA	A02BCno	C03DA no	A12AB no				
1 7	B01AB no	C03CAno	F	H02AB	J01MA				
1 8	B01AB no	C03CAno	F	H02AB	J01MA no	N02AA	B01AC		
1 9	B01AB no	C03CAno	F	H02AB	J01MA no	N02AA	B01AC no		
2 0	B01AB no	C03CAno	F	H02AB	J01MA no	N02AAno			
2 1	B01AB no	C03CAno	F	H02AB no	B01AC	PSB01AC			
2 2	B01AB no	C03CAno	F	H02AB no	B01AC	PSB01AC no	C01DA		
2 3	B01AB no	C03CAno	F	H02AB no	B01AC	PSB01AC no	C01DA no		
2 4	B01AB no	C03CAno	F	H02AB no	B01AC no	B01AF			
2 5	B01AB no	C03CAno	F	H02AB no	B01AC no	B01AFno	N02AA		
2 6	B01AB no	C03CAno	F	H02AB no	B01AC no	B01AFno	N02AA no	PSB01AB	
2 7	B01AB no	C03CAno	F	H02AB no	B01AC no	B01AFno	N02AA no	PS01ABno	A12BA
2 8	B01AB no	C03CAno	M	J01MA	A02BC	H02AB			
2 9	B01AB no	C03CAno	M	J01MA	A02BC	H02ABno	C03DA		
3 0	B01AB no	C03CAno	M	J01MA	A02BC	H02ABno	C03DA no		
3 1	B01AB no	C03CAno	M	J01MA	A02BC no				

3 2	B01AB no	C03CAno	M	J01MA no	A02BC	C01DA			
3 3	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	N02AA		
3 4	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	N02AA no		
3 5	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	B01AC	PSB01AC	
3 6	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	B01AC	PSB01AC no	
3 7	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	B01AC no	H02AB	
3 8	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	B01AC no	H02ABno	C03DA
3 9	B01AB no	C03CAno	M	J01MA no	A02BC	C01DAno	B01AC no	H02ABno	C03DA no
4 0	B01AB no	C03CAno	M	J01MA no	A02BC no	N02AA			
4 1	B01AB no	C03CAno	M	J01MA no	A02BC no	N02AAno			

* Pharmaceutical or hospitalization codes followed by the term "no" indicate that the corresponding condition or event was not present. Conversely, codes preceded by the term "PS" indicate condition or event during the year preceding the index date- that is, before the index date. Codes preceded by the term "S" indicate the specific condition of inappropriate selection (drug class or combination of drug classes). Codes not preceded by "S" or "PS" indicate conditions after the index date. F: female; M: male.

DOCTORAL ACTIVITY REPORT

During my PhD programme, carried out at IRCCS MultiMedica (Milan, Italy), in collaboration with the Epidemiology and Preventive Pharmacology Service (SEFAP) of the Department of Pharmacological and Biomolecular Sciences, I had the opportunity to develop solid expertise in pharmacoepidemiology, pharmacoutilization research, and real-world data analysis. This experience allowed me to combine pharmacological knowledge with epidemiological and data science methods, contributing to a range of interdisciplinary studies focused on the appropriate use of medicines in clinical practice. Building on a solid background in pharmacological sciences, I learned how to integrate clinical and pharmacological knowledge into the design and implementation of studies using real-world data. This integration proved essential for the development of complex research questions, particularly those focused on drug safety, treatment appropriateness, and optimization of medication use in vulnerable populations such as older adults.

Throughout the three years, I progressively acquired and refined a wide set of methodological skills in the following areas:

- I became confident in conducting bibliographic research and in the critical appraisal of scientific literature across a variety of sources, including PubMed, EMBASE, and Web of Science. This allowed me to stay updated on the latest evidence and to contextualize my work within current international research trends. I gained substantial experience in interpreting epidemiological data and translating evidence into operational definitions that could be applied to routinely collected healthcare data and bibliographic search, review and systematic reviews of scientific literature (through PubMed, EMBASE and Web of Science databases) and interpretation of epidemiological data;
- A key component of my training was the ability to organize, manage, and analyze large-scale health databases, particularly administrative healthcare data. I became proficient in data curation, including variable construction, data cleaning, and the management of longitudinal records. These technical skills were essential for the design, conduction, and analysis of pharmacoepidemiological and pharmacoutilization studies, which I carried out

predominantly using healthcare utilization databases from Lombardy Region (Italy) and Danish national registers;

- I developed the ability to build and validate data-driven algorithms aimed at identifying high-risk patients and clinically relevant prescribing patterns. These tools were designed to support the implementation of medication review and deprescribing strategies in primary care. I also acquired a solid understanding of the clinical rationale and evidence base of deprescribing practices, which I applied in both observational studies and intervention-oriented projects;
- In terms of data analysis, I became proficient in using both SPSS and R statistical software, developing specific expertise in techniques such as multivariable regression, time-to-event (survival) analysis, and machine learning approaches for predictive modelling. I applied these skills to evaluate the impact of potentially inappropriate medications on health outcomes and to design prioritization algorithms for individualized medication review interventions.

The core of my PhD research focused on the evaluation of polypharmacy and inappropriate prescribing in the older population, with the aim of developing a prioritization algorithm to support medication review intervention in primary care. I carried out a comprehensive review and operationalization of international appropriateness criteria – including Beers, FORTA, Priscus and EU(7)-PIM- and assessed their applicability using real-world data from Italian healthcare databases to detect potentially inappropriate medications to quantify their predictive value in estimating all-cause hospitalization risk, with the aim of identifying clinically meaningful targets for deprescribing.

This work was further strengthened by a 10-month research stay at the Department of Drug Design and Pharmacology at the University of Copenhagen, Denmark. During this part of my PhD program, I had the opportunity to further enhance my methodological background by training and knowledge sharing in advanced statistical and analytical approaches, including time-to-event analysis and machine learning

models, and I contributed to ongoing projects that further broadened my exposure to international research collaborations and database environments.

Besides my main research project, during my PhD course, I have also collaborated in several studies:

- As part of the LAPTOP-PPI project, a randomized controlled trial focused on deprescribing proton pump inhibitors (PPIs) in older adults, I contributed to the design and implementation of a national survey targeting General Practitioners (GPs). The survey aimed to investigate clinicians' knowledge, attitudes, and perceived barriers related to deprescribing in primary care. Over the course of eight months, we collected 617 responses from across the country, which offered valuable insights into real-world prescribing behavior and informed the development of future intervention strategies. In parallel with this work, I also contributed to a systematic review exploring deprescribing strategies for PPIs in clinical practice. This comprehensive synthesis of the literature aimed to map existing approaches, evaluate their effectiveness, and highlight gaps in evidence to support safer prescribing in the context of long-term PPI use;
- I contributed to a proof-of-concept study that applied network analysis and case-crossover design to real-world data from the Lombardy Region, with the aim of detecting associations between drug use and acute myocardial infarction through a case-crossover design by evaluating patterns of drug use, diagnoses, and their interactions preceding acute myocardial infarction events. The analysis aimed to identify potential safety signals and support earlier detection of adverse drug events;
- I was also involved in a methodological study using Danish national register aimed to develop and test a novel approach to measure co-exposure to antihypertensive medications in free-dose combinations, using Danish national registers. This study analysed over one million individuals aged 65 and older and introduced a new way to assess medication adherence and optimization of cardiovascular treatment strategies in the older population.

Throughout my PhD, I actively participated in national and international conferences (outlined below). This allowed me in sharing experiences and outcomes with other research groups and engaging with other experts is a valuable key point to broaden knowledge and develop and optimize research practices. My contributions were both oral and poster presentations, addressing topics such as deprescribing in general practice, drug safety signal detection, and the use of artificial intelligence in pharmacovigilance.

Date	Title of contribution	Site
01 Jul'25 – 04 Jul'25	Prioritizing Medication Review for Older Individuals: A Real-World Data Study using administrative databases Poster presentation	European Drug Utilization Conference 2025 – EuroDURG (Uppsala, SE)
24 Jun'25 – 25 Jun'25	Prioritizing Medication Review for older Individuals: a Real-World Data Study using administrative databases Oral presentation	Convegno Monotematico SIF (Verona, IT)
06 Apr'25 – 08 Apr'25	Prioritizing medication review for older individuals: A real-world data study using administrative databases Poster presentation	Spring Meeting dei gruppi Giovani Ricercatori SIIA, SIMI e SISA (Rimini, IT)
27 Feb'25 – 01 Mar'25	Evaluating association between inappropriate prescription and hospitalization risk in older adults: evidence from administrative databases Poster presentation	Retreat DiSFeB (Rimini, IT)
18 Nov'24 – 20 Nov'24	Prioritizing Medication Review for Older Individuals: A Real-World Data Study using administrative databases Oral presentation	Nordic PharmacoEpidemiological Network- NorPEN 16th Annual meeting (Copenhagen, DK)
13 Nov'24 – 16 Nov'24	Attitudes and confidence to deprescribing in general practice. Oral presentation	42° Congresso nazionale SIF (Sorrento, IT)

24 Aug'24 – 28 Aug'24	Attitudes and confidence to deprescribing in general practice Poster presentation	2024 ISPE Annual Meeting (Berlin, DE)
17 Jul'24 – 19 Jul'24	Optimizing elderly care in Lombardy: detecting inappropriate prescriptions through survival models using Real World Data Oral presentation	ReTreat PhD, Milan (IT)
25 Feb'24 – 27 Feb'24	Attitudes and confidence to deprescribing in general practice: a focus on cardiovascular therapies Poster presentation	Spring Meeting dei gruppi Giovani Ricercatori SIIA, SIMI e SISA (Rimini, IT)
20 Jul'23 – 21 Jul'23	Evaluation of polypharmacy in elderly patients and potential for a deprescribing approach Poster presentation	ReTreat PhD, Milan (IT)
21 May'23 – 24 May'23	Beta-blockers in post-acute myocardial infarction patients: Drug prescription patterns from 2018 to Italy's first wave of the COVID-19 pandemic. Poster presentation	EAS (Mannheim, DE)
16 Apr'23 – 18 Apr'23	General practitioner attitudes and confidence to deprescribing. A focus on cardiovascular therapies. Poster presentation	Spring Meeting dei gruppi Giovani Ricercatori SIIA, SIMI e SISA (Rimini, IT)

CONGRESS PARTICIPATION

- Participation at SISA- S.I.Te.C.S Regional Congress, 10 Oct'24 – 12 Oct'24 – Milan.
- Participation at ESPACOMP Annual Conference, 30 Nov'23 – 02 Dec'2023 – Budapest.
- Participation at SISA National Congress, 26 Nov'23 – 28 Nov'23 – Naples.

- Participation at SISA- S.I.Te.C.S Regional Congress, 12 Oct'23 – 14 Oct'23 – Milan.
- Participation at DiDFeB retreat Riccione (IT) 16 Feb'23 – 18 Feb'23
- Participation at AIE, Milan (ITA) National congress 22 Nov'22 – 23 Nov'22

Moreover, in the last three years, I attended seminars and educational courses (listed below), in order to keep on training and updating my knowledge:

- Educational session “Critical appraisal of statistics in DUR” at EuroDURG 2025- Uppsala
- Workshop “Cross-national comparisons” at EuroDURG 2025- Uppsala
- Workshop “Communication between professionals and the public” at EuroDURG 2015 – Uppsala
- Workshop “How to describe medication adherence interventions? Bridging the gap between intervention development and reporting guidelines and behaviour change in real life” at ESPACOMP Annual Conference, 30 Nov'23 – 02 Dec'2023 – Budapest.
- SAS institute course “Introduction to data visualization data science and machine learning algorithms” – 20 Nov'23 – 22 Nov'23
- Workshop “Self-reported adherence in research and clinical practice: what are we looking for?” at ESPACOMP Annual Conference, 30 Nov'23 – 02 Dec'2023 – Budapest.
- 4EU+PharmacoEpi Advanced Course – May'23 – Jun'23
- 30° Corso SIB – Metodologia statistica per la ricerca biologica di base ed applicata – 29 May'23 – 01 Jun'23
- EAS Rare Lipid Disorder Courses – “Why do clinicians need to know about rare lipid disorders?” 03 May' 23 Milan, IT
- Corso di Perfezionamento “Farmacovigilanza: safety monitoring, risk management, quality assurance nella digital health era” – AA 2023/2024

Recognizing the importance of scientific dissemination, in the awareness that transferring scientific knowledge within the scientific community and, above all, to

the public is one of the hardest challenges of the “research world” nowadays, I have carried out information and dissemination activities. In particular, I am a member of SEFAPnews editorial-board, that provides monthly newsletters published on SEFAP website (www.sefap.it), on the topic of pharmacovigilance, pharmacoepidemiology, pharmacoutilization and health policies. Furthermore, I was involving in dissemination activities through RicercaMix blog of the Department of Pharmacological and Biomolecular Sciences of the University of Milan (www.ricercamix.org).

During my PhD programme, I contributed to the following publications:

List of publications

1. Rossi A., Scotti, S., Perrella, L., Galimberti, F., Olmastroni, E., Menditto, E., Orlando, V., Ardonio, I., Franchi, C., Casula, M. “Attitudes and confidence toward deprescribing: a survey among Italian general practitioners”
2. Barbieri MA, Abate A, Balogh OM, Pétervári M, Ferdinandy P, Ágg B, Battini V, Cocco M, Rossi A, Carnovale C, Casula M, Spina E, Sessa M. Network Analysis and Machine Learning for Signal Detection and Prioritization Using Electronic Healthcare Records and Administrative Databases: A Proof of Concept in Drug-Induced Acute Myocardial Infarction. *Drug Saf.* 2025 May;48(5):513-526. doi: 10.1007/s40264-025-01515-y. Epub 2025 Feb 7. PMID: 39918677; PMCID: PMC11982071.
3. Abate, A., Poncato, E., Barbieri, M.A. *et al.* Off-the-Shelf Large Language Models for Causality Assessment of Individual Case Safety Reports: A Proof-of-Concept with COVID-19 Vaccines. *Drug Saf* **48**, 805–820 (2025). <https://doi.org/10.1007/s40264-025-01531-y>
4. Barbieri, M.A., Nielsen, S.M.N., Rossi, A. et al. A newly developed method for assessing co-exposure to free dose combinations: a proof-of-concept study using antihypertensive medications in Danish registers. *Aging Clin Exp Res* 36, 226 (2024). <https://doi.org/10.1007/s40520-024-02879-4>
5. Rossi A, Perrella L, Scotti S, Olmastroni E, Galimberti F, Ardoio I, Orlando V, Menditto E, Franchi C, Casula M. Approaches to Deprescribing Proton Pump Inhibitors in Clinical Practice: A Systematic Review. *J Clin Med.* 2024

Oct 21;13(20):6283. doi: 10.3390/jcm13206283. PMID: 39458232; PMCID: PMC11508458.1

6. Barbieri, M. A., Battini, V., Canovale, C., Cocco, M., Papoutusi, D., Dong, G., Rossi, A., Dilsad Peker, S., Van Manen, R., Sameer, T., Sessa, M. “Artificial Intelligence in Pharmacovigilance Signal Management: A Review of Tools, Implementations, Research and Regulatory Landscape”

Publications under review

1. Ompad, G., Saura, P. M., Rossi, A., Olmastroni, E., Casula, M., Sessa, M., “Meta-Analysis and Network Meta-Analysis of Clinical Trials Assessing the Safety of Pharmacological Treatments for Muscular Degeneration in Duchenne Muscular Dystrophy”

Manuscripts submitted

1. Rossi, A., Olmastroni, E., Sessa, M., Casula, M. “Assessing inappropriate prescribing and hospitalization risk in older adults: an analysis of administrative databases in Lombardy region”

Manuscripts ready to be submitted

1. Rossi, A., Olmastroni, E., Omapd, G., Sessa, M., Casula, M. “Machine Learning-Based Prioritization for Medication Review: Minimizing Inappropriate Drug Use in Older Adults Using Real-World Data”

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This thesis is the result of three years of research, learning, and growth, a journey that would not have been possible without the guidance, support, and encouragement of many individuals. I wish to express my deepest gratitude to all who have contributed to this work.

My first and most sincere thanks go to my supervisor, Prof. Manuela Casula. Her constant support, sharp scientific insights, and invaluable mentorship have been the cornerstone of this entire project. She provided me with the intellectual freedom to explore my ideas while always offering the steady guidance needed to navigate the complexities of this research. Her dedication and vision have been a true inspiration. On this same path, I owe a special and gratitude to Dr. Elena Olmastroni. Our daily discussions, shared challenges, and collaborative spirit were not just a support, but a fundamental driving force behind this work. This thesis would not be what it is without our synergistic effort.

I am also profoundly grateful to prof. Paolo Magni as cosupervisor of this project and to Prof. Alberico L. Catapano. Although not an official supervisor, his scientific guidance, immense experience, and insightful perspective have been fundamental to my development as a researcher. My formal gratitude also extends to the PhD Programme Coordinator, Prof. Giuseppe Danilo Norata, and the entire Department of Pharmacological and Biomolecular Sciences at the Università degli Studi di Milano for providing a stimulating academic environment.

This research was conducted within the vibrant and collaborative environment of the Epidemiology and Preventive Pharmacology Service (SEFAP) and at IRCCS MultiMedica. I am indebted to all my colleagues there for creating an atmosphere of mutual support and intellectual curiosity that made every day in the lab a valuable experience.

A special acknowledgment is due for my enriching 10-month stay at the Department of Drug Design and Pharmacology at the University of Copenhagen. This experience was transformative, both professionally and personally. I am particularly grateful to my hosts and colleagues in Denmark for welcoming me into the Drug Safety Group

lead by prof. Maurizio Sessa, for the invaluable knowledge they shared, and for broadening my perspective on pharmacoepidemiological research.

To my friends and fellow PhD candidates, thank you for the camaraderie, the shared frustrations, the endless coffees, and the moments of levity that made this journey bearable and often enjoyable. Your friendship has been a constant source of strength.

Finally, my most heartfelt thanks go to my family. Your unconditional love, endless patience, and constant encouragement have been my foundation, especially during a time of immense personal transformation. The years of this PhD, and particularly my time abroad, challenged me in ways I never anticipated and, in doing so, opened the door to a new and wonderful chapter of my life. This achievement is as much yours as it is mine, and it marks a beginning for which I am profoundly thankful.