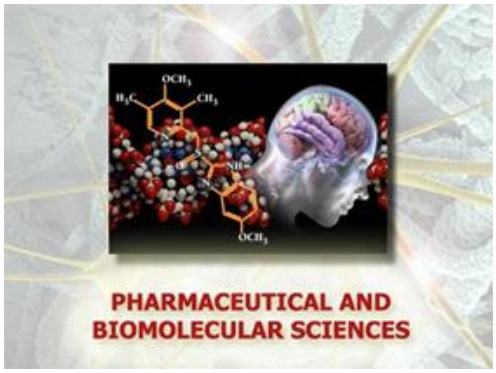

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37th Cycle

Analysis of Real-World Data and update of a Clinical Decision Support System (CDSS) to investigate and support quality and sustainability of pharmacological therapies

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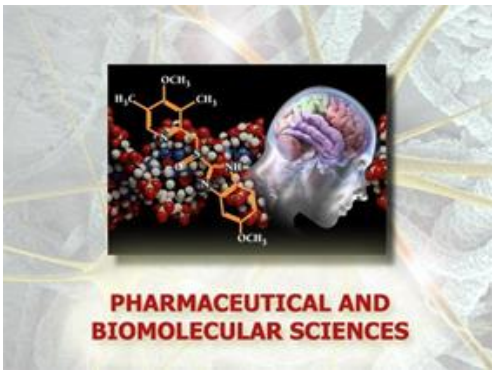

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Revisors: *Prof. Elisabetta Poluzzi, Prof. Enrica Menditto*

Evaluators: *Prof. Clara Cena, Prof. Elisabetta Poluzzi, Prof. Enrica Menditto*

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DIPARTIMENTO DI SCIENZA E TECNOLOGIA DEL FARMACO

DOTTORATO DI RICERCA IN SCIENZE FARMACEUTICHE E BIOMOLECOLARI

CICLO: 37°

TITOLO DELLA TESI: Analysis of real-world data and update of a Clinical Decision Support System (CDSS) to investigate and support quality and sustainability of pharmacological therapies

TESI PRESENTATA DA: Dott.ssa Lucrezia Greta Armando

SUPERVISORE: Prof.ssa Clara Cena

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Ministero dell'Università e della Ricerca
PON RICERCA E INNOVAZIONE 2014 - 2020
REACT EU
UNIVERSITÀ DI TORINO

To the path I never expected,

to the journey that brought me here.

To my loved ones who walked beside me,

and the guides I found along the way.

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PREMISE

This dissertation addresses two main topics: the implementation of digital health technologies to support prescriptive appropriateness and the study of drug use in the real world. The idea for this research project originated from a multi-year collaboration between the supervisor of the research project, Prof. Clara Cena, and the information technology (IT) company Infologic s.r.l. (Padua, Italy) in the context of the continuous update of a clinical decision support system (CDSS) for medication review. The collaboration with the company made it natural to apply for an industrial Ph.D., thanks to funding from the 2014-2020 National Research and Innovation Operational Program *(Programma Operativo Nazionale Ricerca e Innovazione*, PON), which in 2022 funded positions for Ph.D.s in collaboration with companies, with a specific focus on green and sustainability issues. This initiative allowed me to continue the activities started during my first postgraduate work experience, which consisted of a higher education and research apprenticeship carried out in collaboration with the Infologic s.r.l. During the months of apprenticeship, I had the opportunity to delve into the CDSS developed by the company and to work closely with both the software developers and healthcare professionals. This experience reinforced our belief that CDSSs, when appropriately implemented in clinical practice, can be an effective strategy to improve the quality of care, as well as to foster a more rational and informed use of drugs with a view to eco-sustainability and the One Health approach.

In the description of the results of the research, the CDSS developed by the company and improved through collaboration with the Department of Drug Science and Technology (*Dipartimento di Scienza e Tecnologia del Farmaco*, DSTF) will be presented in its overall functioning, illustrating the criteria and how it was updated. The CDSS described is updated to the version of January 2025, the time when this dissertation was written, but please note that the system is constantly being updated and the current version may differ from the one described in terms of the graphics component and some feature. The tables developed during the doctoral program and integrated into the CDSS knowledge-base will be described in general, accompanied by some representative examples. For reasons of company ownership, tables will not be reported in full among the supplementary materials of the dissertation because they are a strategic asset of the company for marketing purposes.

The second topic addressed in this research project concerns drug utilisation research (DUR), the results of which can support healthcare providers in the implementation of strategies to improve the quality of care, with a focus on prescriptive appropriateness and waste reduction to promote sustainable medication use. To this end, research agreements were signed with healthcare facilities in Piedmont and neighbouring regions to exchange anonymized electronic health data to be used in the analyses conducted during the doctoral program. DUR results were numerous and only the main ones that were of greatest interest to the healthcare professionals involved in the research will be discussed in the dissertation.

1. INTRODUCTION

1.1. Digital health technologies to support clinical decision and medication management

Digital technologies are playing a key role in transforming healthcare, driving the evolution of digital health from electronic health records to advanced diagnostic support systems.

The concept of digital health emerged in the early 2000s as a response to the rapid expansion of medical knowledge and the growing integration of technology in healthcare. [1-3] Since then, the digitalization of healthcare and all the elements that revolve around patient care became unavoidable, leading to more efficient workflows and improved patient outcomes.

The World Health Organization (WHO) defines digital health as "*the field of knowledge and practice associated with the development and use of digital technologies to improve health […] Digital health expands the concept of eHealth to include digital consumers, with a wider range of smart and connected devices. It also encompasses other uses of digital technologies for health such as the Internet of Things (IoT), advanced computing, big data analytics, artificial intelligence including machine learning, and robotics*". [4] Since a globally recognised taxonomy is lacking, the term digital health comprises a variety of solutions with different uses and applications, such as mobile health (mHealth), telemedicine and big data applications (including genomics, blockchain and machine learning). [1,3] mHealth, for example, is a branch of electronic health (eHealth) and is generally referred to the use of consumer-facing mobile applications (smartphone apps) to obtain information and communications supporting health. Telemedicine is the set of services that exploit electronic communications and technological supports to assist and visit patients, spread especially during and after the coronavirus disease 19 (Covid-19). Storage, analysis and utilization of big data are also part of the broader concept of digital health, as they exploit digitalized health data to aid diagnosis and treatment selection. [1]

Early digital health technologies were mainly focused on reducing manual errors during the compilation of medical records and orders. Nowadays, thanks to the increasing popularity of artificial intelligence (AI), digital health has expanded its scope to include, amongst others, predictive analytics, personalized medicine and patient engagement tools. [1] Principal differences between traditional and digital health concerns patient-physician relationship, patient care, use of clinical data and physician role (Figure 1).

Traditional healthcare	Digital healthcare
Direct patient-physician relationships	Patient-machine-physician interface
Standardized care based on physician experience and standard clinical workflow: Symptoms, clinical signs, ancillary medical tests, diagnosis, and treatment plan	Individualized care, precision medicine, with non-traditional workflow: Mass screening, early preclinical or asymptomatic diagnosis, diagnosis based on probability, predictive technology, and decision support for physicians
Point of care delivery or examination is at the clinic or lab	Point of care delivery or examination may vary as long as patient is present
Data owned by the institutions/hospitals	Data owned and shared by multiple stakeholders, including the patient
Physician as the central player who makes diagnosis, and prescribes treatment plan	Physician as a consultant, guide or collaborator with the patient's active contribution in the decision making

Figure 1. Differences between traditional and digital health. Source: Yeung AKW, *et al*. Front Public Health 2023 [1]

Despite these advances, some challenges remain to implement new digital technologies in healthcare. First, low digital literacy and/or low access to technology may represent a limitation for both healthcare professionals and patients, especially older adults. Second, poor technology design and inadequate usability could generate resistance among professionals, limiting the adoption of digital tools in clinical practice. Third is the lack of globally recognised regulations to assure quality and effectiveness of the new technology: while the introduction of new drugs requires rigorous studies and authorisation by recognised health authorities, most digital tools (i.e., apps, personal health device) are introduced into the market with little or no quality assurance. [1] Other challenges in the implementation of new health technologies are high costs, privacy concerns, data ownership and alert fatigue. [1] Particularly, alert fatigue occurs when the number of warnings generated by a digital tool is excessive and they lack specificity, leading the user to ignore the alerts. Several systematic reviews of scientific literature have estimated that alert override ranges from 50% to >90%, and recent surveys reveal that a consistent percentage of clinicians complain about the high number of irrelevant alerts and are not satisfied with digital tools. [5,6] Another significant limitation to the introduction of innovative digital technologies into the clinical workflow is low interoperability with digital solutions already employed in the healthcare facility. [1,3] Figure 2 summarizes some possible approaches to overcome these challenges.

Challenges	Possible approaches to overcome
Technical	
Data structure and heterogeneity (interoperability)	Unify data format, security and sharing requirements
Digital technology infrastructure	Cloud computing and storage; use of blockchain for secured and decentralized data storage and transport
Non-technical (4 Ps)	
Patient (lack of acceptance, privacy issue, lack of motivation, fear of technology, etc.)	More "how to use" quick guides and ready-to-help staff; more patient involvement in the design; more support to caregivers; encourage promotion from the patient's attending physicians
Physician (resistance, lack of incentives, fear of losing jobs, changing roles, etc.)	System overhaul and accredited points for continuous professional development schemes; establish clarity in regulation and standardization
Public/society (ethics, acceptance, public education etc.)	Promotional campaigns led by celebrities; evaluate and demonstrate evidence of cost-effectiveness
Policy (ethics, financial, regulatory, especially in less resourceful countries)	Lobbying and public-private partnerships; establish clear legal framework regarding reimbursement schemes and data transparency; provide subsidy to cover high start-up costs or incentivize the use

Figure 2. Challenges to implement digital health and possible solutions. Source: Yeung AKW, *et al*. Front Public Health 2023 [1]

Therefore, for digital health to continue to evolve and enter daily clinical practice, gaps need to be filled by expanding medical knowledge and changing attitudes. [2] Particularly, both the development and implementation of digital health technologies should prioritize interdisciplinary collaboration, including clinicians, pharmacists, informatics and other stakeholders to ensure usability and clinical relevance. Moreover, digital tools should integrate evidence-based guidelines and recommendations that require periodic verification by qualified personnel. Finally, for users to be able to effectively use digital tools, training and education programs should be promoted among both healthcare professionals and patients or caregivers to improve digital literacy.

1.1.1. The role of digital health in healthcare

Patient harm due to medication errors and unsafe drug use has been recognized as a leading cause of mortality and disability worldwide, accounting for nearly half of the overall preventable harm in healthcare. [7] It has been estimated that in Europe costs associated with medication errors accounted for €4.5-21.8 billion/year. [8] Moreover, a recent investigation by the European Medicines Agency (EMA) [9] revealed that medication errors occurring during hospital stays ranges from 0.3% to 9.1%, while up to 2.1% of medication dispensing may present errors. Medication errors represent the most common adverse events in hospitals, with significant consequences both in terms of patient safety and sustainability of healthcare systems. They may occur in all healthcare settings and at any stage of the medication process: administration (54.4% of total estimated medication errors), prescription (21.3%), dispensing (15.9%), monitoring (7.0%) and transition of care (1.4%). [8,9] According to the WHO [10], medication errors are preventable events caused by unreliable medication systems and/or human factors that may lead to inappropriate medication use or harm to the patient. It is estimated that heavy workloads, fatigue, poor work conditions and lack of healthcare personnel contribute to one quarter of medication errors in Europe. Moreover, preventable adverse events related to inappropriate medication use are a leading cause of death worldwide, responsible for greater mortality than breast cancer, acquired immune deficiency syndrome (AIDS) or motor vehicle accidents in the U.S. [9,11] Possible consequences of an excessive or inappropriate use of medications are adverse drug reactions (ADRs), increased risk of toxicity, antimicrobial resistance and prolonged hospital stay, as well as decreased faith in the healthcare service and wastage of public economy. [12] Mental health of the healthcare staff involved in adverse events related to medication errors should also be mentioned, since studies [8,9,13] showed that half of hospital workers become a “second victim” at least once during their career, exhibiting psychosocial disorders such as loss of self-confidence, guilt and fear of litigation.

A report [14] produced by the Institute for Safe Medication Practices (ISMP) described medication errors detected in 2023 that caused potentially fatal or harmful hazards to patients. ISMP is an American nonprofit organization that collaborates with healthcare institutions to provide insights about medication errors and their prevention. Particularly, ISMP launched a program in which patients and practitioners can voluntarily report medication errors, which are then reviewed by the organization offering recommendations

to prevent such errors. Below are some common medication safety issues that could be avoided with system and practice changes, as identified by previous studies: [9,13,15]

- Errors due to omission or delay in medication (i.e., delayed administration of antidotes, reversal agents or rescue agents).
- Administration of medication to the wrong patient.
- Errors associated with allergies or adverse events known for the medication.
- Errors in calculating the dosage for paediatric patients (lack of well-established work protocols).
- Errors due to likeness in labelling or the packaging of medication sold.
- Infusion-related medication errors due to lack of use of smart infusion pumps.
- Errors due to inadequate labelling or unsafe storage of neuromuscular blocking agents (accidental administrations to patients).
- Errors due to wrong administration route (intravenous administration or oral liquid medications).
- Errors in medication reconciliation on hospital admission and discharge.
- Errors due to comprehension problems between patients and practitioners on how to use the medication.

To prevent risks associated with medication errors, the WHO lunched in 2017 a global initiative called “Medication Without Harm” aimed at reducing medication errors by 50.0% over the coming years. [16] In this context, digital health and electronic monitoring systems have been recognized as valuable strategies to prevent and reduce errors associated with every stage of medication use. Three key action areas have been identified by the WHO to avoid medication errors and protect patients from medication harm: high-risk situations, polypharmacy and transition of care. [7,8] Specifically, digital tools can help healthcare professionals identify patients that use high-risk medications, as well as enhance physician’s and patient’s awareness of the appropriate use of medications and support medication review. Transitions of care increase the possibility of communication errors, therefore tools supporting medication reconciliation[i] represent essential elements to promote good

[i] Medication reconciliation differs from medication review. The first is a process to ensure an accurate and consistent medication list during transitions of care; medication review is a periodic assessment of a patient's medications to optimize therapy and increase medication appropriateness. These concepts will be better described in the dedicated chapter (1.2.2).

communication between healthcare professionals and reduce medication errors. [8] Figure 3 highlights four domains within the three key action areas introduced by the WHO to address medication safety.

Figure 3. Key action areas and domains of the strategic framework introduced by the WHO to promote medication safety. Source: WHO. Medication without harm: policy brief. 2023 [7]

A key aspect that has emerged in recent years and is emphasized by the WHO strategic framework is the increasing recognition of the patient's role in managing their own health. Patients have gone from passive stakeholders of care to proactive participants engaged in care-decision making to achieve better outcomes. [2] This shift took place through both an increased health literacy and the adoption of patient-centred approaches, which prioritize education, shared decision-making and the use of digital tools to support self-management and informed choices. [7]

The European Collaborative Action on Medication Errors and Traceability (ECAMET), a European alliance comprising scientific and patients' organizations created in the context of the WHO initiative "Medication Without Harm", identified health technologies with the

highest potential to reduce medication errors and enhance patient safety and empowerment: [9]

- Electronic prescription systems including personalized medication safety alerts (i.e., interactions, duplications) and clinical decision rules to support clinical-decision making. Evidence gathered by the ECAMET [9] showed that fully integrated computerized provider entry systems (CPOEs) can reduce medication prescription errors; despite almost all hospitals included in the ECAMET survey have CPOEs, integration with hospital systems is still limited, with only 20.0% of them being integrated with a CDSS and less than 60.0% with electronic medical records.
- Automated medication cabinets integrated with the information system of the healthcare facility proved effective in improving efficiency of the healthcare staff and reducing healthcare costs. Nevertheless, an ECAMET survey [9] showed that availability of automated drug cabinets is limited and that less than 20.0% of them have a barcode system to verify the selection of medications prior to dispensing.
- Electronic preparation/compounding systems, especially for sterile and injectable preparations. These are advanced technologies for the preparation and mixing of specific medications.
- Systems for placing pharmacy orders and managing medication inventory.
- Point-of-care systems including both barcodes designed to detect medication errors during distribution or administration of drugs and patient identification systems (i.e., barcode bracelet). These allow to verify the right medication, the right patient and the right moment, preventing medication errors during administration and omissions.
- Smart infusion pump systems including alerts about minimum and maximum dosage levels and concentration.

On a global and European level, numerous initiatives have been promoted to favour the adoption of effective healthcare practices that include the use of digital health tools. Those of greatest relevance are the Global strategy on digital health 2020-2025 by the WHO [17] and the European program MyHealth@EU. [18] The first represent a global strategy with the aim to strengthen health systems through the development, adoption and implementation of digital health technologies intended for various types of users, including healthcare

professionals, healthcare providers, industry, consumers and patients. MyHealth@EU is an example of the WHO vision, aimed at facilitating the cross-border transfer of health data between 25 EU Member States by 2025. This service will use electronic prescriptions and the patients' summary health profile to enable European citizens to receive healthcare in the country they are travelling to in the same way as in their country of residence, through a novel digital communication channel that allows patients' data to be exchanged quickly, safely and efficiently.

1.1.2. Classification of digital health technologies

As anticipated in the previous chapters, the term digital health does not match with a single definition, but it encompasses a variety of tools and applications designed to achieve different objectives. Similarly, the classification of digital health technologies is also ambiguous, as it can be based on different criteria, such as scope, technology employed, end user, mode of service delivery, level of interoperability and data security.

The classification proposed by the Digital Therapeutics Alliance in 2023 [19] can represent a reference standard as it derives from a comprehensive review of the most recent publications from regulatory bodies and the global landscape of digital health. In order to promote a consistent and unambiguous understanding of the digital landscape for the stakeholders involved, eight macro-categories of digital health technologies have been identified based on the following criteria: end user; intended benefits/claims; regulatory scrutiny; strength of evidence; intervention type. [19]

The eight categories are summarized in Table 1. Given the complexity of digital health technologies, some digital health applications can include multiple characteristics and fall into different categories.

Table 1. Classification of digital health technologies. Source: Health Advances. Guidance to Industry: Classification of Digital Health Technologies (2023) [19]

Category	End user	Description	Applications examples
Digital health solutions	Industry, admins	Digital health solutions that can be used by companies in the field without necessarily being integrated with hospital or healthcare infrastructure	Data management systems (e.g., blockchain)
Health system operational software	Industry, admins	Enterprise health-information technology intended to provide non-clinical system benefits and support	Hospital information systems, staff management software, telemedicine management systems
Health system clinical software	Healthcare professionals	Enterprise health-information technology and digital health solutions intended to provide clinicians with support managing their patient populations	CDSSs, clinical documentation and image archiving, telemedicine platform
Health and wellness	Patients	Disease-agnostic solutions that capture, store, and sometimes transmit health data and promote general wellbeing and healthy living	Wearables (e.g., smart watch), health diaries, IoT-enabled health sensors
Patient monitoring	Patients	Solutions intended to monitor specific patient health data that may be used to inform management of a specific disease, condition or health outcome	Mobile apps to manage medication adherence, ePROs, non-wearable patient device (e.g., smart scales, pressure monitors)
Care support	Patients	Solutions intended to support patient self-management of a specific diagnosed medical condition through education, recommendations and reminders	Mobile apps, virtual reality, smart drug administration support
Digital diagnostics	Patients, healthcare professionals	Validated digital tools for detecting and characterizing disease measuring disease status, response, progression or recurrence	AI-based technologies, IoT-integrated diagnostic tests, portable diagnostic device
Digital therapeutics	Patients, healthcare professionals	Health software intended to treat or alleviate a disease by generating and delivering a medical intervention that has demonstrable positive therapeutic impact	Chatbots, digital rehabilitation and physiotherapy, disease monitoring product impacting medication delivery

Abbreviations: IoT, Internet of Things; CPOE, computerized provider entry systems; CDSS, clinical decision support system; ePRO, electronic patient reported outcomes; AI, artificial intelligence

Industry and admin-facing technologies are addressed to healthcare providers, hospital administration and non-patient stakeholders in the healthcare industry. These technologies

have an indirect impact on patient care and mostly concern enterprise software, such as data and personnel management systems, which are essential for health systems to operate efficiently. Other examples of possible applications are included in Table 1.

Technologies intended for healthcare professionals include CPOEs, CDSSs and telemonitoring systems able to support physicians and other healthcare professionals in their daily activities. To date, this category does not require special regulation as their impact on patient's care is filtered through the guidance of an authorized healthcare professional. These solutions are particularly relevant because they offer healthcare professionals a vast amount of information to guide clinical decision-making.

Patient-facing technologies have the potential to directly impact clinical outcomes; they include tools intended for patient to use, such as mobile apps and wearables, and could also incorporate features to be used by physicians or other professionals. These may or may not state health claims; in presence of health claims, patient-facing digital health technologies require supporting evidence and regulatory approval. Evidence requirements and regulatory implications may vary as they are established by national and local regulatory authorities and are constantly evolving. Digital therapeutics (DTx) and digital diagnostics are the only products capable of delivering a medication intervention directly through their software and may, therefore, apply for reimbursement by health systems. Other patient-facing digital health technologies can provide clinical recommendations and information that could indirectly improve patient's health and promote healthier living, but they do not serve as or drive diagnosis or interventions on their own. Figure 4 summarises the main differences among patient-facing digital health technologies.

DHT Category	Health & Wellness	Patient Monitoring	Care Support	Digital Diagnostics	Digital Therapeutics
Overview	• Disease-agnostic digital health solutions that primarily capture and store general health data and promote healthy living	• Digital solutions intended to monitor specific health data, which may be interpreted by physician for clinical management	• Digital solutions intended to help patients better manage their care of a specific disease or medical condition	• Validated digital tools and software that deliver a diagnosis or prognosis of a specific disease or medical condition	• Health software intended to treat or alleviate a specific disease or medical condition by generating and delivering a medical intervention
Claims	✗ No claims to treat, improve, or diagnose a medical condition	~ May make non-clinical claims to assess patient data	~ May make non-clinical claims to improving health-adjacent measures (e.g., adherence)	✓ Make a clinical claim to diagnose or assess a specific disease or medical condition	✓ Make a clinical claim to treat or alleviate a specific disease or medical condition
Intervention Delivery	✗ Does not deliver a medical intervention	~ Collects health data to inform HCP decision making around medical intervention	~ May recommend actions for patients to better manage care or inform HCPs but does not deliver medical intervention	✓ Software drives medical intervention through a formal diagnosis or assessment	✓ Software itself generates and delivers a medical intervention
Evidence Requirements	✗ Not required	~ Non-clinical claims to assess patient data, must be validated and meet a regulatory agency's quality requriements	~ Any non-clinical claims (e.g., adherence) must be validated and meet a regulatory agency's quality requirements	✓ Diagnostic accuracy must be validated and meet a regulatory agency's quality requirements	✓ Efficacy claims must meet a regulatory agency's quality requirements
Regulatory Implications	✗ No regulatory oversight	~ May require regulatory approval and labeling	~ May require regulatory approval and labeling	✓ Regulated solution with label for indication, usage, evidence, warnings, etc.	✓ Regulated solution with label for indication, usage, evidence, warnings, etc.

Figure 4. Characteristics of patient-facing digital health technologies. Technologies are ordered from left to right for increasing impact on clinical management, increasing evidence demand, increasing regulatory scrutiny and increasing willingness of stakeholders to pay. Source: Health Advances. Guidance to Industry: Classification of Digital Health Technologies (2023). [19]
Abbreviations: DHT, digital health technology; HCP, healthcare professional

1.1.3. Clinical Decision Support Systems (CDSSs)

To explore the topic of CDSSs, which represents the main theme of this dissertation, a scoping review was carried out during the Ph.D. to summarize the main characteristics of existing CDSSs. A scientific publication resulted from this review [20]; therefore, part of this chapter is already included in an existing publication of which I am first author which is cited below.

CDSSs can be categorized as digital health technologies addressed to healthcare professionals and designed to provide interactive computer-based information to guide professionals in the clinical decision-making process. They were first developed 50 years ago with the aim of promoting optimal problem solving, decision-making and actions by decision makers, as well as making it easier to access to patient data. [21]

Traditional CDSSs consist of three main components: a clinical knowledge-base, the inference engine or processing layer that combines information from the knowledge-base with input data and the user interface. Generally, the knowledge-base incorporates both concepts derived from scientific literature and expert knowledge; it should be kept constantly updated to keep up with the new evidence generated in clinical practice. [22] Traditional CDSSs can offer clinicians patient-specific advice based on globally recognized recommendations, as well as increase physician's adherence to medical guidelines.

A second type of CDSSs is represented by AI-CDSSs, or nonknowledge-based CDSSs, which still require a data source but leverage AI and machine learning to generate recommendations tailored to patient characteristics. These require computer-intensive and time-consuming processes and the analysis of significant amounts of data to provide accurate decisions. [23,24]

CDSSs can be used for multiple purposes, including diagnostics, disease management, prescription, drug control, alarm systems, and much more. However, their implementation in clinical practice still encounters several obstacles, among which low ease of system use, negative end-user attitudes towards the system, non-specific or irrelevant data or documentation, fragmented workflow and financial challenges. [23,24]

Table 2 summarizes the characteristics identified by the scoping review of CDSSs implemented in worldwide clinical practice to aid decision making. Included articles were studies published between January 2017 and January 2022 in which CDSSs were used to analyze patient-specific information and generate case-specific guidance messages through

rule-based software or algorithms; studies also had to report at least one outcome measuring the effect of CDSS on the quality of care provided to patients. For further details on the inclusion and exclusion criteria adopted in the scoping review, please refer to the published article. [20]

Table 2. Characteristics of CDSSs implemented in clinical practice. Source: Armando LG, *et al*. BMJ Health Care Inform 2023 [20]

Characteristics	Number of studies including the characteristic (%)		
	Total studies (n=42)	**Studies with positive results** (n=25)	**Studies with negative or uncertain results** (n=17)
Type of CDSS			
Rule-based (knowledge-base)	22 (52.4)	11 (44.0)	11 (64.7)
Guidelines (knowledge-base)	13 (31.0)	9 (36.0)	4 (23.5)
AI-based	3 (7.1)	2 (8.0)	1 (5.9)
Digital checklist	2 (4.8)	1 (4.0)	1 (5.9)
Predictive models (machine learning)	2 (4.8)	2 (8.0)	0 (0.0)
Purpose of application			
Disease-related			
Disease treatment and management	16 (38.1)	10 (40.0)	6 (35.3)
Risk assessment of adverse outcomes	3 (7.1)	3 (12.0)	0 (0.0)
Diagnosis	1 (2.4)	1 (4.0)	0 (0.0)
Drug-related			
Medication review	12 (28.6)	6 (24.0)	6 (35.3)
Prescriptive appropriateness	7 (16.7)	4 (16.0)	3 (17.6)
Deprescription	3 (7.1)	1 (4.0)	2 (11.8)
End-users			
Multidisciplinary team	18 (42.9)	10 (40.0)	8 (47.1)
Clinician	10 (23.8)	4 (16.0)	6 (35.3)
Pharmacist and/or pharmacy technician	7 (16.7)	6 (24.0)	1 (5.9)
GP	3 (7.1)	1 (4.0)	2 (11.8)
Researcher	3 (7.1)	3 (12.0)	0 (0.0)
Nurse	1 (2.4)	1 (4.0)	0 (0.0)
Platform for CDSS delivery			
Integrated into EHRs	18 (42.9)	11 (44.0)	7 (41.2)
Web-based software	9 (21.4)	6 (24.0)	3 (17.6)
Mobile application	4 (9.5)	2 (8.0)	2 (11.8)
Integrated with CPOE	3 (7.1)	2 (8.0)	1 (5.9)
Integrated into a vital sign monitor	1 (2.4)	0 (0.0)	1 (5.9)
NA	7 (16.7)	4 (16.0)	3 (17.6)
Healthcare facility where the CDSS was used			
Hospital wards	30 (71.4)	19 (76.0)	11 (64.7)
GP clinic	5 (11.9)	1 (4.0)	4 (23.5)
Emergency department	3 (7.1)	1 (4.0)	2 (11.8)
Clinical centre	2 (4.8)	2 (8.0)	0 (0.0)
Community pharmacy	2 (4.8)	2 (8.0)	0 (0.0)
Characteristics of patients for whom the CDSS was used			
High complexity			
Chronic kidney disease	2 (4.8)	2 (8.0)	0 (0.0)
Need for feeding tube	2 (4.8)	2 (8.0)	0 (0.0)
Children	2 (4.8)	2 (8.0)	0 (0.0)
Polymedicated with ≥10 drugs	2 (4.8)	1 (4.0)	1 (5.9)

Need for resuscitation	2 (4.8)	1 (4.0)	1 (5.9)
Therapy with high-risk drugs	1 (2.4)	1 (4.0)	0 (0.0)
Cancer	1 (2.4)	1 (4.0)	0 (0.0)
Medium complexity			
Infectious disease	3 (7.1)	2 (8.0)	1 (5.9)
Opioid use disorder	2 (4.8)	1 (4.0)	1 (5.9)
Need for epidural anaesthesia	1 (2.4)	0 (0.0)	1 (5.9)
Lower complexity			
Unspecified comorbidities	6 (14.3)	2 (8.0)	4 (23.5)
Polymedicated with ≥4 drugs	3 (7.1)	1 (4.0)	2 (11.8)
Asthma	2 (4.8)	2 (8.0)	0 (0.0)
Diabetes	2 (4.8)	1 (4.0)	1 (5.9)
COPD	1 (2.4)	0 (0.0)	1 (5.9)
Adrenal insufficiency	1 (2.4)	0 (0.0)	1 (5.9)
Neuropathy	1 (2.4)	0 (0.0)	1 (5.9)
NA	8 (19.0)	6 (24.0)	2 (11.8)

Abbreviations: CDSS, clinical decision support system; AI, artificial intelligence; GP, general practitioner; EHR, electronic health record; CPOE, computerized provider/physician order entry; NA, not available; COPD, chronic obstructive pulmonary disease

As shown in Table 2, CDSS proved effective in supporting clinical practice and improving treatment outcomes in different healthcare scenarios in 25 studies out of 42 (59.5%). As expected, most of the CDSSs effectively implemented in clinical practice were knowledge-base CDSS, including both validated criteria to identify potentially inappropriate medications (PIMs) and guidelines, since these are the simplest and fastest systems to be developed and used. In the majority of the studies analyzed, the implementation of CDSSs in clinical practice improved disease management, increasing the number of PIMs detected, reducing the number of patients that experienced adverse outcomes and enhancing the prescription of appropriate treatments. This aspect is particularly important for certain categories of patients, such as complex patients suffering from multiple chronic diseases, who often need their polytherapy to be reviewed due to the high number of medications co-prescribed by different specialists. Two particularly interesting aspects characterized successful studies more than unsuccessful ones: first is the participation of pharmacists in the studies as part of the multidisciplinary team or as the principal investigator; secondly, the presence of a period of education and training for healthcare professionals on the use of the CDSS implemented.

Despite the mostly positive results, the reported evidence does not allow solid conclusions to be drawn on the effect of CDSSs in real clinical practice, both due to the heterogeneity of the interventions implemented and the limited number of CDSSs analysed. However, it is possible to derive some general characteristics that CDSSs should possess in order to favour

their adoption: ease of use; immediate availability of patient information; integration into health facility information systems to reduce work time and the risk of errors during data transfer; use by different healthcare professionals involved in patient management, including pharmacists; active patient involvement in the management of his or her disease.

To conclude, although further research is needed to establish the definitive impact of CDSSs in clinical practice, the identification of these key characteristics may provide valuable guidance for the design and implementation of future digital technologies.

1.1.4. Ethical aspects related to digital health

To ensure that the benefits of digital technologies are equally distributed among the population and that their risks are minimized, some ethical issues related to the integration of these technologies in clinical practice should be addressed. Indeed, despite their potential to revolutionize care management, digital technologies could negatively impact the quality of patient care when used improperly or by unqualified personnel. [25] There are four main aspects to consider when discussing ethics and digital health: equity, data privacy and security, responsibility and autonomy. [26,27] Specifically, equity in access to digital technologies is a crucial issue to consider as there is considerable risk that these tools will exacerbate existing inequalities. Factors such as the availability of digital infrastructure, digital literacy and economic resources greatly influence the adoption of digital innovations, disadvantaging communities with limited resources or low technological knowledge. Another element of inequity to consider is related to the use of algorithms and predictive machine learning models, which can reflect and amplify existing biases in the data used to train them. To mitigate these risks, it is important to design intuitive and accessible tools, as well as to provide support and guidance for appropriate use of technologies. [26,28] Additionally, ensuring the inclusion of a wide variety of representative data from different demographic groups in algorithm development and rigorous model validation can help reduce algorithm biases and ensure transparency. Researchers should expand the inclusion of participants with diverse backgrounds and belonging to groups that are often marginalized (such as older adults) in technology research and design to enable better representation of different levels of digital literacy and technology access. [26]

Adhering to data privacy standards is essential for health technologies since they collect vast amounts of personal and sensitive data from patients and/or users. Although this data is critical for providing personalized recommendations and developing predictive models, the use of large-scale repositories creates challenges for data management and ownership, data transfer and storage and privacy protection. [26] Moreover, consent for secondary use of data (i.e., marketing and research) is unlikely to include an exhaustive list of all possible data uses, posing a challenge to the principle of informed consent and/or placing individuals in the position of accepting the terms without fully understanding the implications of their decision. [28,29] Misuse or breach of data could result in discrimination, legal issues and loss

of trust in healthcare systems. Therefore, appropriate technology support systems should be adopted to ensure robust security measures. [29]

Responsibility is another aspect to consider when using digital technologies. It refers to the balance of power, trust and the relationship between stakeholders. In particular, public trust should be built on accountability, transparency and benefit-sharing. Clinical decision support technologies have the potential to undermine current norm of professional accountability, making it more complicated to assign responsibility to individual practitioners. Systems should be designed so that users can clearly understand how recommendations or outcomes are generated. Explainability is crucial not only to foster user trust, but also to ensure that clinicians can justify decisions made with the support of digital tools. Lack of transparency can limit the acceptance of these technologies and compromise the quality of care. Therefore, it is essential to elaborate specific and robust evidence standards to guide the adoption of digital health technologies. [26,29]

Finally, digital technologies also influence the empowerment of patients and healthcare professionals. On the one hand, tools such as wearable devices can promote patient empowerment, enabling patients to better manage their own health. On the other side, the use of decision support systems could reduce physicians' autonomy, prompting them to rely on machine suggestions instead of exercising their own clinical judgment. This raises questions about who is liable in case of errors: the practitioner, the patient, the system, or the manufacturer of the technology? Clarification of responsibilities is essential to avoid situations of ambiguity and ensure ethical and safe use of these technologies. [30] In this regard, the European eHealth Network (eHN) published in 2022 16 ethical principles that provide a framework for European citizens' trust in digital health (Table 3). [28]

To conclude, ethical integration of digital health should be supported by policies that promote continuing education to healthcare professionals, patient participation and validation of technologies prior to large-scale adoption. In this way it is possible to ensure that digital technologies contribute to improving public health while minimizing ethical and legal risks. [30]

Table 3. European ethical principles of digital health. Source: Serussi B, *et al*. MEDINFO 2023 [28]

Base Digital Health on humanistic values
1. Digital Health complements and optimizes face-to-face healthcare
2. Individuals are informed about the benefits and limits of Digit al Health
3. Individuals are informed about the functioning of Digital Health services and can easily customize interactions with them
4. When AI is used, all reasonable efforts are made to make it explainable and without discriminatory bias
Enable individuals to manage their Digital Health and data
5. Individuals are actively involved in shaping the European and national frameworks of Digital Health and data
6. Individuals can easily and reliably retrieve their health data in a commonly used format
7. Individuals can easily get information on how their health data have been or may be accessed and for which purpose
8. Individuals can easily and reliably grant access to their health data and exercise their rights, including objection when applicable
Make Digital Health inclusive
9. Digital Health services are accessible by all, including by people with disabilities or low levels of literacy
10. Digital Health services are intuitive and easy to use
11. Individuals have access to Digital Health training
12. Digital Health services include support through human communication when needed
Implement eco-responsible Digital Health
13. Environmental impacts of Digital Health are identified and measured
14. Digital Health services are developed in compliance with eco-design best practices
15. Re-use and recycling of Digital Health equipment is ensured
16. Digital Health stakeholders are committed to reducing their ecological footprint

Abbreviations: AI, artificial intelligence

1.2. Support for prescriptive appropriateness

Appropriateness of prescriptions can be defined as the accuracy of drug prescriptions in terms of correspondence between therapeutic indication and diagnosis, but it also refers to the result of a multidimensional and personalized assessment of pharmacological therapies in patients with varying degrees of therapeutic complexity.

In Italy, the concept of prescriptive appropriateness is included in article 1, paragraph 2, of Legislative Decree 30/12/1992, no. 502, which states that the National Health Service (NHS) should ensure, through public resources, the essential levels of care defined by the National Health Plan in compliance with the principles of dignity of the human person, need for health, equity in access to care, quality of care and its appropriateness with regard to specific needs, as well as economy in the use of resources. [31] Therefore, appropriateness of prescriptions represents not only a regulatory requirement for healthcare professionals to comply with, but also a cardinal principle for ensuring the quality and effectiveness of care. This concept is supported and enhanced by a wide range of international recommendations and guidelines, most notably documents published by the WHO in the early 2000s [32,33], which emphasize some certain unavoidable focal points, namely effectiveness, efficiency and consistency: “appropriateness is a complex, fuzzy issue that defines care that is effective (based on valid evidence), efficient (cost-effective), and consistent with the ethical principles and preferences of relevant individuals, communities or society”. [32] Moreover, appropriate use of medications requires that “patients receive medications appropriate to their clinical needs, in doses that meet their individual needs, for an appropriate period of time, and at the lowest cost to them and their community”. [33] These principles, while representing a universal recommendation, must be adapted to the clinical needs of individual patients and to different economic and healthcare contexts. [32,33]

Linked to the concept of prescriptive appropriateness is the definition of evidence-based medicine (EBM), which is promoted by the above-mentioned documents in order to improve overall health. Indeed, prescriptive appropriateness is based on the use of diagnostic and therapeutic interventions supported by the best available scientific evidence. Similarly, EBM aims to combine scientific evidence with clinical expertise and patient preferences, ensuring that every medical decision meets the standards of effectiveness, efficiency and sustainability. With this in mind, prescriptive appropriateness represents an essential element to translate principles of EBM into daily clinical practice. [33]

Below is a summary of the 12 key interventions advocated by WHO to promote more rational and appropriate use of medications (Table 4). [33]

Table 4. Key interventions to promote a more rational use of medications. Source: WHO. Promoting rational use of medicines [33]

1	Establishment of a multidisciplinary national body to coordinate policies on medicine use
2	Use of clinical guidelines
3	Development and use of national essential medicines list
4	Establishment of drug and therapeutics committees in districts and hospitals
5	Inclusion of problem-based pharmacotherapy training in undergraduate curricula
6	Continuing in-service medical education as a licensure requirement
7	Supervision, audit and feedback
8	Use of independent information on medicines
9	Public education about medicines
10	Avoidance of perverse financial incentives
11	Use of appropriate and enforced regulation
12	Sufficient government expenditure to ensure availability of medicines and staff

As previously mentioned, ensuring the appropriateness of prescriptions means not only selecting the right medication based on evidence-based recommendations, but also tailoring the choice, dosage and duration to the specific needs of patients. When medications are prescribed without adequate consideration of the patient's clinical context (such as comorbidities and age-related physiological changes), potentially inappropriate prescriptions (PIPs) can occur. PIPs are one of the main determinants to medication-related harm and medication-related problems (MRPs), which may result in ADRs, decreased treatment efficacy, increased healthcare costs and reduced patient safety.

In the following chapters, MRPs and supporting tools will be addressed, as well as categories of patients who are most likely to suffer medication-related harm. Tools mentioned below may or may not be integrated in digital health technologies to assist healthcare professionals in identifying, resolving and preventing PIPs and MRPs, thus improving patient outcomes and ensuring safer medication practices.

1.2.1. Medication-related problems (MRPs) and potentially inappropriate prescriptions (PIPs)

A MRP is defined as “an event or circumstance that involves drug therapy that actually or potentially interferes with the desired health outcomes” and contributes significantly to both high healthcare costs and ADRs. [34] Particularly, moderate ADRs have been identified as a major cause of hospitalization in the U.S., while severe ADRs could result in permanent harm or death. Moreover, it has been estimated that, in the U.S., 25-75% of hospitalizations could be avoided through optimization of pharmacological therapies. [35] Therefore, early recognition and resolution of MRPs are needed to increase patient safety and reduce healthcare costs. [34]

From a pharmacological perspective, MRPs can lead to intrinsic or extrinsic toxicity. The first refers to the unintended interaction between the intrinsic characteristics of the drug and the human body, such as both common and rare ADRs (i.e., constipation when using opioid medications or anaphylactic shock). Extrinsic toxicity is caused by problems due to the handling of the drug by healthcare professionals or patients. [36]

From a patient perspective, there are four categories of MRPs: problems in obtaining the medication, problems in taking the medication, medication effects and problems in communication and care coordination (Table 5). [37]

Table 5. Categories of MRPs with representative problems from a patient perspective. Source: Nicosia *et al*. J Gen Intern Med 2019 [37]

1. Problems with obtaining medications	- Problems with medication costs and/or insurance coverage - Expired medications/disposal issues - Problems related to prior authorization for medications - Problems getting to the pharmacy - Problems understanding and obtaining refills and renewals
2. Problems with taking medications	- Forgetting to take medications - Problems with organizing medications - Problems with medication dosing/frequency/schedule - Problems administering medications (e.g., large pills difficult to swallow)
3. Problems with medication effects	- Concerns about whether medications are effective - Problems with current side effects of medications - Concerns that long-term medication use may induce future side effects - Concerns about interactions between medications
4. Problems with communication, care coordination and medication information	<u>Communication between patients and clinicians</u> - Poor relationship with primary care provider leads to uncertainty, concerns, or distrust of medications - Lack of an advocate during appointments leads to suboptimal communication and decisions around medications - Conflicts between patients and clinicians over whether to stop a medication - Confusing medication information (e.g., prescription inserts, advertisements) <u>Communication challenges within the healthcare system</u> - Difficulties communicating among multiple prescribers leads to suboptimal medication use

Ayalew and coworkers identified the most common causes of MRPs through a revision of scientific literature, such as polypharmacy, old age, gender, the presence of multiple concomitant diseases, lower educational level and functional dependence; they also highlighted that more than 40% of hospitalizations caused by MRPs are potentially preventable. [35] Similarly, Rogan *et al*. identified polypharmacy, lower level of formal education, lower incomes, low self-confidence and type of insurance plan as the most common factors associated with the occurrence of MRPs, while DDIs, untreated conditions, ADRs and unknown indication of drugs were identified as the most common MRPs in a population of community-dwelling patients. [34]

A subcategory of MRPs is represented by PIPs, defined as “the prescription of medications associated with a higher risk of adverse outcomes such as drug interactions, falls and cognitive impairment”. They also include the omission of potentially beneficial drugs and the use of inappropriate doses or for inappropriate periods of time. [38]

The best-known PIPs are definitely PIPs in older patients, and among them the American Beers criteria [39] and the European screening tool of older people's prescriptions (STOPP). [40] These are validated tools available to clinicians to assess the quality of drug therapies, which can be stand-alone tools or integrated into computer systems such as CDSSs.

The **Beers criteria** were first published in 1997 and, to date, last updated in 2023. They consist of recommendations to identify potentially harmful drugs or drugs to be avoided in older patients and are classified according to the severity of potential harm to the patient (major or minor severity) and the quality of evidence (excellent, limited, moderate). Beers criteria recommendations are distributed in six tables: 1) potentially inappropriate medication use in patients ≥65 years of age; 2) potentially inappropriate medication use in patients ≥65 years of age due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome; 3) medications to be used with caution in patients ≥65 years of age; 4) drug-drug interactions (DDIs) that should be avoided in patients ≥65 years of age; 5) medications that should be avoided or have their dosage reduced in the presence of variable levels of renal function in patients ≥65 years of age; 6) medications with strong anticholinergic properties. [39]

Similarly to the Beers criteria, the latest version of the **STOPP** (2023) includes a list of 130 drugs or drug classes that should be discontinued or discouraged in most older patients or those with certain conditions related to medication use (e.g., dosing) or clinical (e.g., dementia diagnosis). Potentially inappropriate medications in patients ≥65 years of age according to the STOPP are distributed in twelve sections based on the apparatus on which they act. In parallel with the STOPP, the screening tool to alert to right treatment (**START**) was published, which in its most recent version (2023) includes 56 drugs that it is advisable to prescribe to older patients with specific conditions because they may improve their condition, including preventing the occurrence of specific iatrogenic conditions. START recommendations are also distributed into eleven sections based on the function of the medication under consideration. [40]

Other tools to assess the appropriateness of prescriptions include:

Anticholinergic cognitive burden (ACB) scale and drug burden index (DBI) [41,42]: tools to assess the overall anticholinergic load of prescribed medications, which is useful in reducing the risk of cognitive adverse effects, especially in older patients.

Deprescribing guidelines (Canada) [43]: set of guidelines and algorithms developed since 2013 by a team of three researchers with degrees in pharmacy to help physicians identify and discontinue PIPs safely and gradually. To date, guidance for deprescription of proton pump inhibitors (PPIs), antihyperglycemics, antipsychotics, benzodiazepine receptor agonists (BZRAs), cholinesterase inhibitors (ChEIs) and memantine have been made available to the public.

CredibleMeds database [44]: online resource supported by the Safe Use Initiative of the U.S. Food and Drug Administration (FDA) first launched in 1999 that ranks drugs according to their risk of QT prolongation and *torsades de pointes*.

Micromedex® [45]: online database periodically updated based on the results of clinical research and systematic reviews published in international scientific journals that provides indications about drug interactions and their severity. Interactions are classified into contraindicated, major, moderate or minor.

Medication-related falls screening and scoring tool [46]: medications that increase the risk of falls, particularly useful for frail patients.

Medication appropriateness index (MAI) [47]: method for assessing drug therapy appropriateness through the identification of any duplicate drugs or drugs that cause pharmacological interactions.

A wide variety of other tools have been published in the scientific literature to prevent MRPs and support the deprescription of PIPs.

1.2.2. Medication review

Healthcare systems in Europe and globally are facing critical challenges with medication-related harm, compounded by resource constraints and a strained workforce. [48] Indeed, the aging of the population and the increasing number of patients with multimorbidity are leading to increasing complexity in therapy management, especially during transitions of care, defined as times when patients move from one care setting to another. [49-50] It has been reported by the International Pharmaceutical Federation (FIP) that more than 40% of medication errors are attributable to inadequate therapeutic reconciliation during hospital admission, transfer between healthcare settings and at discharge. It is estimated that the resulting harmful effects could be avoided in about 20% of cases through the implementation of processes to optimize the management of medications. Moreover, the same report points out that, in standard care, unintentional medication discrepancies (defined as changes in therapy caused by reasons unrelated to alterations in health status) affect about 56% of patients facing a transition of care. [50]

In this context, medication review has been identified as a potential strategy to mitigate the risk of medication-related harm by assessing therapeutic regimens to optimise safety and effectiveness. [48] In 2019, the WHO recommended structured medication review as an effective process to reduce MRPs and shared an exhaustive list of internationally available guidance on appropriate polypharmacy management. [51] Moreover, recent studies [52-54] support the participation of pharmacists in the process of medication review: pharmacists, as medication experts, should enhance their clinical role through activities that promote pharmacotherapy optimization, leading to improvements in both medication-related outcomes and overall health outcomes.

In Italy, the medication review process is supported by the Recommendation no. 17 of the Ministry of Health [55], as well as by a recent inter-society document signed by the leading national scientific societies working in the fields of geriatrics, internal medicine, general medicine and pharmacology. [56] Specifically, Recommendation no. 17 addresses the issue of **medication reconciliation**, defined as a formal process that allows the detection and knowledge of the pharmacological therapy being followed along with other information about the patient and enables the prescriber to carefully consider whether to continue, vary or discontinue it in whole or in part. This process is intended to ensure that accurate and complete medication information is communicated at all transfer of care in order to prevent

medication discrepancies such as omissions, duplications and dosing errors. It should include four steps, as reported by the Italian Ministry of Health and Canberra Health Services: [55,57]

1. Documenting a complete medication history following interview with the patient or his/her caregiver (**medication recognition**);
2. Verifying the accuracy of this history with at least one additional source of information (e.g., HER, GP) to create a best possible medication history (BPMH);
3. Reconcile the BPMH against the medications prescribed to the patient to identify discrepancies, work to resolve discrepancies and document the plan for rectifying the discrepancies;
4. Provide an accurate list of prescribed medications to the patient and to healthcare professionals involved in each transition of care.

The intervention of **medication review**, instead, is promoted by the document from the Italian Geriatrics Academy *et al*. [56] and consists in a structured process to identify actual or potential MRPs and provide evidence-based recommendations to optimise the use of medications, including deprescription of PIPs. Medication reconciliation and medication review are two interconnected, complex processes that require multiple steps, reliable data sources and the efforts of several healthcare professionals. These should be performed for every polytherapy patient, although in clinical practice this is hardly applicable; therefore, a practical way to distribute limited resources and ensure good quality of care is to prioritize patients deemed to be at higher potential risk for potential MRPs. In addition, these interventions should be patient-centred and patients should be included in the decision-making process to consider their preferences in treatment decisions. [57,58]

1.2.3. Complex patients in need of medication review

In recent years, the prevalence of so-called complex patients is increasing due to various factors, including progressive aging of the population, improvements in treatment and increased multimorbidity and polypharmacy. Although there is no consensus on the definition of patient complexity, it is well known that greater complexity is associated with greater risk of adverse health outcomes, increased need of clinical support and higher healthcare costs. [59]

In Italy, the prevalence of patients who would benefit from medication review is estimated to be significant, especially among older patients. According to the 2023 report on the use of medications by the Italian Medicine Agency (*Agenzia Italiana del Farmaco*, AIFA) [60], about 68% of individuals aged 65 years and older take at least 5 different medications, while 29% use 10 or more different drugs in one year. The average number of active ingredients taken by older patients is 9.7 per year, ranging from 7.7 in the 65-69 age group to 11.8 in the over-85 population. [61] This trend is more pronounced in central and southern regions of Italy, where the percentage of older people taking more than 10 medications exceeds the national average. Moreover, according to the *Istituto Nazionale di Statistica* (Istat), 21% of the Italian population is affected by two or more concomitant chronic diseases, and the prevalence of multimorbidity is expected to increase by at least 11% by 2028. In addition, the pandemic of 2020 has made this situation even more complex, leading to worsening health status and decreased psychological well-being. [62] The major cause of multimorbidity and associated polypharmacy is aging. With advancing age, the likelihood of multiple coexisting diseases increases significantly, often making it difficult to determine which condition is more prognostically significant. This complexity is further compounded by age-related physiological changes, which can alter drug metabolism and increase susceptibility to adverse effects, making the management of multimorbidity even more challenging. Therefore, periodic revision of drug therapies is essential to ensure safety and efficacy of treatments in patients with polypharmacy and multimorbidity. [63]

A narrative review of 2022 [59] identified eight domains who contribute to patient complexity:

1. Patient demographics;
2. Patient personal characteristics or behaviour, such as language barriers;
3. Socio-economic factors;

4. Medical and mental health, such as illness severity and psychiatric disorders;
5. Patient risk of mortality;
6. Healthcare system, such as care coordination;
7. Medical decision-making;
8. Environment, such as pollution.

Recognizing complex patients may improve the decision-making process, the coordination of care and reduce the risk of hospitalizations, thus reducing potentially preventable healthcare costs. Moreover, identification of complex patients can support the selection of patients who would benefit most from medication review. In this regard, several recommendations were disseminated to favour the identification of medically complex patients. [64,65] The most commonly used criteria include:

- Polypharmacy, typically defined as the use of ≥4 prescribed drugs over 3 months, particularly complex polypharmacy, defined as the use of ≥10 drugs; [66]
- Multimorbidity, defined as the presence of ≥2 chronic conditions; [67]
- Regular use of high-risk medications or of medication commonly associated with medication errors (i.e., anticholinergic drugs and pain management medications);
- Recently discharged with medication changes;
- Respiratory disease or cardiovascular disease and polypharmacy;
- Older patients (≥65 years) with polypharmacy and one risk factor among impaired renal function, low cognition, low medication adherence, high fall risk, unplanned hospitalization, nursing homes or care homes;
- Severe frailty, particularly patients who are isolated or housebound or who have had recent hospital admissions and/or falls;
- Medication costs that exceed a certain level.

Therefore, the definition of patient complexity is not limited to the assessment of the number of prescribed medications and coexisting diseases, but it refers to a multidimensional concept that takes into accounts the interactions between patient-specific factors and the surrounding environment. [59]

1.3. Quality and sustainability of care: the One Health approach

The concept of One Health was introduced in the 2000s, although it has been adopted as a comprehensive approach in its current sense only in recent years thanks to the promotion by institutes such as the WHO and the European Commission. The One Health approach consists of a healthcare model that integrates different disciplines at the local and international level, such as public health, veterinary, epidemiology, ecology and agriculture. Its main objective is to promote the collaboration of experts from various fields to improve the health of people and animals, including pets, livestock and wildlife. In particular, it intends to prevent, detect and respond to global health threats such as pandemics, climate change and pollution and antimicrobial resistance. The concept behind One Health is that human health, animal health and ecosystem health are inextricably linked and, therefore, to achieve global health it is necessary to address the needs of the populations, particularly of the most vulnerable, taking into account the relationships among these elements. As the human population grows and expands, interactions with the environment and wildlife become more frequent, intensifying these relationships. Consequently, exploitation of natural resources, along with climate change, further exacerbate these dynamics, fuelling the spread of vector-borne diseases, a problem that is further accelerated by increased global travel and trade. [68-70]

Implementing the One Health approach may lead to greater sustainability of the healthcare system through various pathways, including prevention of communicable diseases, integrated surveillance and interdisciplinary collaboration, contributing to improve the quality of care provided. Therefore, adopting this approach is essential to ensure global health and more sustainable healthcare systems. [68-70]

1.3.1. Green medicines

The increase in the production and consumption of medications, fostered by scientific and technological progress in recent decades, is accompanied by a growing environmental problem: contamination resulting from pharmaceutical residues that have the potential to cause damage to both the ecosystem and human health. In a One Health perspective, raising awareness among citizens and healthcare professionals about the potential environmental impact of drugs is critical to encourage appropriate use of medications and the adoption of sustainable strategies that protect human, animal and ecosystem health. [71-74]

Several studies [71-74] have found the presence of drugs and pharmaceutical residues in the environment, particularly in water sources around the world. Pharmaceutical residues and drugs can end up in the environment through several pathways, including use, disposal and production. The main sources of pharmaceutical contamination are:

- Human excretion: most drugs, after being taken, are not fully metabolized by the organism and are excreted unmodified through urine and faeces. Moreover, also when metabolized they can originate active metabolites capable of damaging the ecosystem. In this way, pharmaceutical residues end up in sewage systems and a significant portion reaches water bodies since wastewater treatment plants are unable to remove all the residues, to the point of contaminating surface and groundwater. Even though the amount of medications and their metabolites accumulated in seas and rivers is in the nanogram and microgram range, their combined effects and the co-occurrence of other chemical contaminants, such as cosmetics and pesticides, must be considered.
- Improper disposal of medications: many citizens and healthcare professionals are unaware of the risks associated with the improper disposal of medicines and often flush them down the toilet or drain or throw them in the household waste, contributing to the leakage of drugs into the environment.
- Veterinary and agricultural use: antibiotics and other drugs used in intensive farming for the prevention of diseases in livestock animals can accumulate in soil or leach into groundwater. Moreover, aquaculture and the spreading of wastewater treatment sludge onto agricultural land are major contributors to the dispersion of drugs and pharmaceutical residues in water.

- Industrial discharges: the production of drugs involves the use of large quantities of chemicals, some of which can be released into the environment, particularly in some areas of the world where strict regulations to reduce pollution are lacking.
- Discharge from hospitals and healthcare facilities.
- Point-of use emissions of medications in gaseous form, such as anaesthetic gases and pressurised inhalers.

The consequences of environmental drug contamination, especially in water, are still being studied, but scientific evidence in recent years suggests the potential for harmful effects on the ecosystem and the aquatic environment, as well as possible direct and indirect risks to animals and human health. Even though direct effects of drug pollution on human health are not yet known, there are some well-known and long-studied harmful effects on animals. These include the loss of reproductive capabilities of some species of male fish and the disruption of oogenesis in amphibians due to chronic exposure to contraceptive drugs, the near extinction of vultures in India due to the widespread consumption of diclofenac-treated cattle carcasses and increased mortality of some fish due to exposure to psychoactive drugs such as fluoxetine that make them more vulnerable to predator attacks. All these factors can disrupt the balance of the ecosystem, alter the food chain, reduce biodiversity and potentially lead to toxicity of plants and animals that could be unknowingly consumed. Moreover, the accumulation of antibiotics in the environment not only impairs the ability of microorganisms to metabolize soil and water organic substances, but also contributes to the phenomenon of antimicrobial resistance by selecting resistant bacterial strains. Finally, drugs and their metabolites have been detected in several drinking water sources, raising concerns about contamination of water resources. [71,73]

Several initiatives have been promoted to mitigate the environmental impact of drugs and support their safe and sustainable use. At a European level, a directive that came into effect in 2006 from the European Union (Directive 2001/83/EC) indicates a requirement for pharmaceutical manufacturers to provide an assessment of the potential environmental risk for all new medications being applied for marketing authorization. The European Medicine Agency (EMA) identified the Environmental Risk Assessment (ERA) as a two-tier environmental impact classification system: first, medications should be evaluated according to their intrinsic characteristics (environmental hazard); second, environmental risk should be assessed as the ratio between the predicted environmental concentration (PEC) and the

predicted no-effect concentration (PNEC) in surface waters. The PEC can be estimated considering the predicted drug consumption, while the PNEC is derived from measurements of medication toxicity in different organisms and ecosystems. The ERA assessment is not without limitations: first, it does not apply to medications that have been approved before 2006, which, therefore, remain in circulation without an assessment of their environmental risk; furthermore, the ERA is not a binding criterion for the marketing authorization of a medication, which may be authorized because of the favourable risk-benefit ratio despite the potential for environmental harm. Additionally, ERAs are difficult to find and often are not available to the public. [71,73,74]

Another initiative promoted by the European Union through the Erasmus+ programme aimed at addressing the emerging problem of drug pollution to protect global health is the project "Planetary Health Education in Prescribing" (PlanED Prescribing). This project is addressed to future prescribers and involve eight European medical schools; its objective is to create and disseminate education material with information to promote environmentally sustainable prescribing while ensuring optimal patient care. PlanED Prescribing aspires to provide pharmaceutical companies with harmonised criteria and assessment methods to determine the environmental impact of medications, as well as to ensure availability and transparency of environmental data to all stakeholders, including final users. [74]

Not only government authorities but also professionals in the field have recognized in recent years the extent of the problem and the significant lack of studies and training in this area. Eco-pharmacovigilance, i.e., the study of the effects of pharmaceuticals on the environment, is gaining more and more relevance due to the increasing awareness of medications as emerging pollutants with the potential to damage water sources, soil and ecosystems. As their global consumption continues to rise, concerns about persistence, bioaccumulation and toxicity of pharmaceutical residues on wildlife and human health have led to a growing focus on monitoring, risk assessment and development of sustainable pharmaceutical practices. Regulatory agencies, researchers and pharmaceutical industries are working together to implement strategies aimed at minimizing environmental contamination and promoting sustainable drug design, disposal and waste management. An example is represented by the Pharmaceutical Group of the European Union (PGEU), an association representing more than four hundred thousand community pharmacists in 32 European nations which called for actions to reduce the impact of pharmaceuticals on the environment. In collaboration with

the EMA and the European Commission, the PGEU presented to member states a program consisting of several key points to mitigate the problem of pharmaceutical pollution. [75] The program includes:

- Raise awareness among the public on the prudent use of medications.
- Develop information materials and guidelines to promote informed drug use and prescribing for healthcare professionals.
- Include specific courses on the topic in the academic training of pharmacy students, with the goal of continuing education in the post-academic path.
- Develop and enforce quality standards in pharmaceutical development to promote more sustainable production.
- Allocate more resources to ensure proper drug disposal.
- Reduce pharmaceutical waste by promoting appropriate prescription and dispensation of adequate type and number of medications.

Promote the design of “greener” drugs that are effective for the patient but degrade rapidly in the environment should also be an aspect to pay attention to. In this regard, numerous efforts are being made in Europe to develop less environmentally harmful drugs. However, such an effort, if limited to the continental scale, is unlikely to prove sufficient. In addition, the research and production of more sustainable active ingredients raises questions about the time and cost required by these processes. At the moment, incentives for the development of active substances with more environmentally friendly characteristics are insufficient, and companies tend to focus more on green chemistry in industrial production rather than on designing more sustainable molecules. A possible starting point for the discovery of more sustainable drugs is illustrated in the study by Moermond and colleagues (Figure 5). [76]

The benefits of applying the GREENER criteria need to be weighed against their impact on patient needs, safety, efficacy and global healthcare costs.

Finally, in order to apply these policies, it is crucial to identify and develop new tools and study models, which requires a great deal of collaboration from authorities in the field.

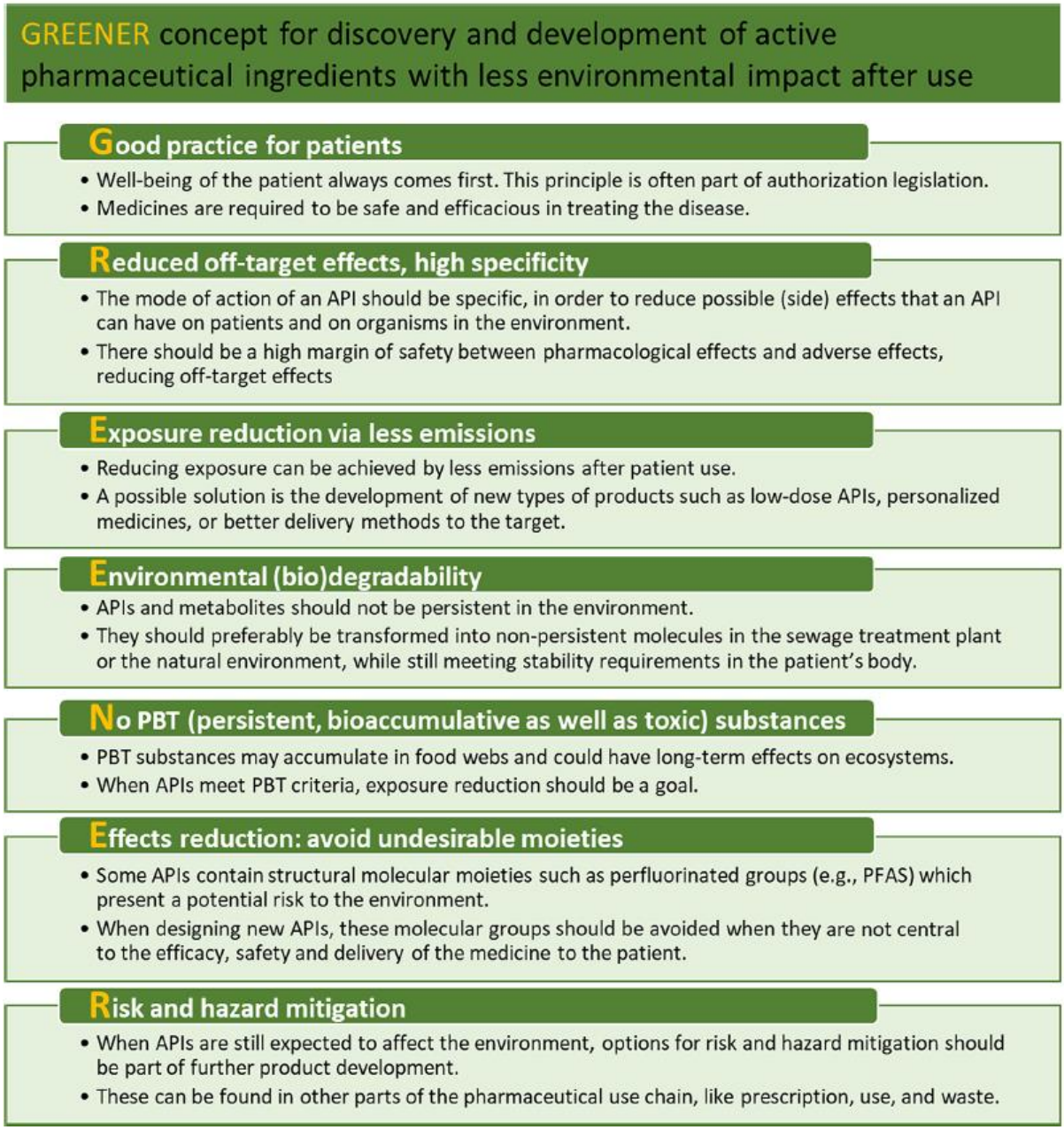


Figure 5. GREENER concept for discovery and development of drugs with lower impact on the environment. Source: Moermond CTA, *et al*. Environmental Science & Technology 2022. [76]
Abbreviations: API, active pharmaceutical ingredient; PBT, persistent, bioaccumulative, toxic; PFAS, perfluorinated alkylated substance

1.4. Drug utilization research (DUR) and real-world data (RWD) analysis as data sources to optimize drug therapies

With the increase in medication consumption and the use of digital technologies capable of collecting, storing and processing large amount of health data, there is a need to design and implement systems aimed at monitoring pharmacological therapies and related comorbidities, with the ultimate perspective of optimizing therapeutic approaches. In addition, annual reports of the national Medicines Utilisation Monitoring Centre (*Osservatorio Nazionale sull'Impiego dei Medicinali*, OsMed) by the AIFA [77] have repeatedly pointed out that pharmaceutical spending is difficult to contain. Therefore, DUR aimed at evaluating and understanding the processes of prescribing, dispensing and consumption of medications, as well as testing innovative interventions to improve the quality of these processes, is of considerable relevance to both healthcare professionals and policy makers, as it can support decision-making in the economic, administrative and political spheres.

DUR was first defined in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" [78]; it can be divided into both descriptive and analytical studies and it represents an essential element of pharmacoepidemiology, so much so that the two terms are often used as synonyms. The primary objective of DUR is to facilitate the rationale and appropriate use of medications [78], and it has recently been promoted by European initiatives such as Digital Health Europe [79] and the European Innovation Partnership on Active and Healthy Aging (EIP on AHA) [80], which also emphasize the importance of improving the use of health data, including those on medication use. Health data collected through EHRs, medical claims and various other more or less extensive records constitute a valuable source of real-world evidence (RWE). [81] These data fall under the broader definition of real-world data (RWD), i.e., data on the health status of patients or healthcare services provided collected primarily for administrative purposes. RWD analysis, parallel as DUR, has been gaining increasing relevance in recent years as it offers the possibility of designing and implementing improvement actions aimed at rationalizing and optimizing available resources and possible interventions. Indeed, the potential expected benefits of drug therapies are not always reflected in clinical practice. Although all new medications available on the market have been shown to exert beneficial effects in pre-registration

studies net of adverse effects, their use does not translate into the expected benefits in all patients. Therefore, early identification of factors that may affect the outcomes of drug therapies represents a first step in designing and implementing programs to improve the efficiency and effectiveness of pharmacological therapies. [82,83,84]

Gaining knowledge about current drug therapies can occur at different scales: from the individual patient to the entire population. The analysis of RWD enables the examination of drug therapies on a large scale in a given area and over a defined period of time and provides a comprehensive overview of treatment choices. In addition, analysis of dispensations of medications belonging to the drug classes that have the greatest impact on the expenditure of the healthcare facility can help contain healthcare costs and identify areas where action can be taken to reduce wasted resources. Examples of DUR and RWD analysis include recognition of prescriptive patterns, identification of factors capable of exerting adverse health effects on patients (e.g., DDIs, suboptimal medication adherence) and assessment of the risk of occurrence of ADRs. Still, DUR can allow the evaluation of prescriptive appropriateness, which is one of the elements in the assessment of the effectiveness of the healthcare process and is closely related to possible adverse reactions, hospitalizations and mortality, aspects that strongly affect the performance and expenditure of the NHS. [85] For these reasons, DUR and RWD analysis could provide the quantitative support to design and implement interventions aimed at improving the quality of current drug therapies. [86]

Despite randomized clinical trials (RCTs) remain the gold standard to evaluate medication efficacy and drug-related issues, they are unable to provide information on the post-marketing use of medications on a large scale, as opposed to RWD. Therefore, observational databases and RWD become fundamental to provide evidence from the real world. Italy is rich of RWD gathered from electronic health data collected at a local, regional and national level. There are three types of sources of Italian RWD on health: claims databases, EHRs and medical registries. Such data are routinely collected by local healthcare services as part of institutional activities, particularly regarding the provision of health services covered by the NHS (claims database). Claims database commonly available in Italy are summarized in Figure 6. [82]

Claims databases	Description
Healthcare service provision database	Unique patient identifier, date of birth, sex First and last date of LHU/regional healthcare service use
Hospital discharge records database	Unique patient identifier Up to six diagnoses codes in ICD-9 CM Up to six procedure codes in ICD-9 CM Date of hospital admission and discharge
Co-payment exemptions database	Unique patient identifier Diagnoses for diseases exempting patients from co-payment coded in ICD-9 CM
NHS-covered drug dispensing in community pharmacies	Unique patient identifier Drugs coded in ATC 5th-level coding system and the Italian marketing authorization code
NHS-covered drug dispensing in hospital pharmacies on discharge	Unique patient identifier Drugs coded in ATC code 5th-level classification system and the Italian marketing authorization code
Outpatient specialist care, diagnostic tests and outpatient procedure database	Unique patient identifier Specialist examinations and diagnostic tests coded using national coding system In some regions main diagnoses and test results also available
Birth registry	Unique patient identifier for both mother and child Information on live and still births Information for both mother (BMI, before pregnancy, smoking, etc.) and child
Emergency department database	Unique patient identifier Dates of admission and discharge Diagnoses coded using ICD-9 CM (as both primary and secondary diagnosis) Procedures coded using ICD-9 CM

Figure 6. Italian claims database. Source: Trifirò G, *et al*. Drug Safety 2019. [82]
Abbreviations: LHU, local health unit; ICD-9 CM, international classification of diseases ninth edition; NHS, national health service; ATC, anatomical therapeutic chemical; BMI, body mass index

Despite their extent, these data are subject to some limitations in terms of quality and accuracy (Figure 7).

Healthcare information	Claims	EHRs	Drug registries
Acute conditions	+++	++	+*
Chronic conditions	++	+++	+*
Indication for drug use	NA	+	+*
Outpatient drugs covered by the NHS: drug prescribing in primary care	NA	+++	+*
Outpatient drugs covered by the NHS: drug dispensing of primary care prescriptions	+++	NA	NA
Outpatient drugs not covered by the NHS: drug prescribing in primary care	NA	++	NA
Outpatient drugs not covered by the NHS: drug dispensing of primary care prescriptions	NA	NA	NA
Outpatient NHS-covered drug dispensing of specialist prescriptions	+++**	++***	NA
Outpatient non-NHS-covered drug prescribing by specialists	NA	+***	NA
Inpatient drug prescribing/dispensing	NA	NA	NA

*Availability strongly related to the drug the registry is created to study

**These drugs are fully captured unless patients purchase the medicines out of pocket

***These drugs are captured if the general practitioner issues the prescription that is initially issued by a specialist

Figure 7. Strengths and limitations of Italian claims databases, EHRs and medical registries: + indicates minimal information collected, ++ indicates moderate amount of information collected, +++ indicates large amount of information collected accurately. Source: Trifirò G, *et al*. Drug Safety 2019. [82]
Abbreviations: EHRs, electronic health records; NHS, national health service; NA, not available

1.4.1. Management of health data and privacy legislation

The use of health data is regulated by national and European regulations governing the collection, processing, analysis and storage of health information and is constantly evolving. At the moment (January 2025), the regulations governing the use of data on drug use in Italy are the General Data Protection Regulation (GDPR, EU Regulation 2016/679) [87], the Legislative Decree 196/2003 [88], the Ministerial Decree 30 November 2021 [89] and the 2024 guidelines on observational studies by the AIFA. [90] Particularly, the GDPR establishes the principles of personal data protection, imposing strict requirements for informed consent, data collection and information security, while the Legislative Decree 196/2003 and the Ministerial Decree 30 November 2021 are two national regulations governing, respectively, the processing of health data and the conduction of nonprofit clinical trials and data transfer in Italy. Finally, AIFA recently approved the "Guidelines for the classification and conduction of observational studies" involving the use of drugs; this standard specifies how to collect and use data resulting from the use of drugs in the real world. [90]

Observational studies that exploit health data are of particular importance for the evaluation of medication safety under normal conditions of use and on large numbers of subjects, for insights into efficacy in real-life conditions, for assessment of prescriptive appropriateness, and for pharmacoeconomic evaluations. To fall into this category, the observational study must have characteristics such that there are no additional risks due to experimental treatments and/or interventions, it must be performed according to current clinical practice and the subjects involved must be offered the best conditions of clinical care and monitoring according to current practice. For these reasons, the procedures and methodologies applied are different from what is expected in experimental clinical trials. These can have different study designs:

- Retrospective observational study: designed to collect and process data on patients already undergoing a treatment strategy through secondary collection and analysis of relevant clinical data.
- Prospective observational study: it involves a prospective collection of data on patients who fit the inclusion criteria described in the study protocol.
- Two-way observational study: both previous designs are applied.
- Cross-sectional observational study: data is collected at a single point in time to assess the prevalence of a condition or characteristic within a population. It provides a

snapshot of information based on a single observation at the start of the study, without tracking changes over time.

They also include follow-up visits, the administration of questionnaires or interviews and economic-health surveys. [90]

All observational studies carried out in Italy must be based on a detailed study protocol and comply with national regulations regarding privacy, informed consent and data security. Specifically, studies on drug use (excluding dissertations and analyses of clinical data performed within facilities and institutions for administrative purposes of evaluation, management and control) must be evaluated by relevant Ethics Committees to ensure compliance with regulations and protection of patients' rights. In addition, it is essential that the AIFA receive notification for each observational study through the Registry of Observational Studies (RSO). Moreover, in order to conduct studies on drug use, informed consent should be obtained from patients through a simplified procedure compared to that required for clinical trials. Informed consent should be explicit, revocable and limited to the purpose of the study. In some cases, the analysis and processing of health data may be carried out without explicit consent following the approval of the Data Protection Authority and the favourable opinion of the relevant Ethics Committee. This may occur when patient contact is impossible or overly burdensome, when the study has a significant public interest or when data are used in aggregated or anonymized form. Finally, management of health data must adhere to the basic principles of data security and all documentation collected must be retained for a minimum period of 7 years. [90]

2. AIM

This Ph.D. dissertation entitled “Analysis of real-world data and update of a Clinical Decision Support System (CDSS) to investigate and support quality and sustainability of pharmacological therapies” was made possible thanks to the introduction, in the past years, of a Ph.D. programme designed to foster collaboration between academy and industry, particularly Action IV – Education and research for recovery within the Recovery Assistance for Cohesion and the Territories of Europe (REACT-EU) programme aimed at fostering crisis repair in the context of the Covid-19 pandemic and its social consequences and for preparing a green, digital and resilient recovery of the economy. [91,92] The idea behind this research project originated from the long-standing collaboration between the DSTF and Infologic s.r.l., an IT company based in Padua, Italy. The partnership between the DSTF and Infologic s.r.l. was mainly focused on updating the knowledge-base of a CDSS developed by the company; the REACT-EU programme enabled the strengthening of collaboration by promoting a Ph.D. research project aimed at co-developing and testing an updated version of the Infologic’s CDSS designed to support medication review, reduce MRPs and improve quality and sustainability of care. These topics well adapt to the themes promoted by the REACT-EU initiative, since a well-designed platform to support clinical decisions can foster safer and more rational use of healthcare resources, essential element of a sustainable and innovative healthcare system.

The primary objective of this research project was to update the Infologic’s CDSS by expanding its knowledge-base and features, in order to encourage its adoption by healthcare facilities. In fact, as numerous studies [93,94] have shown, the adoption of digital health technologies and platforms to support clinical decision not only promotes technological transition, but also has the potential to contribute to the definition of a more sustainable model for managing chronicity and multimorbidity. By integrating evidence-base recommendations for appropriate drug use, these digital tools can offer personalized suggestions to optimize pharmacological therapies of polytreated patients. Furthermore, using such technologies can reduce MRPs and hospitalizations, leading to decreased healthcare expenses and resource utilization. Ultimately, the implementation of digital solutions in clinical practice could result in improved health outcomes, increased patient

satisfaction and a more effective healthcare system. Specifically, by improving and testing the CDSS in clinical practice, the project aimed to:

- ensure that the information populating the CDSS existing **knowledge-base** is **evidence-based**, **up-to-date** and **verified** by professionals with a background in medication use;
- **enrich the CDSS knowledge-base** with key information that a platform for medication review should include to ensure completeness of medication analysis and, consequently, higher quality and sustainability of prescribed therapies, selected after discussion with healthcare professionals and bibliographic research. This includes information on the potential environmental impact of medications with the aim of raising awareness about sustainable healthcare practices and promoting a more rational and informed use of drugs;
- test the CDSS to **assess the needs of prescribers and hospital pharmacists in the management of pharmacological therapies** and to gauge their attitude toward the use of a platform for medication review through a qualitative survey. In fact, although the use of digital tools such as CDSSs has been shown to improve the quality of care and reduce the risk of MRPs and ADRs, the opinion of clinicians toward their introduction into clinical practice is controversial. [20,95] Therefore, testing an updated version of the CDSS in Piedmontese clinical contexts could provide the platform developers with the necessary inputs for its further improvement and implementation in clinical practice.

Secondary objective of the research project is to conduct DUR through the analysis of anonymized electronic health records collected by Italian healthcare facilities with which the DSTF holds agreements for research purposes. By leveraging this RWD on drug use, it is possible to gain insights into patient preferences, prescription patterns of GPs and treatment outcomes. The results of RWD analysis could provide healthcare providers with the insights needed to enhance decision-making process; this could facilitate optimized resource allocation, reduced waste and improved patient care. Additionally, RWD analysis could help identify areas for intervention to promote the population well-being.

2.1. NavFarma® CDSS

NavFarma® [96] is a platform designed by Infologic s.r.l. to allow Italian healthcare facilities to implement new models of drug therapy management.

Infologic s.r.l. is a small Italian company based in Padua focused on developing IT solutions applied to the management of various kinds of data; for the health section, the NavFarma® platform was developed, on which the professional tutor of this Ph.D. thesis (Eng. Pierluigi de Cosmo) and three software developers are working.

NavFarma® was first developed more than ten years ago and it originally included recommendations on potential drug-drug interactions and general information on medications marketed in Italy, such as pharmaceutical forms, dosage and presence of known allergens. Over the years, its knowledge-base has been enriched with additional drug information mainly due to the boost given by the collaboration with the DSTF: potentially inappropriate medications in older patients according to the Beers criteria [97] and the STOPP [98], the ACB scale [41], characteristics of medications regarding splitting and crushing and potential drug-herb interactions are just a few examples of the knowledge-base update that has been done in recent years (see later for the description of the CDSS knowledge-base).

NavFarma® is accessible online following activation, upon payment of a fee, of an account by the Infologic company; it is currently employed in some Italian healthcare facilities, such as hospitals and territorial and regional pharmaceutical services, including two facilities in the Piedmont Region. The main purpose of NavFarma® is to support clinical decision, especially with regard to medication review and assessment of prescriptive appropriateness. Through the platform's various features, this CDSS can offer to physicians, specialists, pharmacists or patients and caregivers suggestions and recommendations to optimize prescribed therapies and improve their management. Particularly, NavFarma® provides healthcare professionals with a solution for the **centralized management of patient therapies**, ensuring an integrated approach that promotes continuity of care, improves treatment effectiveness and increases patient satisfaction. In fact, it provides a repository where the patient's overall therapy and all the relevant clinical information can be maintained to avoid the dispersion of information: by entering the patient's social security number (*codice fiscale*), it is possible for Infologic

clients to create a new patient profile or to extract the information already available in the platform for a specific patient.

In the first hypothesis, the healthcare professional user of the CDSS need to enter patient's information into the different tabs of the software (Figure 8): biographical information ("*Anagrafica*"), general patient information ("*Scheda paziente*"), diagnosis and pharmacological therapies ("*Terapie*") and a questionnaire to be administered to the patient to investigate its adherence to prescribed therapy ("*Questionario*"). These tabs, plus one other tab added during the course of the Ph.D., are shown in the figure below.

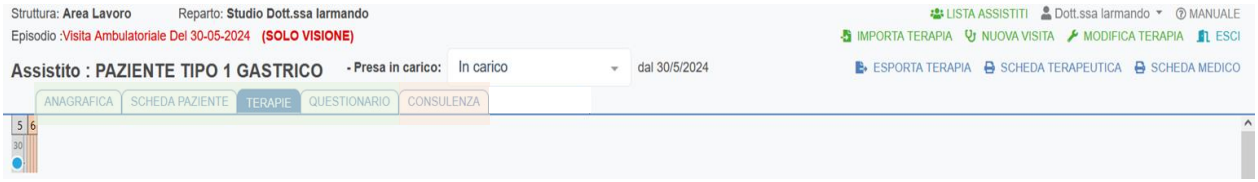


Figure 8. Patient profile on NavFarma®, including 6 tabs with specific information: 1) biographical information ("A*nagrafica*"); 2) general patient information ("*Scheda paziente*"); 3) diagnosis and pharmacological therapies ("*Terapie*"); 4) questionnaire to measure patient medication adherence ("*Questionario*"); 5) space for the clinical pharmacist to enter his/her own recommendations on the patient's therapy based on the system's alerts (consultation for the physician) ("*Consulenza*"); 6) space for hooking up with data from the ADCare® smartphone application developed by Infologic srl ("*Diario ADCare*"). Tabs 5 and 6 (highlighted in orange) have been implemented recently and were not yet operational at the time of this figure

In the second scenario, patient information is already available in the platform or, in the case of territorial or regional pharmaceutical services using the CDSS, they can be derived from drug dispensing data including the medications reimbursed by the Italian NHS dispensed by territorial pharmacies; the CDSS user may visualise existing information and make the appropriate changes, justifying the reason for change if desired.

In the ideal case, all three actors (territorial pharmaceutical services, GPs and hospitals) in a specific region or local health authority (LHA) should have the platform to ensure consistent, evidence-based patient care at all points of service and to minimize medication errors and MRPs. Figure 9 shows in detail the contents of the therapy tab within the NavFarma® platform ("*Terapie*").

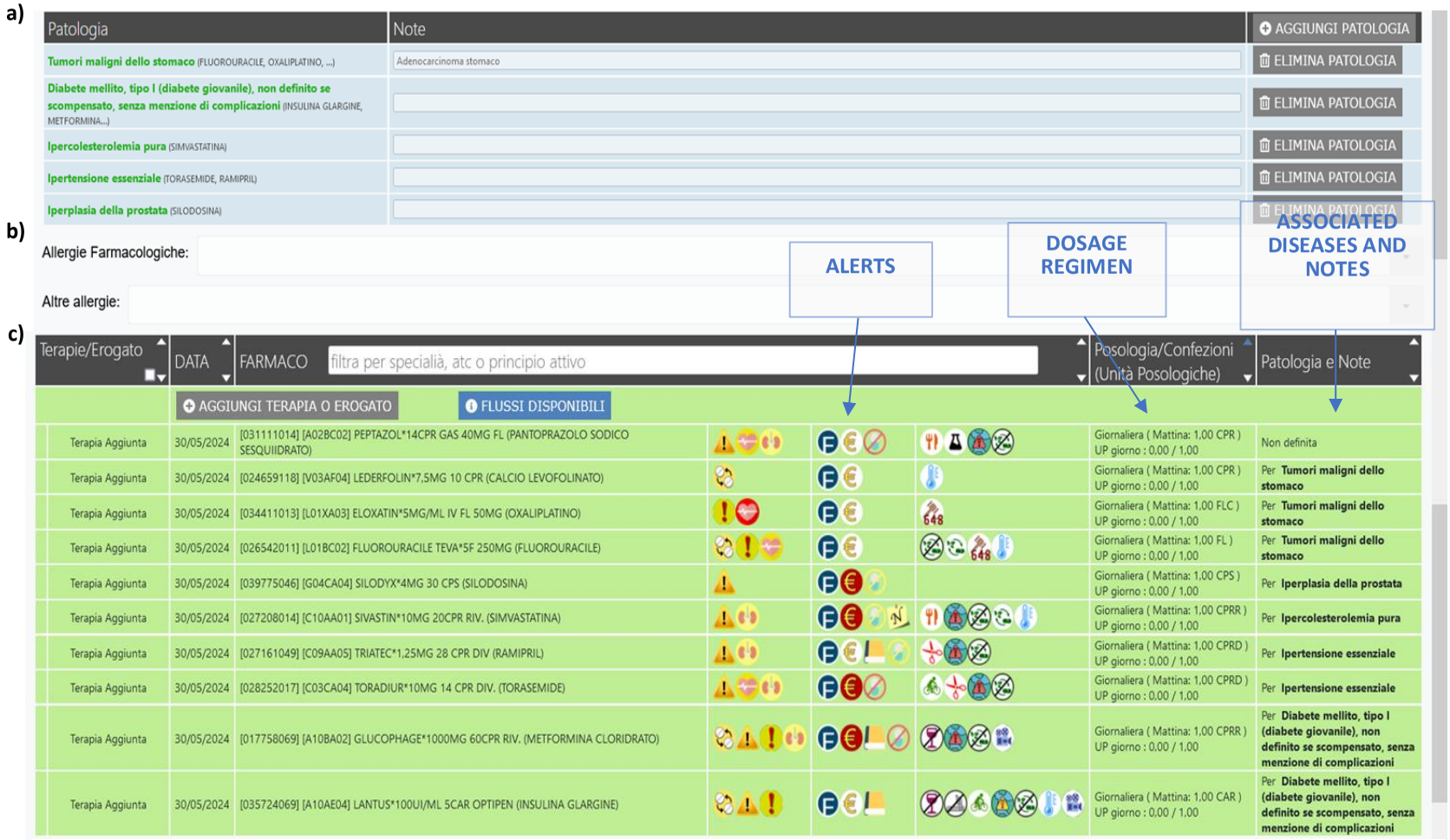


Figure 9. Information on the patient's diagnosis and pharmacological treatment on NavFarma®. The top part (**section a**) contains the patient's diagnoses coded according to the Italian version of the International Classification of Diseases, 9th revision (ICD-9). **Section b** includes known pharmacological allergies and other allergies. **Section c** contains the pharmacological therapy prescribed to the patient, with alerts (warnings), general information and recommendations for appropriate use of drugs, as well as the dosage regimen and associated diseases. The information shown in this figure refers to a model patient and the figure was obtained in June 2024; therefore, alerts also include information that was updated or created during the PhD. This information will be discussed in the results chapter

The second main feature of NavFarma®, as well as the most important one, is represented by its **knowledge-base**, consisting of a set of databases that communicate with each other and that constitute the tools **to support healthcare professionals in the process of medication review** and optimization of patients' pharmacological therapies. Within the system, the knowledge-base that has been updated with this Ph.D. project appears in the form of alerts associated with specific icons (Figure 9, section c – alerts).

An adequate and effective knowledge-base should provide rapid and complete information about medications, their interactions and the correct way to prescribe them (prescriptive appropriateness). Going into more detail about the information included in the NavFarma® knowledge-base, prior to this Ph.D. project it included:

- Potential contraindicated and major drug interactions according to the Micromedex® [45] (drug-drug interactions, drug-food interactions, drug-ethanol interactions, drug-lab interactions, drug-tobacco interactions, drug-pregnancy interactions, drug-lactation interactions) and Codifa [99] databases (drug-drug interactions);
- PIPs in older patients according to the Beers criteria 2019; [100]
- PIPs in older patients according to the STOPP criteria version 2; [38]
- ACB score; [41]
- Drugs with a high risk of adverse events for those who handle them (Recommendation no. 7 of the Italian Ministry of Health); [101]
- Link to the summary of product characteristics (*riassunto delle caratteristiche del prodotto*, RCP);
- Public price and reimbursement price;
- Description of any directives limiting the prescription (*note AIFA* and *legge 648/1996*); [102,103]
- Recognized national or international guidelines for the treatment of specific diseases: hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD), major depressive disorder and bipolar disorder updated in early 2021;
- Allergen-containing drugs (gluten, lactose, glucose, phenylalanine and active ingredients known as allergens for specific patients);
- Medications with doping properties;
- Medications that can and cannot be crushed and/or divided with instructions for crushing (Recommendation no. 19 of the Italian Ministry of Health); [104]

- Potential interactions between drugs and substances that could be included in dietary supplements (herbs, vitamins, minerals). In 2020, the database of drug-herb interactions, elaborated by researchers of the DSTF, [105] has also been made available for free on a site on the NavFarma® domain (DAHLIA) [106] for consultation by healthcare professionals and patients or caregivers;
- Storage temperature of medications;
- Videos linked to some drugs such as insulins and bronchodilators showing how to administer or manage certain medications correctly;
- Drug-associated diseases. Patient diseases can be associated with drugs, and they are classified according to the Italian version of the ICD-9. [107]

The information abovementioned are made available to users in the form of alerts associated with each medication added by the healthcare provider in the patient's therapy record. Each alert includes a short tooltip, a longer description with information for the healthcare professionals and, in some cases, a short sentence with information for the patient: patient information is formulated in plain language and it can be included in an Illustrated Treatment Sheet (ITS) for the patient to support him or her in managing pharmacological therapy.
A more detailed description of the alerts and icons shown in Figure 9 will be provided in the results chapter.

To sum up, the research period at the Infologic company, spent during the second year of the Ph.D. programme, included 6 months devoted to implementing the tables constituting the knowledge-base in collaboration with the NavFarma® programmer, although testing to the system, dialogue with the company and updating the tables was carried out consistently throughout the Ph.D. period.

3. METHODS AND MATHERIALS

3.1. Update of the NavFarma® knowledge-base

The knowledge-base of NavFarma® includes various tables which, after being appropriately linked to each other and to the latest handbooks of medications marketed in Italy by the company's programmer, constitute the system's information database. All tables are prepared with the Microsoft Excel programme; they include several columns with drug-specific information that can be associated with an active ingredient, a pharmacological class or a specific medication. The information feeding the tables is extracted from verified sources of national and international relevance, such as official guidelines, validated lists of potentially inappropriate medications, case reports or studies conducted with a scientific approach (non-systematic review of the scientific literature). All tables require periodic updating and revision to keep up with the latest scientific evidence.

For this dissertation, I selected the most relevant tables I have worked on over the past three years: some tables were created from scratch with the participation of the Infologic's IT staff, while others were already implemented in the CDSS knowledge-base during the previous years I worked for the company, but they have been extensively updated during the Ph.D. All tables contain information in Italian language as it is the only language available for the NavFarma® CDSS.

The following chapters describe how the tables selected for this Ph.D. thesis were prepared and updated. A total of four tables created during the Ph.D. and integrated into the CDSS knowledge-base at the beginning of the third year will be described in detail:

1. **Environmental impact of drugs**;
2. **Potentially nephrotoxic drugs** or drugs that may worsen renal function;
3. **Drugs with a known risk of long QT** and *torsade de pointe*;
4. **Guidelines for deprescription** and tapering dose.

Other already existing tables were revised during the research period at the Infologic company and subsequently but will not be discussed in detail in this dissertation: particularly, the largest revisions involved updating the recommendations on drug choice drawn from the main international **guidelines for the treatment of chronic diseases**, the **2023 Beers and STOPP criteria** [39,40] and **drug-herb interactions**.

3.1.1. Environmental impact data of drugs

This table includes information on the environmental impact of medications, particularly on waters, and general recommendation on how to dispose of unused or expired medicines.

First, an Internet search was made in order to identify documents published by internationally relevant research groups or official institutions, such as the European Commission and the European Parliament, the WHO and the FDA. The following keywords were used: "*drug environmental impact*", "*proper disposal of medicines*", "*pharmaceuticals in environment*", "*drug environmental risk assessment*", "*eco-toxicity of medicines*", "*pharmaceuticals in water*", "*green medicines*", "*eco-friendly drug list*". The same keywords were combined to conduct a search on the Scopus citation database to identify Italian and international scientific publications containing lists of medicines to be monitored in the environment. The final research was done between August and December 2022.

One main source [108] was used to set up the initial database to be implemented in the NavFarma® CDSS: the "Pharmaceuticals and Environment" database, a free web-based database that includes environmental information for medications. [109] The database was developed by Region Stockholm and launched at the janusinfo.se website [110], which provides information to support healthcare professionals in their everyday work since 2016. The aim of this database is to provide information about environmental hazard and risk associated with active pharmaceutical ingredients for human use on the Swedish market; the information was obtained from three sources:

1. Environmental information from the EMA's European Public Assessment Reports;
2. Environmental information on Fass.se [111], the pharmaceutical industry's total inventory of medicinal products marketed in Sweden;
3. Environmental risk assessment for certain substances based on concentrations measured in the environment in Sweden and effect studies.

It should be emphasised that these assessments may differ from one another; the "Pharmaceutical and Environment" database includes all publicly available information with source reference, whereas in the table implemented for the NavFarma® CDSS, only the most recent assessment was selected.

In autumn 2024, information extracted from the “Pharmaceutical and Environment” database has been revised to keep the table (henceforth called “green table”) updated with new evidence.

Information about the environmental classification of the existing “Pharmaceuticals and Environment” database

The environmental classification of pharmaceutical substances includes the ***environmental hazard*** and the ***environmental risk***. *Environmental hazard* expresses the inherent and environmentally harmful characteristics of the pharmaceutical substance, and it includes data on the substance’s resistance to degradation in aquatic environments (**persistence**), its ability to accumulate in adipose tissue of aquatic organisms (**bioaccumulation**) and its potential to poison aquatic organisms (**toxicity**). Each characteristic is assigned a numerical value from 0 to 3, and their sum (0-9) makes up the hazard score: the higher the value, the more dangerous the substance is for the environment. As a preventive measure, authors of the “Pharmaceuticals and Environment” database assigned the highest hazard value in case of incomplete data for a certain active pharmaceutical ingredient.

Environmental risk refers to the likelihood of the pharmaceutical substance producing toxic effects on aquatic organism, and it is assessed by comparing the substance predicted environmental concentration (**exposure**) and the concentration expected to be harmless to aquatic animals and plants (**toxic risk**). Exposure can either be based on the current use of a substance in Sweden or on the expected use in Europe. The risk level defined by the authors are: insignificant, low, moderate, high, cannot be excluded, exempt (EMA has determined that substances such as vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines and herbal medicines are exempt from environmental risk assessment). If data are lacking, the authors indicate for the active substance that environmental risk cannot be excluded.

Figures 10 and 11 show the criteria for assigning the hazard score and the environmental risk, respectively.

Persistence	
Is degraded slowly or is potentially persistent	3
Is degraded	0
Bioaccumulation	
Has high potential for bioaccumulation	3
Has low potential for bioaccumulation	0
Toxicity	
Very high toxicity	3
High toxicity	2
Moderate toxicity	1
Low toxicity	0

Figure 10. Hazard score criteria of the Swedish "Pharmaceutical and Environment" database

Risk classification		
Insignificant	if PEC/PNEC	≤0.1
Low	if PEC/PNEC	>0.1–≤1
Moderate	if PEC/PNEC	>1–≤10
High	if PEC/PNEC	>10

Figure 11. Environmental risk classification of the Swedish "Pharmaceutical and Environment" database. PEC: predicted environmental concentration of an active pharmaceutical ingredient; PNEC: predicted no effect concentration for aquatic organisms

Development of the green table for implementation in the NavFarma® knowledge-base

Pharmaceuticals detected in samples collected by Zuccato *et al*. [112] from effluents of nine Italian sewage treatment plants (Cuneo, Varese, Monza, Latina, Cosenza, Naples, Cagliari, Palermo) were used as a starting point to write the texts of the green table from the assessments in the "Pharmaceuticals and Environment" database. These pharmaceuticals and their potential risk to the environment (as measured by Zuccato *et al*.) are listed in Table 6.

Table 6. Pharmaceuticals in effluents of urban sewage treatment plants (median of nine sewage treatment plants) detected by Zuccato *et al*. [112]

Active pharmacological ingredient	Environmental risk
Amoxycillin	Insignificant pollutant in Italy
Atenolol	**Priority pollutant in Italy**
Bezafibrate	**Priority pollutant in Italy**
Carbamazepine	**Priority pollutant in Italy**
Ciprofloxacin	Second line pollutant in Italy
Clarithromycin	**Priority pollutant in Italy**
Cyclophosphamide	Insignificant pollutant in Italy
Diazepam	Insignificant pollutant in Italy
Enalapril	Insignificant pollutant in Italy
Erythromycin	**Priority pollutant in Italy**
Ethinylestradiol	Insignificant pollutant in Italy
Furosemide	**Priority pollutant in Italy**
Hydrochlorothiazide	**Priority pollutant in Italy**
Ibuprofen	**Priority pollutant in Italy**
Lincomycin	**Priority pollutant in Italy**
Methotrexate	Insignificant pollutant in Italy
Ofloxacin	**Priority pollutant in Italy**
Omeprazole	Insignificant pollutant in Italy
Ranitidine	Second line pollutant in Italy
Salbutamol	Second line pollutant in Italy
Spiramycin	**Priority pollutant in Italy**
Sulphamethoxazole	Second line pollutant in Italy

Each of these pharmaceuticals was searched in the Swedish "Pharmaceuticals and Environment" database in order to extract the key hazard and environmental risk information and to create a limited number of texts in Italian language to associate with the extracted information. Table 7 shows the information extracted from the Swedish database ("**Original assessment**" and "**Original score**") and its association with the texts in Italian language ("**Short text**" and "**Description**") and the new scores ("**New score**") assigned for the development of the green table; the new score (minimum value 0 - maximum value 12) was given to assign medicines alerts of increasing severity to be shown in the CDSS according to their overall environmental impact.

Table 7 was later used as a guide for implementing the green table. Since the "Pharmaceutical and Environment" database contains information for 851 active

pharmaceutical ingredients (data from December 2024), drug dispensing data collected during the Ph.D. for the time period 2020-2021 were used to select the 200 most prescribed drugs to be used to complete the green table.

For the development of the final green table, other information in addition to the Swedish database was taken into account and given a score to be added to the previously calculated one: scientific literature or documents published by international research organizations containing lists of pharmaceuticals detected in European waters and information on how to properly dispose of the medicine. Table 8 shows the additional sources consulted to develop the green table, the associated Italian texts and the scores awarded.

Table 7. Guide for the creation of texts in Italian language to be associated with the information in the "Pharmaceutical and Environment" database

Environmental classification	Short text (in Italian language)	Description (in Italian language)	Original assessment (quotes from the database)	Original score	New score
Persistence	*Non persistente*	Il farmaco viene degradato nell'ambiente acquatico (non è persistente)	- degraded in the environment - is not persistent	0	0
	Formazione di metabolita persistente	Il farmaco viene degradato nell'ambiente acquatico; tuttavia, potrebbe formarsi un metabolita persistente	- forms a persistent metabolite	0	1
	Potenzialmente persistente (dati insufficienti)	I dati disponibili non sono sufficienti per escludere la persistenza del farmaco nell'ambiente; pertanto, la sostanza è considerata potenzialmente persistente nell'ambiente acquatico	- data is missing - data is lacking - lack of data - no data - cannot be excluded	NA / 3	1
	Parzialmente persistente	Il farmaco non viene degradato facilmente nell'ambiente acquatico (potenzialmente persistente)	- potentially persistent - not readily (bio)degradable or inherently degradable	3	2
	Persistente	Il farmaco viene degradato lentamente nell'ambiente acquatico (persistente)	- slowly degraded in the environment - is persistent	3	3
	Molto persistente	Il farmaco non viene degradato nell'ambiente acquatico (molto persistente)	- very persistent in the environment - highly persistent in the environment	3	3
Bioaccumulation	*Assenza di bioaccumulo*	Il farmaco non possiede il potenziale di bioaccumularsi negli organismi acquatici	- does not have the potential for bioaccumulation - no potential to bioaccumulate	0	0
	Basso potenziale di bioaccumulo	Il farmaco possiede un basso potenziale di bioaccumulo nel tessuto adiposo degli organismi acquatici	- low potential for bioaccumulation - no data - conclusion B	0	1
	Possibile alto potenziale di bioaccumulo (dati insufficienti)	I dati disponibili non sono sufficienti per escludere il potenziale di bioaccumulo nel tessuto adiposo degli organismi acquatici	- no data - cannot be excluded - data are lacking	NA / 3	2
	Alto potenziale di bioaccumulo	Il farmaco possiede un alto potenziale di bioaccumulo nel tessuto adiposo degli organismi acquatici	- high potential for bioaccumulation - has the potential to bioaccumulate - enough to bioconcentrate effectively	3	3
Toxicity	*Bassa tossicità acuta*	Il farmaco possiede bassa tossicità acuta verso gli organismi acquatici	- low acute toxicity	0	1
	Bassa tossicità cronica	Il farmaco possiede bassa tossicità cronica verso gli organismi acquatici	- low chronic toxicity	0	1
	Potenziale tossicità (dati insufficienti)	I dati disponibili non sono sufficienti per escludere una potenziale tossicità verso gli organismi acquatici (potenziale tossicità)	- no data - lack of data - environmental risk cannot be significantly calculated - cannot be excluded	NA / 3	1

	Moderata tossicità acuta	Il farmaco possiede moderata tossicità acuta verso gli organismi acquatici	- moderate acute toxicity	1	2
	Moderata tossicità cronica	Il farmaco possiede moderata tossicità cronica verso gli organismi acquatici	- moderate chronic toxicity	1	2
	Alta tossicità acuta	Il farmaco possiede alta tossicità acuta verso gli organismi acquatici	- high acute toxicity	2	3
	Alta tossicità cronica	Il farmaco possiede alta tossicità cronica verso gli organismi acquatici	- high chronic toxicity	2	3
	Molto elevata tossicità acuta	Il farmaco possiede elevata tossicità acuta verso gli organismi acquatici	- very high acute toxicity	3	3
	Molto elevata tossicità cronica	Il farmaco possiede elevata tossicità cronica verso gli organismi acquatici	- very high chronic toxicity	3	3
Risk	*Impatto ambientale non significativo*	L'uso del farmaco ha un impatto ambientale non significativo	- insignificant environmental risk - is not considered to pose an environmental risk	NA	0
	Potenziale rischio di impatto ambientale (dati insufficienti)	I dati disponibili non sono sufficienti per escludere il rischio di impatto ambientale (potenziale rischio di impatto ambientale)	- cannot be excluded, since there is not sufficient ecotoxicity data available - ecotoxicity data are missing - no obvious environmental risk	NA	1
	Impatto ambientale basso	L'uso del farmaco ha un basso impatto ambientale	- low risk - the levels in the environment are probably well below the concentrations	NA	1
	Impatto ambientale moderato	L'uso del farmaco ha un impatto ambientale moderato e, nel caso di antibiotici, può aumentare il rischio di selezione di resistenza batterica	- risk for selection of antibiotic resistance - moderate risk	NA	2
	Impatto ambientale alto	L'uso del farmaco ha un alto impatto ambientale e, nel caso di antibiotici, può aumentare il rischio di selezione di resistenza batterica	- high risk	NA	3
Environmental impact	*Esente dalla valutazione sull'impatto ambientale*	Secondo quanto dichiarato dall'Agenzia Europea dei Medicinali, le vitamine, gli elettroliti, gli amminoacidi, i peptidi, le proteine, i carboidrati, i lipidi, i vaccini e i prodotti medicinali erboristici non costituiscono un rischio significativo per l'ambiente e sono privi di impatto ambientale	- the use of amino acids, proteins and peptides is not considered to have any environmental impact	NA	0

Abbreviations: NA, not applicable

Table 8. Italian texts and scores associated with additional information from the literature review

Source	Additional information	Description (in Italian language)	Score
FDA Flush List[113]	Medicines on the flush list are those (1) sought-after for their misuse and/or abuse potential and (2) that can result in death from one dose if inappropriately taken. If a drug take-back program is not available, flushing medicines on the flush list helps keep everyone in your home safe by making sure these powerful and potentially dangerous medicines are not accidentally or intentionally ingested, touched, misused, or abused	Flush List (FDA 2017): è possibile smaltire il farmaco nel lavandino o wc per prevenire danni ad animali o persone in caso di ingestione accidentale	- 0.5
Zuccato *et al*.[112]	Insignificant pollutant in Italy	Uno studio (Zuccato et al., 2006) ha rilevato residui di farmaco negli impianti di depurazione delle acque reflue di diverse città italiane e nelle acque superficiali dei fiumi Po e Lambro. Le concentrazioni di farmaco rilevate non rappresentano un pericolo per l'ecosistema ma andrebbero tenute sotto controllo	+ 0
Zuccato *et al*.[112]	Second line pollutant in Italy	Uno studio (Zuccato et al., 2006) ha rilevato concentrazioni di farmaco non trascurabili negli impianti di depurazione delle acque reflue di diverse città italiane e basse concentrazioni nelle acque superficiali dei fiumi Po e Lambro. A causa della sua elevata stabilità nell'ambiente, il farmaco è considerato un inquinante da monitorare	+ 0.5
Zuccato *et al*. [112]	Priority pollutant in Italy	Uno studio (Zuccato et al., 2006) ha rilevato concentrazioni non trascurabili di farmaco negli impianti di depurazione delle acque reflue di diverse città italiane e nelle acque superficiali dei fiumi Po e Lambro. A causa della sua elevata stabilità	+ 1

		nell'ambiente, il farmaco è considerato un inquinante prioritario	
Surface water Watch List of the European Commission[114]	Watch list of substances for which the information available indicates that they may pose a significant risk, at Union level, to or via the aquatic environment, but for which monitoring data are insufficient to come to a conclusion on the actual risk posed. The monitoring of the substances in the watch list should generate high-quality data on their concentrations in the aquatic environment	Watch List (Commissione Europea 2022): potenziale inquinante ambientale da monitorare	+ 0.5
Groundwater Watch List of the European Commission[115]	Substances, including emerging pollutants, for which groundwater quality standards or threshold values should be set. The groundwater Watch List is a tool to gather evidence to support any future decision to include new pollutants of European wide or national concern	Groundwater Watch List (Commissione Europea 2016): sostanza da monitorare per ridurre l'impatto ambientale dei farmaci	+ 0.5

Finally, the information obtained for each drug analysed was combined to obtain the final score and an overall description. The final scores were divided into 4 ranges, each one associated with a level of environmental impact and a short text to be used as a tooltip in the CDSS. The 4 levels of environmental impact are:

- **No environmental impact**: score = 0
- **Low environmental impact**: score = 1 – 4.5
- **Medium environmental impact**: score = 5 – 8.5
- **High environmental impact**: score > 8.5

3.1.2. Potentially nephrotoxic drugs

The bibliographic search to identify scientific papers for the creation of the table was conducted in July 2023. First, a Google search was conducted to identify relevant keywords; then, the final search was conducted on Scopus on July 12, 2023 with the keywords shown in Figure 12.

```
nephrotoxicity AND burden AND measure
nephrotoxicity AND burden AND prescription
nephrotoxicity AND burden AND drug SEARCH WITHIN health record
score AND predict AND acute AND kidney AND injury
score AND predict AND acute AND kidney AND injury AND NOT machine AND learning
drug AND induced AND kidney AND injury AND risk AND assessment
drug AND induced AND nephrotoxicity AND risk AND score
risk AND scoring AND system AND drug AND induced AND nephrotoxicity
risk AND scoring AND system AND drug AND induced AND kidney AND injury
drug AND induced AND acute AND kidney AND injury AND assessment AND prescription AND data
```

Figure 12. Keywords for searching scientific papers on potentially nephrotoxic drugs

More than 100 articles resulted from each query, which were selected based on titles. A total of 17 articles were initially selected to create the table on potentially nephrotoxic drugs. Characteristics of these studies are summarized in Table 9.

Table 9. Studies initially included for the creation of the table on potentially nephrotoxic drugs

Source	Title	Study type	Additional information
Stottlemyer BA, *et al*. Drug Safety 2023[116]	"Expert consensus on the nephrotoxic potential of 195 medications in the non-intensive care setting: a modified Delphi method"	Expert consensus (physicians and pharmacists)	**Table's main source** with drugs rating 0-3 (0: not nephrotoxic, 3: definite nephrotoxicity)
Gray MP, *et al*. Drug Safety 2022[117]	"Consensus obtained for the nephrotoxic potential of 167 drugs in adult critically ill patients using a modified Delphi method"	Expert consensus (physicians and pharmacists)	**Table's main source** with drugs rating 0-3 (0: no nephrotoxic potential, 3: definite nephrotoxic potential)
Welch HK, *et al*. Pharmacotherapy 2018[118]	"Drug-associated acute kidney injury identified in the United States Food and Drug Administration adverse event reporting system database"	Retrospective pharmacovigilance disproportionality analysis (voluntary reporting)	Drugs categorized as known, possible or new potential nephrotoxins
Naughton CA. Am Fam Physician 2008[119]	"Drug-induced nephrotoxicity"	Insights from scientific evidence	Pathophysiologic mechanisms of renal injury of known nephrotoxins and clinical recommendations

Sales GTM, *et al*. Rev Assoc Med Bras 2020[120]	"Drug-induced nephrotoxicity"	Insights from scientific evidence	Mechanisms of renal injury of direct known nephrotoxic drugs
Dobrek L. Life 2023[121]	"A synopsis of current theories on drug-induced nephrotoxicity"	Literature review	Risk-factors of drug-induced kidney disease and commonly used nephrotoxic drugs
Pazhayattil GS, *et al*. Int J Nephrol Renovas Dis 2014[122]	"Drug-induced impairment of renal function"	Insights from scientific evidence	Risk-factors of nephrotoxicity and mechanisms of drug-induced renal impairment of known nephrotoxic drugs
Perazella MA, *et al*. CJASN 2022[123]	"Drug-induced acute kidney injury"	Insights from scientific evidence	List of medications associated with acute kidney injury and acute tubular injury
Bentley ML, *et al*. Crit Care Med 2010[124]	"Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies"	Insights from scientific evidence	Mechanisms of acute kidney injury of known nephrotoxic drugs
Mody H, *et al*. Clinical Pharmacology in Drug Development 2020[125]	"A review on drug-induced nephrotoxicity: pathophysiological mechanisms, drug classes, clinical management, and recent advances in mathematical modeling and simulation approaches"	Literature review	List of commonly known drug-induced nephropathies and associated drugs
Awdishu L, *et al*. BMC Nephrology 2017[126]	"The 6R's of drug induced nephrotoxicity"	Insights from scientific evidence	**Not included in the final table** (no additional information)
Sutherland SM. Pharmacotherapy 2018[127]	"Electronic health record–enabled big-data approaches to nephrotoxin-associated acute kidney injury risk prediction"	Insights from scientific evidence	**Not included in the final table** (no additional information)
Ehrmann S, *et al*. Ann Intensive Care 2019[128]	"Nephrotoxic drug burden among 1001 critically ill patients: impact on acute kidney injury"	Case-control study on critically ill patients	**Not included in the final table** (framework to approach drug-induced nephrotoxicity)
Roughead EE, *et al*. Drug Safety 2022[129]	"Medicine-induced acute kidney injury findings from spontaneous reporting systems, sequence symmetry analysis and a case–control study with a focus on medicines used in primary care"	Literature review	**Not included in the final table** (study aimed at consolidating existing evidence of medicine-induced kidney injury)

Wang L, *et al*. Pediatric Research 2017[130]	"Electronic health record-based predictive models for acute kidney injury screening in pediatric inpatients"	Retrospective cohort study on children	**Not included in the final table** (choice not to include children because a separate knowledge-base should be made)
Goswami E, *et al*. Am J Health-Syst Pharm 2019[131]	"Evidence-based development of a nephrotoxic medication list to screen for acute kidney injury risk in hospitalized children"	Expert consensus (physicians and pharmacists)	**Not included in the final table** (choice not to include children because a separate knowledge-base should be made)
UK Renal Pharmacy Groups 2019[132]	"The renal drug handbook – The ultimate prescribing guide for renal practitioners, 5th edition"	Clinical guideline	Drug dosages to be used with normal or impaired renal function **included in the final table**

Two studies (Stottlemyer *et al*. [116] and Gray *et al*. [117]) were used as main sources to create the table and to set the records with drugs to write information for. From the 17 initially selected sources, 6 studies were excluded because they did not add additional information or involved specific information for children. The remaining selected sources were used to integrate the existing information; if there were drugs in these sources that were missing from the first two studies, they were included in the final table.

The following information were extracted from the selected studies and included in separate columns of the table:

- Potentially nephrotoxic drug;
- Information related to critical or non-critical patients;
- 7-level risk score of nephrotoxicity in non-critical patients according to Stottlemyer *et al*.; [116]
- Short text associated to the 7-level risk score;
- Short text for critical patients;
- Comprehensive and concise description;
- Mechanism of renal toxicity;
- Drug dosage with normal or impaired renal function;
- Sources.

Risk scores according to Stottlemyer and Gray and colleagues [116,117] ranged from 0 to 3, corresponding to seven nephrotoxicity categories: 0 – no potential nephrotoxicity, 0.5 – unlikely to possible, 1.0 – possible, 1.5 – possible to probable, 2.0 – probable to definite, 3 –

definite. These were reduced to four risk scores to comply with NavFarma® characteristics. In addition, one additional risk score corresponding to the category “unknown nephrotoxicity risk” was added to include drugs from other studies for which one of the four selected risk scores could not be assigned.

The final risk categories of potentially nephrotoxic drugs included in the table implemented on the NavFarma® knowledge-base are:

- **Unknown risk**;
- 0 – **insignificant risk**;
- 0.5-1 – **low risk**;
- 1.5-2 – **moderate risk**;
- 2.5-3 – **high risk**.

In the case of two sources reporting different risk categories for the same drug, the higher one was chosen.

3.1.3. Drugs with a known risk of long QT

The literature search to create the table on drugs that may prolong the QT interval began on March 22, 2023. After an initial search on Google, the citation databases Scopus and PubMed were used.

Some of the keywords used were “QT prolongation drug list”, “QT prolongation risk”, “risk score for QT prolongation” and “drugs causing QT prolongation”.

The bibliographic search resulted in the selection of 44 articles and scientific papers. In addition, Micromedex® [45] and The Devon Formulary [133] databases were also used to create the table.

As a result of full-text reading, 6 articles were removed because they used CredibleMeds® [44] as their main source, which consists of a rich online database containing recommendations for the use of drugs capable of prolonging the QT interval. CredibleMeds® is copyrighted and cannot be used for commercial purposes; therefore, it was not possible to use this source to enrich the knowledge-base of the NavFarma® CDSS.

The remaining 40 sources used to create the table to be implemented on NavFarma® are presented below (Table 10).

Table 10. Sources for the creation of the table on drugs that may prolong the QT interval

Source	Source or study type
Micromedex® online database[45]	Insights from scientific literature
South & West Devon Formulary and Referral[133]	Insights from scientific literature
Hazell L, *et al*. J Clin Pharmacol 2017[134]	Insights from scientific literature
Raschi E, *et al*. Plos One 2013[135]	Reports of ADRs or case reports
Poluzzi E, *et al*. Pharmacoepidemiol Drug Saf 2009[136]	Reports of ADRs or case reports
Ng PW, *et al*. Aust NZ J Med 1996[137]	Reports of ADRs or case reports
Lee KW, *et al*. Am J Cardiol 2004[138]	Reports of ADRs or case reports
Tay KY, *et al*. Pharmacoepidemiol Drug Saf 2014[139]	Reports of ADRs or case reports
Zeltser D, *et al*. Medicine (Baltimore) 2003[140]	Reports of ADRs or case reports
Uchikawa M, *et al*. Drugs - Real World Outcomes 2022[141]	Reports of ADRs or case reports
Bibawy JN, *et al*. Circ Arrhythm Electrophysiol 2013[142]	Reports of ADRs or case reports
Lazzerini PE, *et al*. Circ Arrhythm Electrophysiol 2021[143]	Evaluation of patients' clinical data (e.g., ECG)
Fan W, *et al*. Cardiovascular Drugs and Therapy 2023[144]	Evaluation of patients' clinical data (e.g., ECG)
Hegde V, *et al*. Eur Heart J Case Re 2023[145]	Reports of ADRs or case reports
Özmen N, *et al*. Anatol J Cardiol 2015[146]	Reports of ADRs or case reports
Weeke P, *et al*. Europace 2013[147]	Reports of ADRs or case reports
Grande I, *et al*. Hum Psychopharmacol Clin Exp 2011[148]	Reports of ADRs or case reports

Feng PF, *et al*. Mol Pharmaceutics 2019[149]	*In vitro* or laboratory animal study
Nij Bijvank SWA, *et al*. Nederlands Tijdschrisfft voor Obstetrie en Gynaecologie 2004[150]	Reports of ADRs or case reports
Ürge J, *et al*. Scandinavian Journal of Gastroenterology 2008[151]	Reports of ADRs or case reports
Jao YTFN. International Journal of Cardiology 2016[152]	Reports of ADRs or case reports
Castello Viguer MT, *et al*. Revista Espanola de Cardiologia 1999[153]	Reports of ADRs or case reports
Segura I, *et al*. Resuscitation 1999[154]	Reports of ADRs or case reports
Rao KA, *et al*. Mayo Clin Proc 1994[155]	Reports of ADRs or case reports
Rong Lu H, *et al*. British Journal of Pharmacology 2012[156]	*In vitro* or laboratory animal study
McBride L, *et al*. J Oncol Pharm Practice 2021[157]	Reports of ADRs or case reports
Teng C, *et al*. Int J Med Sci 2019[158]	Reports of ADRs or case reports
Okabe Y, *et al*. Heart Vessels 2018[159]	Evaluation of patients' clinical data (e.g., ECG)
De Vecchis R, *et al*. Eur J Clin Pharmacol 2018[160]	Evaluation of patients' clinical data (e.g., ECG)
Nakayama M, *et al*. Circulation Journal 2015[161]	Evaluation of patients' clinical data (e.g., ECG)
Goto M, *et al*. Intern Med 2014[162]	Evaluation of patients' clinical data (e.g., ECG)
Haga Y, *et al*. Clin Toxicol (Phila) 2020[163]	Reports of ADRs or case reports
Park J, *et al*. Yonsei Med J 2013[164]	Reports of ADRs or case reports
De Ponti F, *et al*. Drug Saf 2002[165]	Insights from scientific literature
Poluzzi E, *et al*. Plos One 2015[166]	Reports of ADRs or case reports
Sasaoka S, *et al*. Plos One 2016[167]	Reports of ADRs or case reports
Fahey OG, *et al*. J Oncol Pharm Practice 2020[168]	Insights from scientific literature
Ali Z, *et al*. Expert Opinion on Drug Safety 2021[169]	Reports of ADRs or case reports
Prescrire editorial staff. Prescrire International 2021[170]	Insights from scientific literature
Giraud EL, *et al*. Lancet Oncol 2022[171]	Insights from scientific literature

Abbreviations: ADRs, adverse drug reactions; ECG, electrocardiogram

Drugs were categorized into 4 levels of risk based on the information extracted from the sources consulted:

- **High risk** of occurrence of long QT syndrome and *torsade de pointes*;
- **Moderate risk** of occurrence of long QT syndrome;
- **Low risk** of occurrence of long QT syndrome in presence of risk factors;
- **Uncertain risk** of occurrence of long QT syndrome.

3.1.4. Guidelines for deprescription or tapering dose

The Excel table integrated into the NavFarma® knowledge-base contains recommendations for deprescribing and/or reducing the dose of specific drugs or drug classes considered appropriate for this process in older patients. As for previous tables, recommendations included in the table are based on the revision of the available scientific literature on deprescribing, as well as on the Beers and STOPP criteria [39,40], which are internationally recognized standards for identifying PIPs for older patients. The drug classes included in the table have been classified according to the priority of the recommendation related to clinical risk.

The literature search was conducted in autumn 2023 on Google and on the citational databases Scopus and PubMed. Scientific papers, documents prepared by scientific societies or healthcare facilities and free online databases were used to identify relevant sources.

A total of 20 sources were selected to feed the table, as summarized in Table 11.

Table 11. Sources for the creation of the table on deprescription and tapering dose

Source	Title	Source type	Drug class of interest
American Geriatrics Society. JAGS 2023[39]	"American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults"	Expert consensus	Various
O'Mahony D, *et al*. Eur Geriatr Med, 2023[40]	"STOPP/START criteria for potentially inappropriate prescribing in older people: version 3"	Expert consensus	Various
PrescQIPP 2020[172]	"IMPACT - Improving medicines and polypharmacy appropriateness clinical tool"	Guideline	Various
Società Italiana di Gerontologia e Geriatria 2018[173]	"Manuale di competenze in geriatria"	Clinical manual	Various
Primary Health Tasmania 2022[174]	"A guide to deprescribing antihypertensives"	Guideline	Antihypertensives
Del-Pino M, *et al*. Prim Health Care Res Dev 2023[175]	"Analysis of deprescription strategies of proton pump inhibitors in primary care: a narrative review"	Literature review	PPIs
Rossio R, *et al*. Internal and Emergency Medicine 2022[176]	"Prescription appropriateness of anticoagulant drugs for prophylaxis of venous thromboembolism in hospitalized multimorbid older patients"	Analysis of patients' data	Anticoagulants

Tsai C, *et al*. Clin Respir J 2018[177]	"Inhaled corticosteroids and the risks of low-energy fractures in patients with chronic airway diseases: a propensity score matched study"	Analysis of patients' data	ICs
Ross SB, *et al*. J Am Geriatr Soc 2020[178]	"COVID-SAFER: deprescribing guidance for hydroxychloroquine drug interactions in older adults"	Analysis of patients' data	Hydroxychloroquine
Choosing Wisely Canada 2019[179]	"A toolkit for reducing inappropriate use of benzodiazepines and sedative-hypnotics among older adults in hospitals"	Online toolkit	BZRAs
Choosing Wisely Canada 2019[180]	"A toolkit for deprescribing proton pump inhibitors in EMR-enabled primary care settings"	Online toolkit	PPIs
Choosing Wisely Canada 2019[181]	"A toolkit for reducing inappropriate use of benzodiazepines and sedative-hypnotics among older adults in primary care"	Online toolkit	BZRAs
Muriel J, *et al*. Acta Pharm 2023[182]	"Long-term deprescription in chronic pain and opioid use disorder patients: pharmacogenetic and sex differences"	Analysis of patients' data	Pain therapy
Pottie K, *et al*. Can Fam Physician 2018[183]	"Deprescribing benzodiazepine receptor agonists: evidence-based clinical practice guideline"	Guideline	BZRAs
Potter K, *et al*. Plos One 2016[184]	"Deprescribing in frail older people: a randomised controlled trial"	Analysis of patients' data	Various
Lui E, *et al*. Can Pharm J (Ott) 2021[185]	"Pharmacist-led sedative-hypnotic deprescribing in team-based primary care practice"	Analysis of patients' data	BZRAs
Langford AV, *et al*. Med J Aust 2023[186]	"Clinical practice guideline for deprescribing opioid analgesics: summary of recommendations"	Guideline	Pain therapy
Woodward MC, *et al*. J Pharm Pract Res 2003[187]	"Deprescribing: achieving better health outcomes for older people through reducing medications"	Insights from scientific literature	Various
Roux B, *et al*. Eur Geriatr Med 2019[188]	"Prescription and deprescription of medications for older adults receiving palliative care during the last 3 months of life: a single-center retrospective cohort study"	Analysis of patients' data	Pain therapy
Capiau A, *et al*. Eur Geriatr Med 2023[189]	"Therapeutic dilemmas with benzodiazepines and Z-drugs: insomnia and anxiety disorders versus increased fall risk: a clinical review"	Literature review	BZRAs

Abbreviations: PPIs, proton pump inhibitors; BZRAs, benzodiazepine receptor agonists; ICs, inhaled corticosteroids

The following information were extracted from the selected sources:

- Drug or drug class;
- Reason for deprescription;
- How to deprescribe or tapering dose;
- Clinical risk high, medium or low;
- Deprescription priority high, medium or low;
- List of sources consulted.

3.2. Pilot study to test the NavFarma® CDSS

A pilot study to test the updated version of the CDSS was conducted in summer 2024. The objectives of the pilot study were to verify that the information included in the updated knowledge-base behaved as expected, was accurate and suitable for medication review, and to collect feedback from NavFarma® users to further implement the software. Particularly, the pilot study aimed to address the following research question: how can the alerts generated by NavFarma® and verified by pharmacists be made readily accessible to physicians to support informed clinical decision-making?

The Mauriziano Hospital in Turin was identified as the facility in which to conduct the pilot study as its Hospital Pharmacy has employed NavFarma® from the Infologic company for years to support clinicians in some departments with a consultation service for medication review. The pilot study involved the collaboration with a hospital pharmacist at the Mauriziano Hospital who selected critically ill patients admitted to the internal medicine department and performed therapy data collection on the testing updated version of NavFarma®. Patient data were collected from the hospital's electronic medical records and then entered into NavFarma® anonymously by replacing the patient's name with a sequential number. Inclusion criteria were:

- Patients over 65 years of age;
- Presence of ≥2 diseases (multimorbidity, as defined by the WHO); [67]
- Use of ≥5 different drugs (polypharmacy, generally accepted definition); [66]
- Availability in the electronic medical record of patient gender and age, list of diagnoses, pharmacological therapy at baseline prescribed by both GPs and hospital specialists, dosage regimen and any other relevant clinical information.

Medication review was performed by researchers at the DSTF on patients' baseline therapies using information entered on NavFarma®. The study outcome was individual reports including an assessment of PIMs and risks associated with therapy (identified with the support of the CDSS) and advice on how to optimize pharmacological therapy. Reports were prepared manually and then transmitted to the hospital pharmacist to enable a discussion with the internist physician.

Moreover, an opportunity arose to present NavFarma® to two interdisciplinary care groups (*Gruppi Interdisciplinari Cura*, GIC) of the *Città della Salute e della Scienza di Torino* Hospital

(Turin) in order to collect impressions and suggestions from the healthcare professionals involved. Within the *Città della Salute e della Scienza di Torino* Hospital, a GIC is a clinical team composed of hospital pharmacists and various clinical specialists who periodically discuss and establish the most appropriate care pathways for patients with specific diseases through a comprehensive view of the patient and an interdisciplinary clinical approach. In particular, it was possible to collaborate with two hospital pharmacists of the *Città della Salute e della Scienza di Torino* Hospital who participate weekly in the GIC on multiple myeloma and gastric cancer. First, the CDSS was presented to the two hospitals pharmacists, showing a possible working strategy for reviewing the therapy of complex patients. Secondly, hospital pharmacist prepared a short presentation to illustrate the potential of the software to the GIC clinicians, who showed interest in learning about a possible output of NavFarma® useful for reviewing their patients' therapies. For this reason, hospital pharmacists were asked to collect some examples of patient therapies discussed in the GIC on multiple myeloma and gastric cancer with the aim of preparing a model of a possible medication review report including recommendations from NavFarma®. Finally, reports were drafted at the DSTF based on the therapy models and transmitted to hospital pharmacists for collecting feedback from clinicians.

Specifically, the following MRPs and alerts showed by NavFarma® were used to prepare medication review reports:

- Contraindicated or major DDIs. DDIs are periodically extracted by the NavFarma® knowledge-base from the most recent versions of the Micromedex® [45] and Codifa® [99] databases;
- PIPs according to the Beers [39] and the STOPP [40] criteria (2023 update). Based on their description, these can be classified into PIPs valid in most older patients and PIPs valid depending on the presence of a certain patient clinical condition (conditioned PIPs); each PIP was then evaluated by the researcher to determine whether it could be applicable for the specific patient (applicable PIPs) or not (non-applicable PIPs). For example, a PIP valid in most older patients could be non-applicable if the medication daily dosage is below a certain dosage; a conditioned PIP could be non-applicable if the patient does not suffer from Parkinson disease;
- ACB score [41] (2012 update). It includes a list of medications with possible or definite anticholinergic effects and their score of 1 (possible anticholinergics from *in vitro*

data), 2 (determine anticholinergics from literature evidence) or 3 (determine anticholinergics from expert opinion);

- Potentially nephrotoxic drugs. It includes information revised during the Ph.D. and is described in chapter 4.1.2;
- Drugs that may prolong the QT-interval. It includes information revised during the Ph.D. and is described in chapter 4.1.3;
- Guidelines to treat specific diseases. In case of a PIP, available guidelines (updated during the Ph.D.) were checked to suggest more appropriate first-line drugs;
- Recommendations for deprescription of specific drugs in certain conditions. These were checked to verify the presence of indications on how to deprescribe a PIP according to the latest version updated during the Ph.D. (chapter 4.1.4).

The pilot study achieved significant progress, enabling the successful proposal, development, and implementation of essential new features on NavFarma® to streamline the medication review process. In particular, thanks to the experience of the pilot study, a dedicated space for pharmacists was introduced to systematically evaluate MRPs and PIPs. In addition, the workflow has been vastly improved through the integration of an automated and editable medication review report, improving both the efficiency and accuracy of pharmacists' evaluations. To encourage the use of these new features by NavFarma® users, a series of webinars were organized in fall 2024 to illustrate the new version of the CDSS. Feedback and suggestions from participants to the webinars were collected through a survey and findings will be used to further improve NavFarma®.

3.3. DUR and RWD analysis

As many studies have shown [190-192], electronic health records are a source of RWE, which have proven to be a feasible data source for observational retrospective studies aimed at identifying trends, outcomes and associations that can inform clinical practice and guide future research. The aim of this activity was to collect large amounts of real-world health data to conduct DUR with the following objectives: 1) to investigate the use of specific drugs in a given area; 2) to stratify chronic patient populations based on common characteristics (e.g., medication adherence and comorbidities) to promote interventions to improve prescription appropriateness.

Anonymized electronic health records were collected from the LHAs *Azienda Sanitaria Locale di Ciriè, Chivasso e Ivrea* (ASL TO4) and *Azienda Unità Sanitaria Locale Valle d'Aosta* (AUSL VdA). Before data collection could proceed, two research agreements had to be arranged with the LHAs to regulate the exchange of anonymized personal data for research purposes: 1) "*Analisi di database amministrativi per studi di farmacoutilizzazione e farmacoepidemiologia nella popolazione degli assistiti dell'A.S.L.TO4*" between the DSTF and the ASL TO4; 2) "*Analisi di database amministrativi per studi di farmacoutilizzazione, farmacoepidemiologia e farmacovigilanza nella popolazione degli assistiti dell'Azienda USL della Valle d'Aosta*" between the DSTF and the AUSL VdA. Moreover, the opinion of Ethics Committees responsible for the ASL TO4 and the AUSL VdA has been sought to carry out retrospective DUR.

Due to the different nature of the two LHAs, and especially because of the complex data protection regulation (GDPR 679/2016) [87], different types of electronic health records were collected from the two facilities.

The ASL TO4 outlines an area in the Piedmont Region that extends north from the city of Turin toward the Valle d'Aosta Region and west toward France. It includes 177 municipalities divided into 5 health districts that include both rural and urban areas. The ASL TO4 provides healthcare to about 520,000 inhabitants, corresponding to 12.2% of the overall regional population (nearly 4.3 million inhabitants at the end of 2023). [193] The research agreement with the DSTF involves the Territorial Pharmaceutical Services of the ASL TO4, with whom there has been a close relationship of mutual cooperation for several years. Territorial Pharmaceutical Services represent a regional structure with functions aimed at promoting

the appropriate use of drugs to ensure pharmaceutical care for the population of the territory in compliance with national and regional regulations; in particular, they govern the proper management of medicines reimbursed by the Italian NHS dispensable by community pharmacies. Therefore, only **drug dispensing data from community pharmacies** of the ASL TO4 were collected. Data were collected at different times from 01/01/2018 to 30/09/2023; they are organized into monthly databases submitted periodically by community pharmacies to the ASL TO4 for administrative purposes. Drug dispensing data include records of all dispensations of medications reimbursed by the Italian NHS prescribed by GPs and paediatricians. They include the following information:

- Year and month of billing;
- Anonymous unique patient identifier;
- Date of birth and gender of the patient;
- Province and municipality of residence of the patient, if available;
- Regional code of the prescriber, if available;
- Date of dispensation;
- Name of the medication and ministerial product code (hereafter Minsan);
- Active ingredient;
- Anatomical Therapeutic Chemical (ATC) Classification code; [194]
- Number of dispensed packages;
- Public product price;
- Date of death, if present (data updated to September 2023);
- Chronic disease exemption codes, if available.

The following retrospective observational studies were conducted with drug dispensing data of the ASL TO4 (studies in bold will be discussed in detail):

- Study to describe the use of drugs for the treatment of benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS) in adult men in the ASL TO4. A network-based approach and persistence measures were adopted as robust and feasible ways for understanding patterns of medication-taking behaviour and assessing patient compliance. [195]

- **Study to describe the use of antidiabetic drugs in treatment-naïve adult patients in the ASL TO4**. Adjustments to first-line metformin monotherapy were analysed; medication adherence and persistence to antidiabetic drugs were assessed.
- Study to evaluate the impact of the lockdowns implemented in 2020 during the Covid-19 pandemic on prevalence of antidepressants use in the population of the ASL TO4. An Interrupted Time Series (ITS) analysis was used to assess the effect of lockdowns on the observed outcomes. [196]
- Study to describe persistence and adherence to antithyroid drugs in the ASL TO4.
- Study to describe persistence and adherence to statins in a population of chronic patients at risk for hypercholesterolemia. Patients with statin prescriptions for the treatment of familial hypercholesterolemia or mixed dyslipidemia, patients with statin prescriptions and an exemption for prior cardiovascular events, diabetes, chronic kidney disease (CKD) or hypertension and patients prescribed statins at the highest marketed dose were considered at risk.
- **Study to evaluate the impact of the introduction of the "*Nota 100*" by the AIFA on the use of antidiabetic drugs** (ITS analysis).

Otherwise than the ASL TO4, the AUSL VdA is the only LHA in the Valle d'Aosta Region, with the mission of ensuring adequate and uniform levels of care for approximately 125,000 citizens living in the 74 municipalities of the Valle d'Aosta. Valle d'Aosta is the smallest Italian region, with an area equal to one hundredth of the national territory, located in the northwest of Italy on the border with France and Switzerland. It is a predominantly mountainous region and has three hospitals run directly by the region and 4 districts. Because of this peculiarity, it was possible to collect health data from both the territory and hospitals in the entire region. Particularly, the following health data were collected from the AUSL VdA: 1) **drug dispensing data from community pharmacies** of the AUSL VdA (collection period from 01/01/2016 to 31/12/2022); 2) **drug dispensing data from hospital pharmacies** of the AUSL VdA (from 01/01/2018 to 31/12/2022); 3) **hospital discharge records** (*Schede di Dimissione Ospedaliera*, SDO) from 01/01/2016 to 31/12/2021; 4) **laboratory test results** for measurement of cholesterol, glucose, glomerular filtration rate (eGFR) and creatine phosphokinase (CPK) (from 01/01/2018 to 31/12/2021).

As with the ASL TO4 data, these are also collected for administrative and reimbursement reasons and are not intended for research purposes. Drug dispensing data of the AUSL VdA contains information similar to the ASL TO4 drug dispensing data. In order to perform DUR, a linkage between drug dispensing data (both form the ASL TO4 and the AUSL VdA) and a dataset of the AIFA [197] was made to match to each medication of interest the number of dosage units, the dosage of individuals units and the Defined Daily Dose (DDD). [194] SDO include the unique patient identifier, dates of hospitalization and discharge, reason for hospital admission and up to 5 secondary diagnoses coded with ICD-9 codes. Laboratory data contains date, description and results of the exam associated with the unique anonymous patient identifier. These data were used **to investigate the use of lipid-lowering drugs in the AUSL VdA** and to characterize population of patients using these drugs.

The most relevant studies carried out during the Ph.D. have been the subject of poster presentations at national and international scientific conferences, as well as of publications in international scientific journals. [198-203] In this dissertation, only the results related to the **study of antidiabetic drug use in the ASL TO4** and **lipid-lowering drug use in the AUSL VdA** will be discussed in detail, as they are considered most relevant to the promotion of interventions to improve prescription appropriateness. For the other studies, the analysis methodologies used (in general) and the list of accepted publications (results section, chapter 4.3.3) are given below.

All data cleaning and analysis were performed using Microsoft Access and the R statistical and programming language (version 4.0.5; https://cran.r-project.org/).

Part of the methodologies described below has been previously published in internationally accepted scientific papers of which I am first author or co-author. [200,203,204]

Drug Prescription Network (DPN) approach to study prescription patterns

Network (graph) theory and DPNs have been used for the study of drug prescriptions in two previous studies by Cavallo *et al*. and by Bazzoni *et al*. [205,206] Based on these studies, my research group at the DSTF developed a methodology to identify prescription patterns of specific drug classes through the creation of DPNs. [204] In brief, in a DPN, each active ingredient associated with an ATC code is represented as a *node*, and two active ingredients

co-dispensed to the same patient are represented as an *edge* linking the nodes. Node diameter and edge thickness are proportional to the number of dispensations (Figure 13). Although the use of DPNs is still limited, it has been shown to be a useful means to identify PIPs, potential DDIs, and to assess epidemiological models on a large scale.

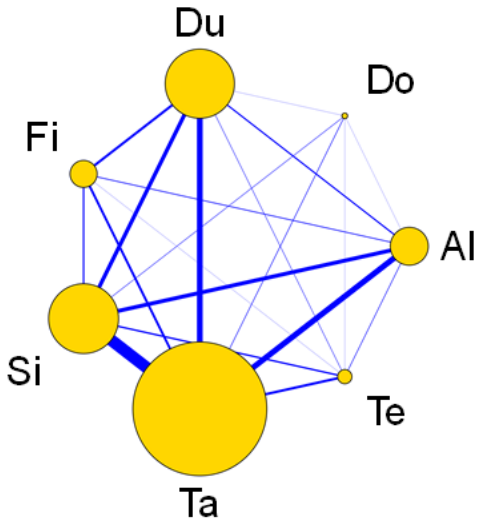


Figure 13. Example of a DPN for drugs to treat benign prostatic hyperplasia (from drug dispensing data of the ASL TO4, data published by Miglio *et al*.) [204]

Assessment of persistence to pharmacological treatments

Persistence to pharmacological treatments is the maintenance of drug therapy over time, that is, the period starting from the first prescription or the beginning of the observation period in which a patient is covered by the prescribed therapy until a discontinuation of a duration longer than an allowed gap. [207]

In our analysis, we considered patients to be persistent until the **first discontinuation** of the study drug(s) lasting longer than the allowed gap. We chose the duration of the allowed gap based on the drug class analysed and on previous studies [208,209] published in the scientific literature (e.g., 1.5 times the duration of the last dispensation or 60 days). The choice of a variable length of grace period makes it possible to consider the various commercially available pack sizes, which can vary from 10 to 100 units, rather than a fixed number of days of pack duration.

After the first discontinuation, the patient could re-start taking the prescribed therapy; we did not consider re-initiation of therapies in the assessment of persistence to treatments.

To measure persistence with administrative drug dispensing data, the date of the first dispensation during the observation period was taken as the index date. Then, a longitudinal

dataset of drug supply was created for each enrolled patient, and the number of days of drug supply was calculated based on a predetermined daily dose (DDD [194] – or 1 unit/die for medications such as statins). Treatment persistence was estimated using Kaplan-Meier survival analysis, where a patient's persistence is expressed as the time from the index date to the first discontinuation of a study drug. For this purpose, each dispensation is considered as a treatment event, and consecutive treatment events (separated from each other by periods lasting less than the allowed gap) form the treatment episodes (Figure 14). To measure the duration of each dispensation, the total amount of active ingredient dispensed was divided by the predetermined daily dose.

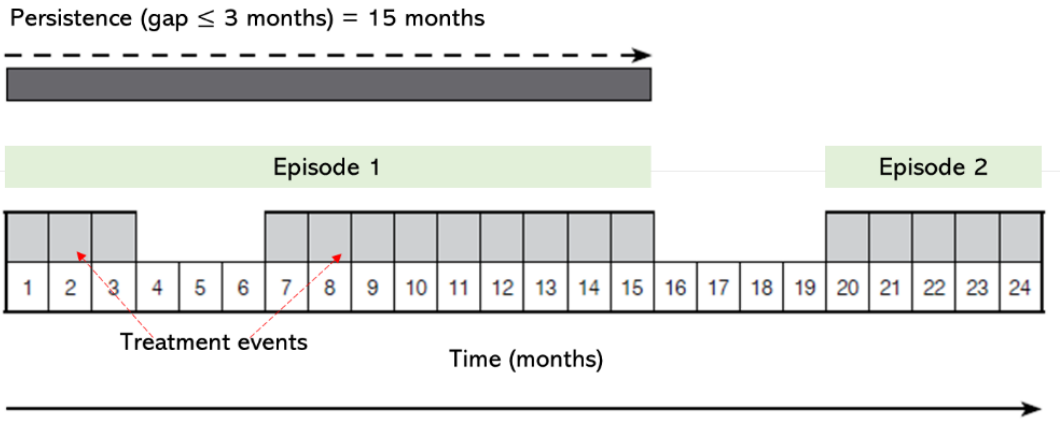


Figure 14. Definition of persistence, treatment events and treatment episodes. Figure adapted from Lenzi J. *Calcolo dell'aderenza alle terapie farmacologiche a partire dai flussi amministrativi correnti*. *XIC Convegno Italiano degli Utenti di Stata* (2017) [210]

In our analysis, persistence was expressed both as a continuous variable, i.e., number of days the therapy is available or time to discontinuation (represented with Kaplan-Meier curves) and a dichotomous variable, i.e., proportion of persistent and non-persistent patients at the end of the observation period.

Assessment of medication adherence

As opposed to persistence, medication adherence is "the process by which patients take their medications as prescribed, composed of **initiation**, **implementation** and **discontinuation**" (Figure 15). [211]

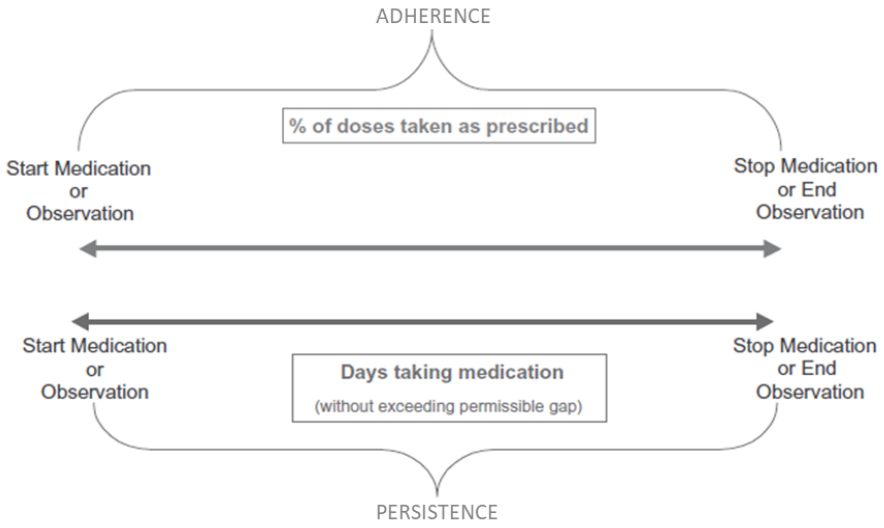


Figure 15. Definitions of medication adherence and persistence [207]

The time when the patient takes the first dose of a prescribed medication represents **initiation** of the treatment, followed by **implementation** of the dosing regimen, defined as "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen". **Discontinuation** marks the end of treatment, when medication doses are no longer being taken. [212]

Medication adherence can be measured by a variety of methods, including indirect methods that exploit drug prescription/dispensing data to get an estimate of the real-world use of a specific drug by a population. Two of the most widely used indirect methods are the **Medication Possession Ratio (MPR)** and the **Proportion of Days Covered (PDC)**. [213] Although they are often used as synonyms, the MPR places the sum of all days of drug supply in the numerator, whereas the PDC places the number of days in treatment at the numerator, so if there are overlaps between one treatment event and the next, with the PDC they are counted only once. For both measures, the denominator corresponds to the length of the observation period. [210] Figure 16 shows the difference in the measure of medication adherence between MPR and PDC.

$$MPR = \left(\frac{Sum\ of\ days\ supply\ for\ all\ fills\ in\ period}{Number\ of\ days\ in\ period}\right) \times 100\%$$

$$PDC = \left(\frac{Sum\ of\ days\ in\ period\ covered\ by\ supply}{Number\ of\ days\ in\ period}\right) \times 100\%$$

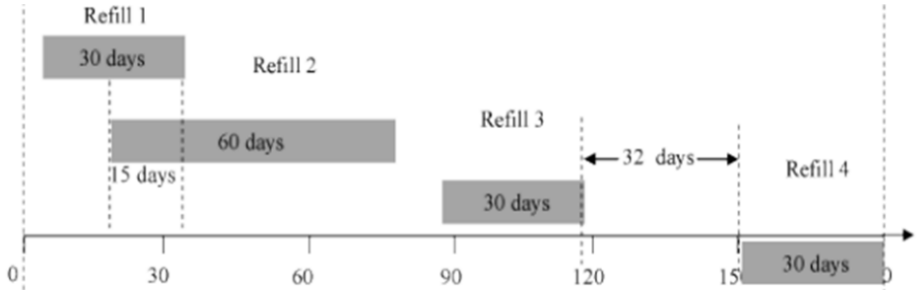


Figure 16. MPR *vs* PDC. In this example: [210]
$MPR = (30 + 60 + 30 + 30) \div 180 \times 100\% = 83\%$
$PDC = (30 + 60 - 15 + 30 + 30) \div 180 \times 100\% = 75\%$

In our analysis, we chose to measure the MPR for specific drugs or drug classes for patients starting therapy after a period of wash-out: by using a wash-out of 1 year or more in which we exclude from the analysis patients who have received dispensations of the study drug, we assume that the remaining patients are treatment-naïve and that the first dispensing date following the wash-out is their index date.

As for persistence, we divide the total amount of active ingredient dispensed by a predetermined daily dose to measure the duration of each dispensation or treatment event and we allow a grace period (gap) of variable duration to consider consecutive events. Again, adherence results can be expressed as the median adherence of the population or as the proportion of patients with specific adherence thresholds during the observation period. We chose the following thresholds as recommended by the AIFA: [214]

- Adherent patients: MPR ≥80%
- Partially adherent patients: 40 ≤ MPR < 80%
- Non-adherent patients: MPR <40%

Measuring medication adherence using drug dispensing data presents some limitations and assumptions. First, drug dispensing data should be complete and accurate. Second, it is assumed that the dispensed medication is taken by the patient with the timing indicated by the physician and at a daily dosage predetermined by the researcher (usually the DDD). Third, we assume that the patient does not procure the medication in other ways or in other places

other than his or her LHA of residence, so if a dispensation is missing, the medication has not been taken and the patient is non-adherent. [215]

Advantages are the low cost of the analysis and the ability to analyse large amounts of RWD. [213]

Prevalence of use of specific drug classes and ITS analysis

Weekly prevalence of users of a study drug was estimated as described by Antonazzo *et al*. [216] with minor modifications. First, for each patient included in the study, a longitudinal dataset of medication supply was created to identify the duration of treatment events and episodes, as described in the previous sections. Second, the entire study period was divided into consecutive weeks, and the number of patients with active treatment episodes in each week was counted. Finally, weekly prevalence was measured by dividing the number of patients with active treatment episodes in each week by the reference population, i.e., the number of inhabitants living in a specific area on 1 January of each corresponding calendar year and belonging to the age and/or gender group considered. The Clopper-Pearson method was used to estimate the 95% confidence interval (CI) for the prevalence values.

Overall prevalence was measured by dividing the number of patients with at least one dispensation of a study drug during the study period by the reference population.

To measure the impact of a regulatory measure on the use of specific drug classes within a population, we chose the method described by Schaffer *et al*. [217] exploiting ITS analysis. ITS methods consist in quasi-experimental designs which can exploit electronic health records routinely collected by healthcare facilities to assess the impact of an intervention. With these methods, it is assumed that the data trend in absence of the intervention can be predicted from data collected prior to the intervention. [218]

In brief, weekly prevalence of users of a study drug was estimated (**observed values**) as described above. Then, an ITS analysis using autoregressive integrated moving average (ARIMA) model was performed after dividing the study period into two segments: before and after the introduction of the regulatory measure. ARIMA model was chosen because it allows the evaluation of lagged intervention effects; through this model, it is possible to predict the weekly prevalence of users of a specific drug (**predicted values**) in absence of the regulatory measure (**counterfactual**). Observed and predicted values were then compared to identify substantial differences in the use of the study drugs. Results of ITS analysis were displayed

as graphical figures rather than through statistical outputs because figures allow to visualise the baseline data trend, the time point when the intervention occurred and its impact on the data.

4. RESULTS

4.1. NavFarma® knowledge-base

What most distinguishes the NavFarma® CDSS from other Italian platforms supporting medication reconciliation and review, freely available or not in Italy (i.e., INTERCheck [219], Mediately [220], EBMEDS [221]), is the richness of its knowledge-base, built through long-standing collaboration with the DSTF. Moreover, Infologic s.r.l. boasts of a direct link both to the Micromedex®'s databases [45], which allows up-to-date pharmacological interactions to be viewed on the NavFarma® platform, and to the Codifa®'s databases [99], which include the handbook of drugs marketed in Italy and general drug information, such as how to prescribe them.

Specifically, NavFarma® is a rule-based CDSS, meaning that all the information and recommendations it provides consist of preformed texts or figures linked to specific codes or rules: ATC or Minsan codes (the Minsan code is the marketing authorization code assigned by the Italian Ministry of Health to approved medications) for drugs, ICD-9 codes for diagnosis, patient gender and age for certain alerts (i.e., alerts related to PIPs in older adults appear only for patients aged 65 years and older). Table 12 summarises all the tables currently included in the NavFarma® knowledge-base.

Table 12. Tables and alerts included in the NavFarma® knowledge-base (update to December 2024)

Pictograms	Table	Last revision	Records (drugs), n[a]	Revised during Ph.D.
Information for system functions				
	Pharmaceutical handbook of medications marketed in Italy	2024 (automatic periodic extraction from Codifa®)	NA	No
NA	Active ingredients translated into Italian from ATC codes	2021 (manual update)	308 (308)	No
	Diseases according to the ICD-9	2019 (manual update)	1040 (NA)	No
NA	Disease tracer drugs	2020 (manual update)	7 (11)	No
NA	List of Italian generic drugs	2024 (periodic extraction from the AIFA)	8140 (362)	No
	Simple disease names associated with ICD-9 codes for the ITS	2019 (manual update)	439 (NA)	**Yes** (design of a new template with specific information for the ITS)

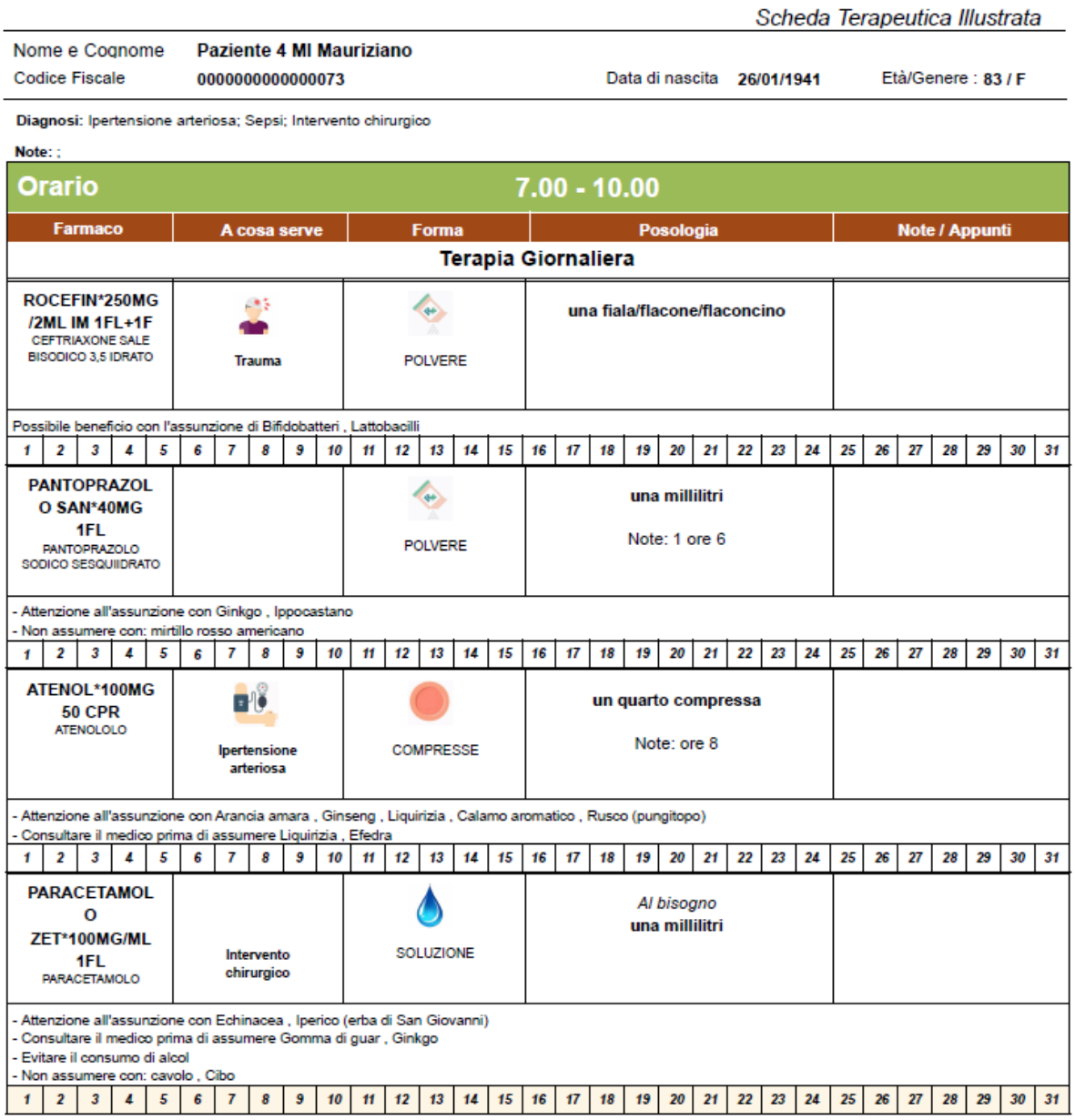
SCHEDA TERAPEUTICA	Pictograms associated with simple disease names for the ITS	2019 (manual update)	291 (NA)	**Yes** (design of a new template with specific information for the ITS)
SCHEDA TERAPEUTICA	Pictograms associated with pharmaceutical forms for the ITS	2020 (manual update)	130 (NA)	**Yes** (design of a new template with specific information for the ITS)
Alerts of prescriptive inappropriateness for healthcare professionals (prescribers and consultants for medication review)				
	Drug-drug interactions (contraindicated, major)	2024 (automatic periodic extraction from Micromedex® and Codifa®)	All drugs on the Italian market	**Yes** (periodic English-Italian translation of interactions)
	PIPs in elderly (Beers, STOPP, EU(7)-PIM, STOPPFrail)	2023 (manual update)	980 (461)	**Yes** (update to the 2023 version of the Beers and STOPP criteria; addition of information for the medication review report)
	ACB score (≥3, <3)	2019 (manual update)	183 (180)	No
	QT prolongation (high risk, moderate-low risk)	2023 (manual update)	397 (394)	**Yes** (created and revised during the Ph.D.)
	Nephrotoxicity (high risk, moderate-low risk)	2024 (manual update)	305 (301)	**Yes** (created and revised during the Ph.D.)
	High risk drugs (Recommendation no. 7 by the Italian Ministry of Health)	2020 (manual update)	105 (105)	No
General drug information and prescriptive information				
	Link to the medication leaflet on the AIFA website	2024 (automatic periodic extraction from the AIFA)	All drugs on the Italian market	No
	Public price (not reimbursed by the Italian NHS, reimbursement price, extra expense for the citizen)	2024 (automatic periodic extraction from Codifa®)	All drugs on the Italian market	No
	Guideline recommendations	2023 (manual update)	491 (415)	**Yes** (update of existing guidelines)
	Deprescription recommendations (high priority, medium-low priority)	2024 (manual update)	110 (110)	**Yes** (created and revised during the Ph.D.)
	Notes by the AIFA	2024 (automatic periodic extraction from Codifa®)	All drugs on the Italian market	No
	Law 648/1996	2023 (manual update)	283 (194)	**Yes** (update to the latest version of September 2023)
Alerts for healthcare professionals and patients and recommendations for use				
	Drug-alcohol interactions	2024 (automatic periodic extraction from Micromedex®)	All drugs on the Italian market	No
	Drug-food interactions	2024 (automatic periodic extraction from Micromedex®)	All drugs on the Italian market	No

	Drug-tobacco interactions	2024 (automatic periodic extraction from Micromedex®)	All drugs on the Italian market	No
	Drug-pregnancy interactions	2024 (automatic periodic extraction from Micromedex®)	All drugs on the Italian market	No
	Drug-lactation interactions	2024 (automatic periodic extraction from Micromedex®)	All drugs on the Italian market	No
	Drug-lab exams interactions	2024 (automatic periodic extraction from Micromedex®)	All drugs on the Italian market	No
	Crushable/not crushable, divisible/not divisible	2020 (manual update)	921 (921)	No
	Doping drugs	2024 (automatic periodic extraction from Codifa®)	All drugs on the Italian market	No
	Environmental impact (moderate-high risk, very low-low risk)	2024 (manual update)	281 (281)	**Yes** (created and revised during the Ph.D.)
	Drug-herb interactions (negative interaction, positive interaction)	2024 (manual update)	597 (281)	**Yes** (new literature review and update)
	Intolerances (lactose, gluten, glucose, phenylalanine)	2024 (automatic periodic extraction from Codifa®)	All drugs on the Italian market	No
	Storage temperature	2024 (automatic periodic extraction from Codifa®)	All drugs on the Italian market	No
	Videos for patients/caregivers on how to use specific medical devices	2020 (manual update)	24 (24)	No

[a] Number of different ATC codes or Minsan codes.
Abbreviations: NA, not available; ICD-9, International Classification of Diseases, 9th revision; ITS, Illustrated Therapeutic Sheet; PIP, Potentially Inappropriate Prescription; PIM, Potentially Inappropriate Medication; STOPP, Screening Tool of Older Persons' Prescriptions; ACB, Anticholinergic Cognitive Burden; AIFA, *Agenzia Italiana del Farmaco* (Italian Medicines Agency); NHS, National Health Service

Pictograms labelled as "**Information for system functions**" are associated with specific functions of the software allowing to visualize and edit the patient's clinical and pharmacological information. Particularly, the ITS is a paper document to be given to the patient that includes all the information necessary for the patient to take the therapy correctly: name and dosage of the medication, what the medication is for, pharmaceutical form, daily/weekly/monthly/cyclic/as needed dosage, time of intake and amount to be taken for each time slot, special recommendations for proper use. Texts in the ITS are schematic and written in simple language; ITS also included pictograms for easy reference. The ITS template was extensively modified during the last year of the Ph.D. programme after

becoming aware of the needs of clinicians. Figures 17 and 18 show the previous version of the ITS *vs* the new one, respectively.



Scheda Terapeutica Illustrata

Nome e Cognome **Paziente 4 MI Mauriziano**
Codice Fiscale **0000000000000073** Data di nascita **26/01/1941** Età/Genere : **83 / F**

Diagnosi: Ipertensione arteriosa; Sepsi; Intervento chirurgico

Note: ;

Orario			**7.00 - 10.00**	
Farmaco	**A cosa serve**	**Forma**	**Posologia**	**Note / Appunti**
		Terapia Giornaliera		
ROCEFIN*250MG /2ML IM 1FL+1F CEFTRIAXONE SALE BISODICO 3,5 IDRATO	**Trauma**	POLVERE	**una fiala/flacone/flaconcino**	
Possibile beneficio con l'assunzione di Bifidobatteri , Lattobacilli				
PANTOPRAZOLO SAN*40MG 1FL PANTOPRAZOLO SODICO SESQUIIDRATO		POLVERE	**una millilitri** Note: 1 ore 6	
- Attenzione all'assunzione con Ginkgo , Ippocastano - Non assumere con: mirtillo rosso americano				
ATENOL*100MG 50 CPR ATENOLOLO	**Ipertensione arteriosa**	COMPRESSE	**un quarto compressa** Note: ore 8	
- Attenzione all'assunzione con Arancia amara , Ginseng , Liquirizia , Calamo aromatico , Rusco (pungitopo) - Consultare il medico prima di assumere Liquirizia , Efedra				
PARACETAMOLO ZET*100MG/ML 1FL PARACETAMOLO	**Intervento chirurgico**	SOLUZIONE	*Al bisogno* **una millilitri**	
- Attenzione all'assunzione con Echinacea , Iperico (erba di San Giovanni) - Consultare il medico prima di assumere Gomma di guar , Ginkgo - Evitare il consumo di alcol - Non assumere con: cavolo , Cibo				

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Figure 17. Excerpt of the previous version of the ITS

a) Scheda Terapeutica Assunzione

Cognome e Nome: Paziente 4 MI Mauriziano (F, 83 anni)

Medicinale / PA	Mattina (07:00 – 10:00)	Pranzo (11:00 – 14:00)	Sera (15:00 – 18:00)	Notte (19:00 – 22:00)	Indicazioni
Terapia per Ipertensione arteriosa					
Ogni giorno ATENOL*100MG 50 CPR *(compresse di* ATENOLOLO)	0.25 compresse ore 8				
Terapia per Sepsi					
Ogni giorno ROCEFIN*250MG/2ML IM 1FL+1F *(polvere di* CEFTRIAXONE SALE BISODICO 3,5 IDRATO)	1 polvere				
Altre terapie					
Ogni giorno POTAS CL FKI*2MEQ/ML 20F10ML *(soluzione (uso interno) di* POTASSIO CLORURO)	1 soluzione (uso interno)				
Altre terapie					
Ogni giorno TACHIPIRINA*10MG/ML IV12SAC *(soluzione (uso interno) di* PARACETAMOLO)	1 soluzione (uso interno)				
Altre terapie					
Ogni giorno PANTOPRAZOLO SAN*40MG 1FL *(polvere di* PANTOPRAZOLO SODICO SESQUIIDRATO)	1 polvere 1 ore 6				

Medicinale / PA	Indicazioni
Terapia per Intervento chirurgico	
Al bisogno PARACETAMOLO ZET*100MG/ML 1FL *(soluzione di* PARACETAMOLO)	Chiedere al medico quanto farmaco assumere e quando

Studio, Data: 02/12/2024

MEDICO: _____

FIRMA MEDICO: _____

b) Scheda Terapeutica Avvisi

Cognome e Nome: Paziente 4 MI Mauriziano (F, 83 anni)

Diagnosi: Ipertensione arteriosa; Sepsi; Intervento chirurgico;
Allergie:
Altre allergie:

Medicinale / PA	Forma farmaceutica	Indicazioni
POTAS CL FKI*2MEQ/ML 20F10ML (POTASSIO CLORURO)	SOLUZIONE (USO INTERNO)	*Ogni giorno*
Rischio ambientale: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata		
TACHIPIRINA*10MG/ML IV12SAC (PARACETAMOLO)	SOLUZIONE (USO INTERNO)	*Ogni giorno*
Rischio ambientale: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata **Possibili effetti con erbe:** Attenzione all'assunzione con Echinacea , Iperico (erba di San Giovanni) **Possibili effetti con erbe:** Possibile beneficio con l'assunzione di Luppolo		
ROCEFIN*250MG/2ML IM 1FL+1F (CEFTRIAXONE SALE BISODICO 3,5 IDRATO)	POLVERE	*Ogni giorno* **Terapia per Sepsi**
Rischio ambientale: Farmaco pericoloso per l'ambiente: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata. Non rilasciare il farmaco nell'ambiente o negli scarichi		
PANTOPRAZOLO SAN*40MG 1FL (PANTOPRAZOLO SODICO SESQUIIDRATO)	POLVERE	*Ogni giorno*
Rischio ambientale: Farmaco pericoloso per l'ambiente: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata. Non rilasciare il farmaco nell'ambiente o negli scarichi **Possibili effetti con erbe:** Attenzione all'assunzione con Ginkgo , Ippocastano		
ATENOL*100MG 50 CPR (ATENOLOLO)	COMPRESSE	*Ogni giorno* **Terapia per Ipertensione arteriosa**
Rischio ambientale: Farmaco pericoloso per l'ambiente: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata. Non rilasciare il farmaco nell'ambiente o negli scarichi **Possibili effetti con erbe:** Attenzione all'assunzione con Arancia amara , Calamo aromatico , Ginseng , Rusco (pungitopo) , Liquirizia **Possibili effetti con erbe:** Possibile beneficio con l'assunzione di Biancospino		
PARACETAMOLO ZET*100MG/ML 1FL (PARACETAMOLO)	SOLUZIONE	*Al bisogno* **Terapia per Intervento chirurgico**
Rischio ambientale: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata **Possibili effetti con erbe:** Attenzione all'assunzione con Echinacea , Iperico (erba di San Giovanni) **Possibili effetti con erbe:** Possibile beneficio con l'assunzione di Luppolo		

Figure 18. Excerpt of the new version of the ITS. The new ITS has been divided into two different reports for the patients: panel **a**) includes the medications to be taken and the dosage regimen; panel **b**) includes recommendations for a proper use of medications, including the drug environmental impact

The new version of the ITS is more compact, as information on when to take the drug and recommendations have been split up, as well as pictograms that have been removed. This simplified version of the ITS arose from the need of clinicians to have a useful tool for the patient that was on one page and would inform the patient when to take their medications. The previous version of the ITS is still available on NavFarma® at the time of writing this thesis with some minor modifications. All three ITS are periodically updated by the Infologic's informatics based on feedback received from NavFarma® users, so these models are not to be considered definitive.

The **other pictograms** represent information associated with specific medications, drugs or drug classes and they constitute the core of the software, i.e., what enables clinical decision support and optimization of drug therapies.

Tables created during the Ph.D. will be described in detail in the following chapters: environmental impact of drugs; potentially nephrotoxic drugs; drugs with a known risk of long QT; guidelines for deprescription or tapering dose.

The other tables revised during the Ph.D. will not be discussed in this dissertation. However, it is worth commenting on the table on guideline recommendations for the treatment of specific chronic conditions. This table, in addition to the tooltip text, includes a treatment algorithm for learning about first-line therapies. Algorithms are figures prepared using Microsoft Power Point; they were updated in 2023 to correspond with the release of new guidelines for the treatment of asthma [222], COPD [223] and type 2 diabetes mellitus. [224] Moreover, treatment algorithms were added for two new conditions, major depressive disorder and bipolar disorder, respectively. Thanks to the relevance of these conditions in the elderly population and to the collaboration of hospital pharmacists and psychiatrists from the *ASL Città di Torino*, treatment algorithms have been the subject of a scientific publication in the *Giornale Italiano di Farmacia Clinica* (GIFAC). [225]

The treatment algorithms are shown below (Figures 19-23).

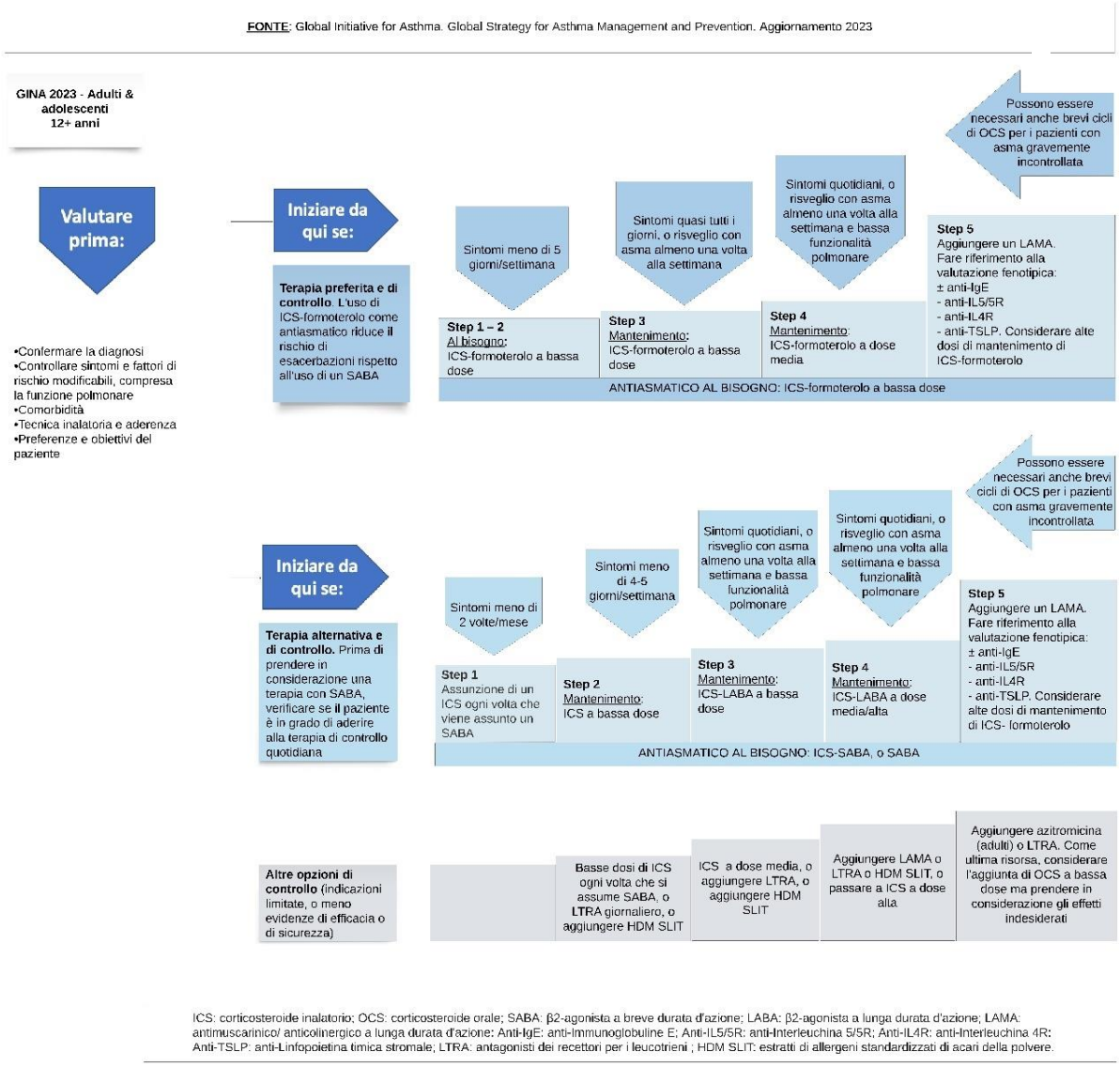
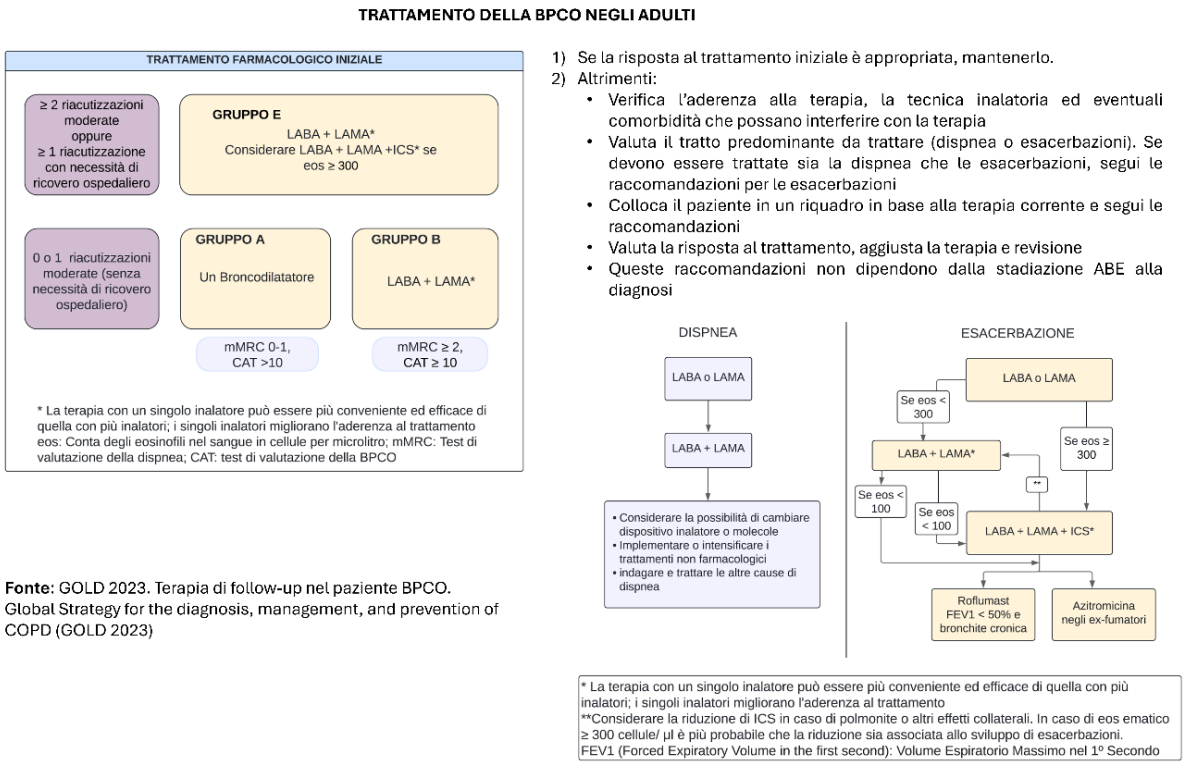


Figure 19. Treatment algorithm for asthma. Translated from the 2023 Global Strategy for Asthma Management and Prevention [222]



Fonte: GOLD 2023. Terapia di follow-up nel paziente BPCO. Global Strategy for the diagnosis, management, and prevention of COPD (GOLD 2023)

Figure 20. Treatment algorithm for COPD. Translated from the 2023 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [223]

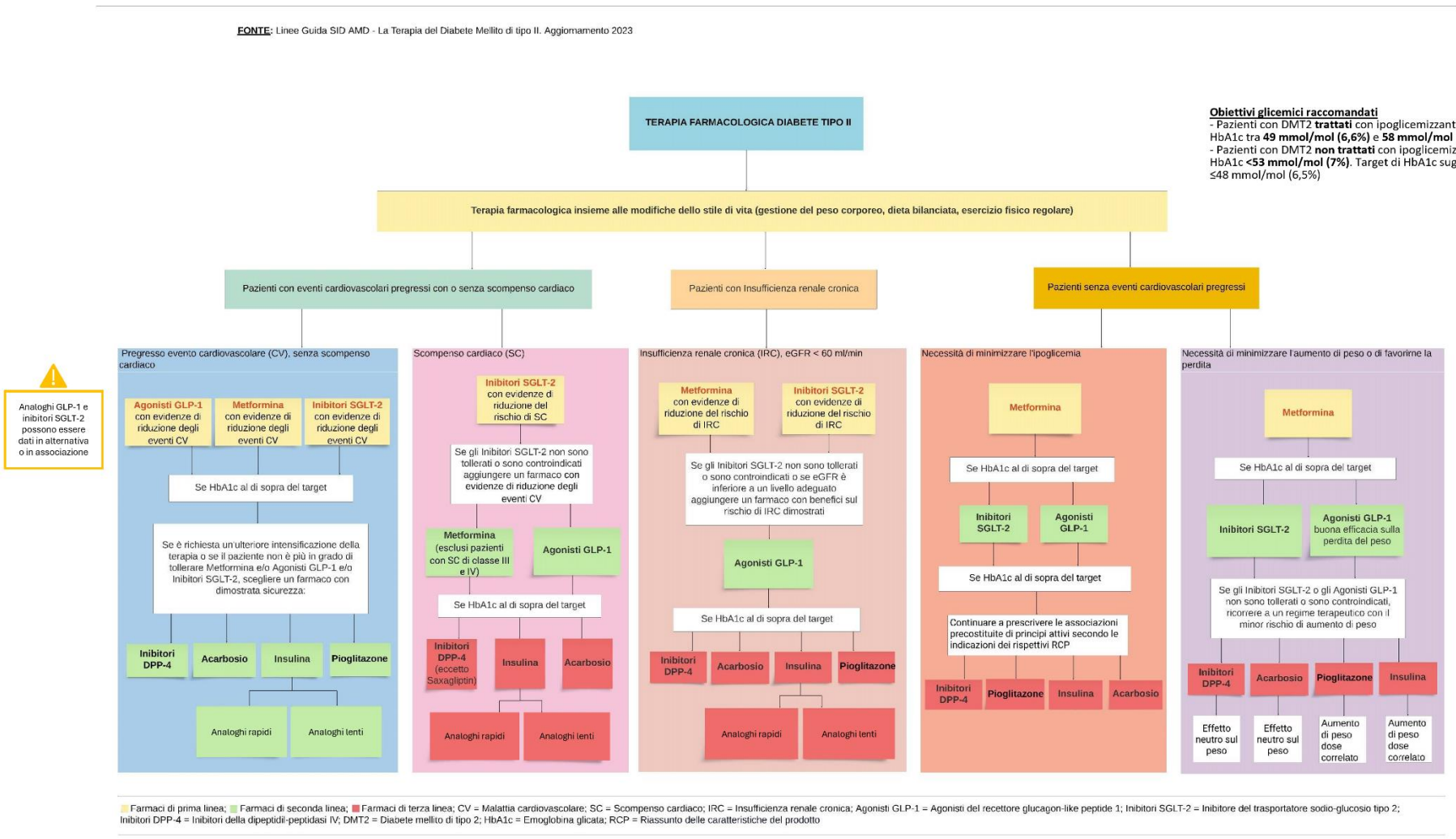


Figure 21. Treatment algorithm for type 2 diabetes mellitus. Created from the 2023 SID/AMD guidelines [224]

Riferimenti
1. APA. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. Third Edition (2010); 2. NICE. Depression in adults: treatment and management. NICE guideline: short version (2018); 3. CANMAT. Clinical guidelines for the Management of Adults with Major Depressive Disorder (2016); 4. 2019 American Geriatrics Society Beers Criteria Update Expert Panel. *J Am Geriatr Soc* 2019;67(4):674-694; 5. Icons from www.flaticon.com

Figure 22. Treatment algorithm for major depressive disorder. Created from the consultation of several guidelines for the treatment of depression [225]

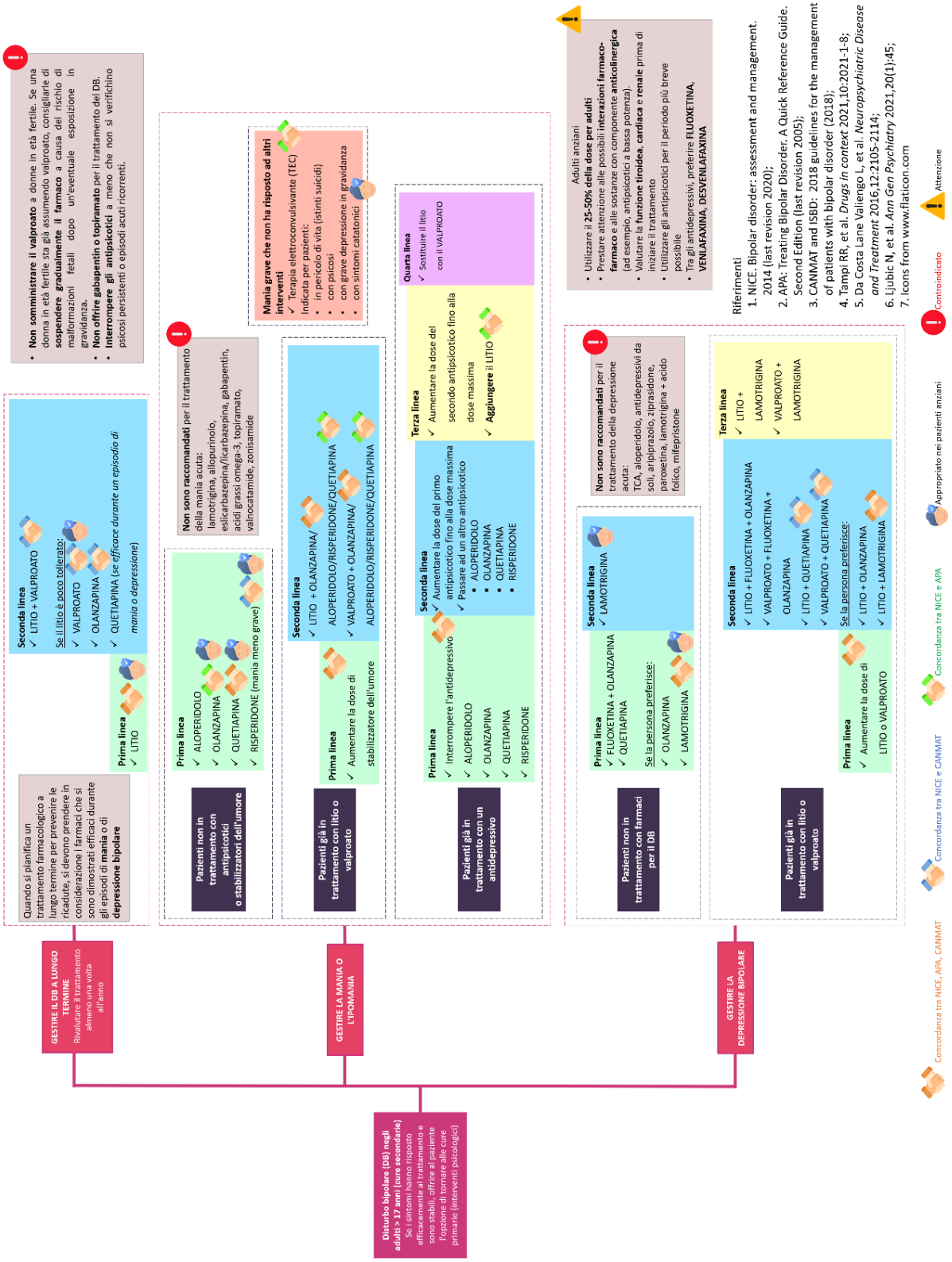


Figure 23. Treatment algorithm for bipolar disorder. Created from the consultation of several guidelines for the treatment of bipolar disorder [225]

4.1.1. Environmental impact of drugs

The initial green table contained 27 columns (as described below) that were combined to comply with the requirements of the NavFarma® developer. In fact, all tables populating the NavFarma® knowledge-base should include the same columns containing the same type of information. For this reason, information initially included in distinct columns (such as bibliographic sources, separate scores and texts for persistence, bioaccumulation and toxicity and description) were merged in a single column ("testo_medico") to create the final table.

The final green table includes 11 columns and 281 records for a total of 281 different ATC and 174 unique drugs. The information (or columns) of the first version of the green table is described below, with the information in the final green table highlighted in blue:

1. **ID**: record identification number;
2. Drug: drug name;
3. **ATC**: ATC code associated to the drug. It should be noted that drugs could have multiple ATC codes according to their main action, e.g., acetylsalicylic acid has 3 ATC codes: A01AD05 when used for local oral treatment; B01AC06 when used as an antiplatelet agent; N02BA01 when used as analgesic. The database contains all the ATC codes associated to the included drugs. This information is required by the CDSS developer as all CDSS knowledge-base is linked to ATC codes;
4. **Tipo**: type of knowledge-base, in this case "green". This information is required by the CDSS developer to implement the new knowledge with the existing one;
5. Pers: short text associated with persistence information extracted from the Swedish database;
6. Score_P: new score associated with persistence;
7. Bioac: short text associated with bioaccumulation information extracted from the Swedish database;
8. Score_B: new score associated with bioaccumulation;
9. Tox: short text associated with toxicity information extracted from the Swedish database;
10. Score_T: new score associated with toxicity;
11. Risk: short text associated with environmental risk information extracted from the Swedish database;
12. Score_R: new score associated with environmental risk;

13. Score_sum: sum of “score_P”, “score_B”, “score_T” and “score_R”;
14. Other_doc: additional sources consulted (see the methods section for clarification);
15. **Tot_score**: “score_sum” with the addition of the scores given to additional sources (see the methods section for clarification);
16. Zuccato: text extracted from the study by Zuccato *et al*.; [112]
17. Lists: texts associated with other sources: FDA Flush List, groundwater Watch List and surface water Watch List; [113-115]
18. Drug_disposal: recommendations on how to dispose of unused drugs. This information is currently not included in the final description, but it was used to write a short text for patients (“testo_paziente” column);
19. Ref: list of sources used to assess the environmental impact;
20. **Testo_tooltip**: short text with information on the final environmental impact assessment associated with the total score (“tot_score” column):
    - **No environmental impact (tot_score = 0)**

      “*Dai dati disponibili su persistenza, bioaccumulo, tossicità e rischio ambientale: il farmaco non rappresenta un pericolo per l'ambiente acquatico*”
    - **Low environmental impact (tot_score = 1 – 4.5)**

      “*Dai dati disponibili su persistenza, bioaccumulo, tossicità e rischio ambientale: il farmaco ha un impatto sull'ambiente acquatico basso*”
    - **Medium environmental impact (tot_score = 5 – 8.5)**

      “*Dai dati disponibili su persistenza, bioaccumulo, tossicità e rischio ambientale: il farmaco ha un impatto sull'ambiente acquatico moderato*”
    - **High environmental impact (tot_score > 8.5)**

      “*Dai dati disponibili su persistenza, bioaccumulo, tossicità e rischio ambientale: il farmaco è un inquinante ad alto impatto per l'ambiente acquatico*”

    In the CDSS, tooltips are graphical elements that display text boxes when hovering over a specific screen component. This information is required by the CDSS developer;
21. Testo_medico_first: extended text with information on drug persistence in the aquatic environment, bioaccumulation and toxicity of the drug to aquatic organisms and drug environmental risk;

22. **Testo_medico**: final extended description of the environmental impact of the drug shown in the CDSS, which include all the information in the other columns: persistence, bioaccumulation, toxicity, risk ("testo_medico_first" column), information extracted from the study by Zuccato *et al*. [112] ("Zuccato" column), information extracted from other sources ("lists" column) and list of sources ("ref" column). This information is required by the CDSS developer;
23. **Testo_paziente**: short recommendation on the correct disposal of the drug that can be printed in a report for patients. This information is required by the CDSS developer;
24. **Eta_min**: the recommendation is valid for patients above the age indicated in this column (information required by the CDSS developer). All column fields are filled with "NULL", as there is no age limit for recommendations on the environmental impact of drugs;
25. **Eta_max**: the recommendation is valid for patients under the age indicated in this column (information required by the CDSS developer). All column fields are filled with "NULL", as there is no age limit for recommendations on the environmental impact of drugs;
26. **Sesso**: the recommendation is valid for patients of the gender indicated in this column (information required by the CDSS developer). All column fields are filled with "NULL";
27. **Last_update**: date of the last update of the information included in the other columns.

Figure 24, panels a, b, c, shows the record for acetylsalicylic acid (ATC B01AC06) including all the columns described above.

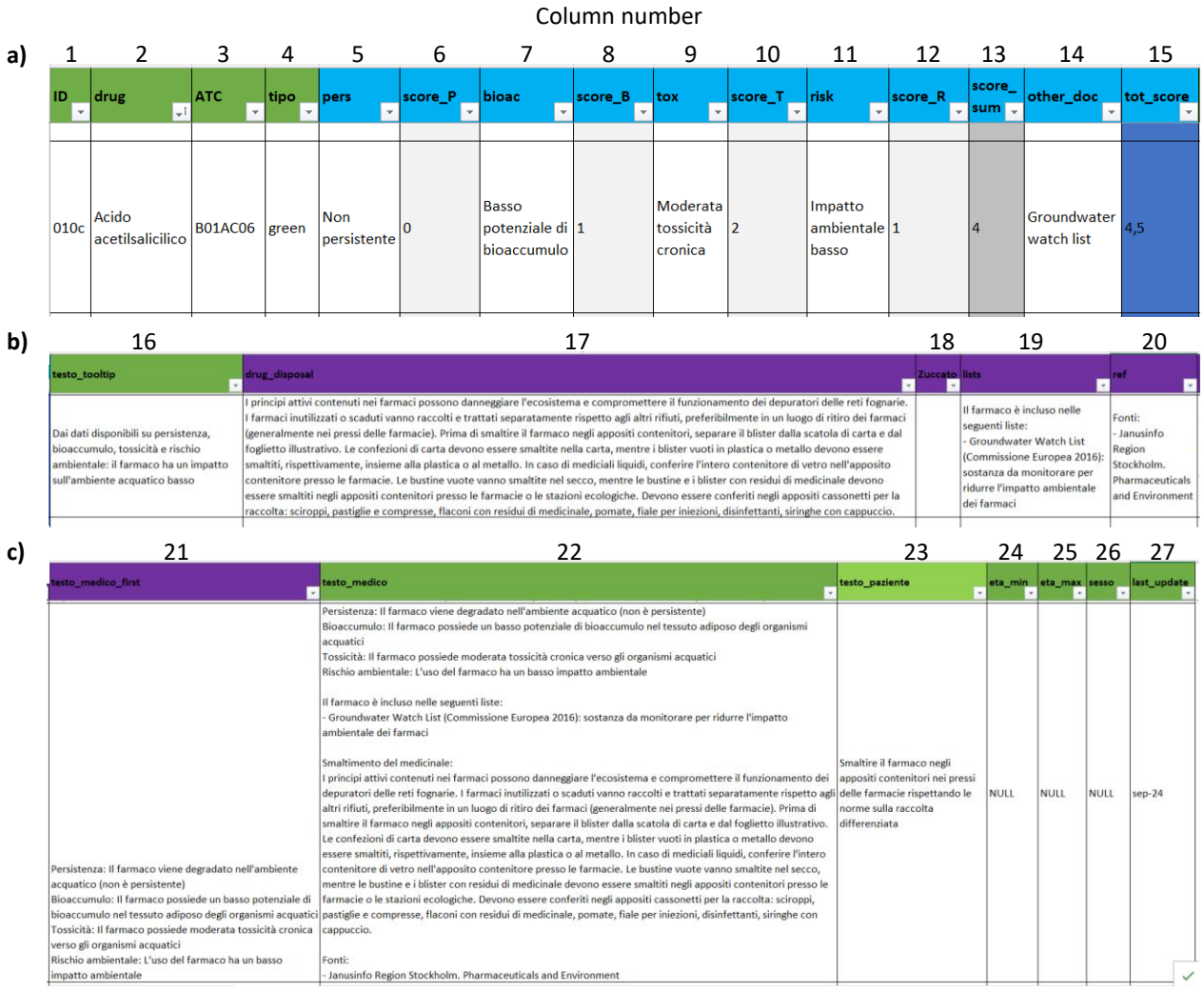


Figure 24. Excerpt of the first version of the green table (record of acetylsalicylic acid, ATC B01AC06). Panel a) columns 1-15; panel b) columns 16-20; panel c) columns 21-27

Acetylsalicylic acid is non persistent as it is degraded in the environment (0 points), it has low potential for bioaccumulation (1 point), has moderate chronic toxicity (2 points) and its use has been considered to result in low environmental risk (1 point). Moreover, it is included in the Groundwater Watch list of the European Commission [115] (+ 0.5 points) and has not been detected in Italian rivers in the study by Zuccato *et al*. [112] (+ 0 point). Therefore, its total score is 4.5 and its tooltip, or short text, is as follows:

"*Dai dati disponibili su persistenza, bioaccumulo, tossicità e rischio ambientale: il farmaco ha un impatto sull'ambiente acquatico basso*".

The complete description for the physician ("*testo_medico*") is derived by combining the texts in the previous columns, including information on the proper disposal of the drug. Figure 25 shows an excerpt of the final version of the green table implemented into the

NavFarma® knowledge-base containing only the useful information for the software. The new column "*icona*" indicates the colour of the tooltip icon: yellow for very low and low environmental risks, red for moderate-high risks.

a)

*ID	*drug	ATC	tipo	icona	*tot_score	testo_tooltip
010c	Acido acetilsalicilico	B01AC06	green	green_yellow.png	4,5	Dai dati disponibili su persistenza, bioaccumulo, tossicità e rischio ambientale: il farmaco ha un impatto sull'ambiente acquatico basso

b)

testo_medico	testo_paziente	eta_min	eta_max	sesso	last_update
Persistenza: Il farmaco viene degradato nell'ambiente acquatico (non è persistente) Bioaccumulo: Il farmaco possiede un basso potenziale di bioaccumulo nel tessuto adiposo degli organismi acquatici Tossicità: Il farmaco possiede moderata tossicità cronica verso gli organismi acquatici Rischio ambientale: L'uso del farmaco ha un basso impatto ambientale Il farmaco è incluso nelle seguenti liste: - Groundwater Watch List (Commissione Europea 2016): sostanza da monitorare per ridurre l'impatto ambientale dei farmaci Smaltimento del medicinale: I principi attivi contenuti nei farmaci possono danneggiare l'ecosistema e compromettere il funzionamento dei depuratori delle reti fognarie. I farmaci inutilizzati o scaduti vanno raccolti e trattati separatamente rispetto agli altri rifiuti, preferibilmente in un luogo di ritiro dei farmaci (generalmente nei pressi delle farmacie). Prima di smaltire il farmaco negli appositi contenitori, separare il blister dalla scatola di carta e dal foglietto illustrativo. Le confezioni di carta devono essere smaltite nella carta, mentre i blister vuoti in plastica o metallo devono essere smaltiti, rispettivamente, insieme alla plastica o al metallo. In caso di mediciali liquidi, conferire l'intero contenitore di vetro nell'apposito contenitore presso le farmacie. Le bustine vuote vanno smaltite nel secco, mentre le bustine e i blister con residui di medicinale devono essere smaltiti negli appositi contenitori presso le farmacie o le stazioni ecologiche. Devono essere conferiti negli appositi cassonetti per la raccolta: sciroppi, pastiglie e compresse, flaconi con residui di medicinale, pomate, fiale per iniezioni, disinfettanti, siringhe con cappuccio. Fonti: - Janusinfo Region Stockholm. Pharmaceuticals and Environment	Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata	NULL	NULL	NULL	sep-24

Figure 25. Excerpt of the final version of the green table implemented in the NavFarma® knowledge-base (record of acetylsalicylic acid, ATC B01AC06). Panel **a**) columns 1-7; panel **b**) columns 8-13

Drugs included in the green table are among the 200 most dispensed drugs in the ASL TO4 between 2020 and 2021. They belong mostly to the drug classes of anti-infectives (26 drugs, 14.9%), antihypertensives (23 drugs, 13.2%), analgesics (11 drugs, 6.3%) and NSAID (10 drugs, 5.7%). Figure 26 shows drugs included in the green table classified according to their risk of environmental damage. The majority of drugs (120 out of 174, 69.0%) were classified as moderately polluting the aquatic environment, while only 6 drugs (3.4%) were recognized as pollutants with high environmental impact to the aquatic environment: amiodarone, betamethasone, bezafibrate, ciprofloxacin, ethinylestradiol, miconazole.

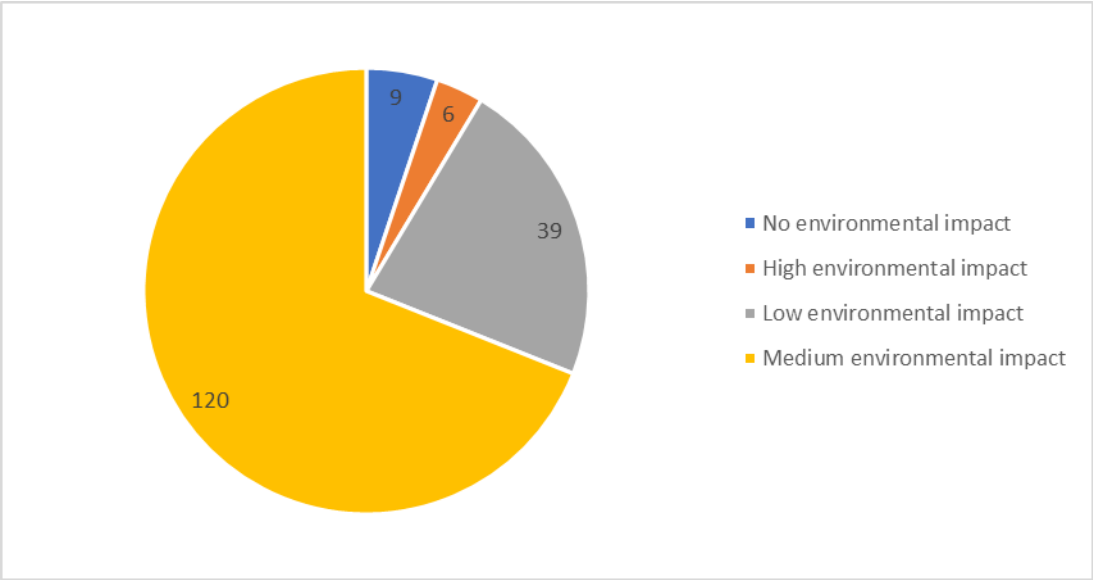


Figure 26. Classification of drugs included in the green table according to their environmental risk

The green table has been implemented in the NavFarma® knowledge-base and information on the environmental impact of drugs is available on the platform for healthcare professionals with a valid account. Figure 27 shows what this information looks like on the NavFarma® platform.

a)

b)

c)

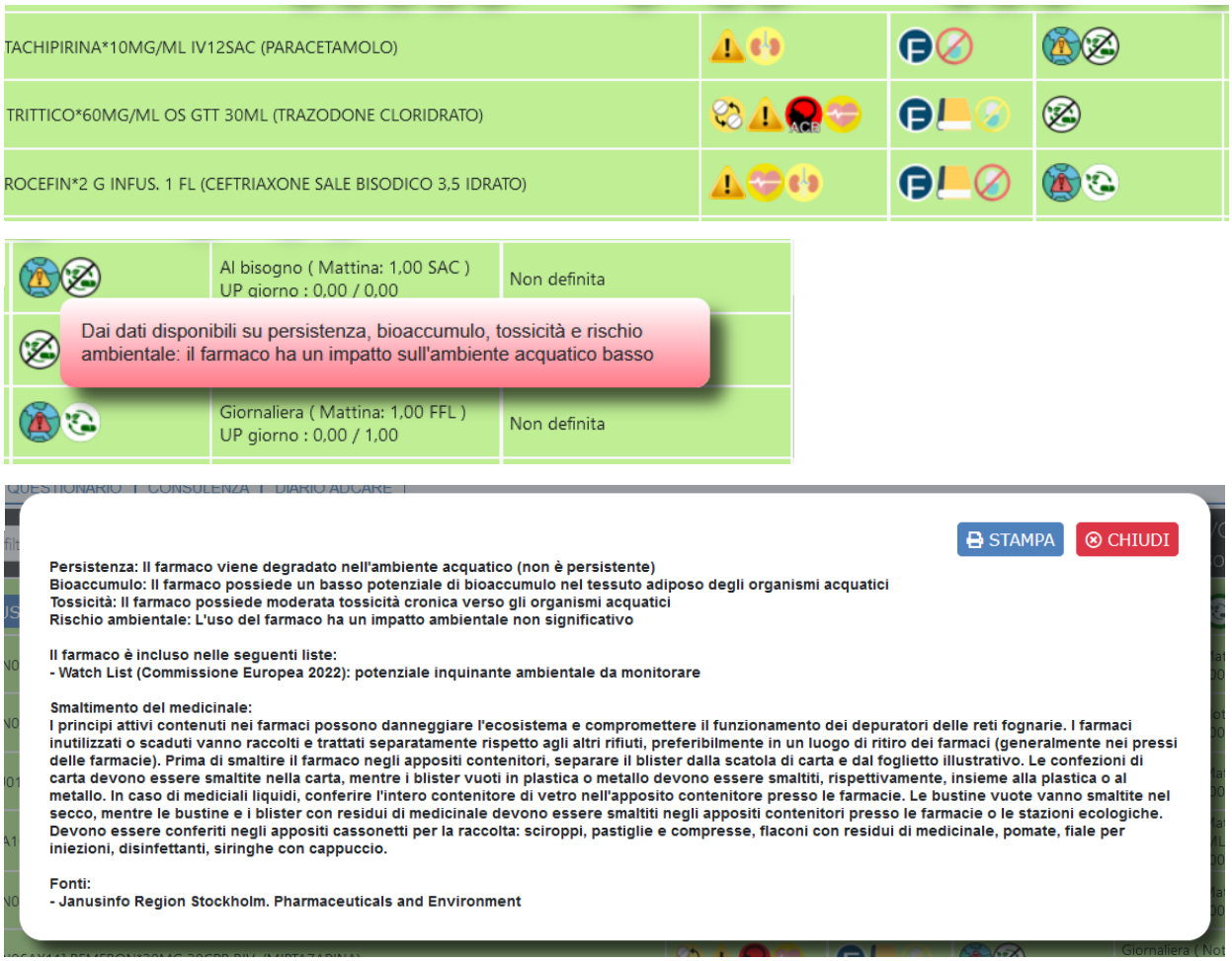


Figure 27. Environmental impact of drugs on the NavFarma® platform. Panel a) alerts associated with prescribed medications, including low environmental impact (yellow icon) for paracetamol and moderate environmental impact (red icon) for ceftriaxone; panel b) tooltip with short text for paracetamol, it appears when you hover the cursor over the yellow icon; panel c) full description on the environmental impact of paracetamol, it appears when you click on the yellow icon

Finally, information on the environmental impact of drugs can be printed in the documentation to be delivered to the patient to help him or her properly manage the prescribed therapy (Figure 28).

Scheda Terapeutica Avvisi

Cognome e Nome: Paziente 1 MI Mauriziano (F, 76 anni)

Medicinale / PA	Forma farmaceutica	Indicazioni
LEVOTIROXINA TEV*100MCG 50CPR (LEVOTIROXINA SODICA)	COMPRESSE	Ogni giorno
Rischio ambientale: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata; **Possibili effetti con erbe:** Attenzione all'assunzione con Cromo , Psillio;		
FOSTER*100/6MCG SOL/INAL120D (BECLOMETASONE DIPROPRIONATO/FORMOTEROLO FUMARATO DIIDRATO)	SPRAY	Ogni giorno
CLAVULIN*OS 12 BUST. 1 G (AMOXICILLINA/ACIDO CLAVULANICO)	POLVERI ORALI	Ogni giorno
Rischio ambientale: Farmaco pericoloso per l'ambiente: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata. Non rilasciare il farmaco nell'ambiente o negli scarichi;		
TACHIPIRINA*120 MG/5ML1FL120ML (PARACETAMOLO)	SCIROPPO	Ogni giorno
Rischio ambientale: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata; **Possibili effetti con erbe:** Attenzione all'assunzione con Echinacea , Iperico (erba di San Giovanni);		
TACHIPIRINA*1000MG 16CPR DIV (PARACETAMOLO)	COMPRESSE DIVISIBILI	Al bisogno
Rischio ambientale: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata; **Possibili effetti con erbe:** Attenzione all'assunzione con Echinacea , Iperico (erba di San Giovanni);		
METOCLOPR SAL*10MG/2ML 5F2ML (METOCLOPRAMIDE CLORIDRATO)	SOLUZIONE (USO INTERNO)	Al bisogno
Possibili effetti con erbe: Attenzione all'assunzione con Cola;		
CONTRAMAL*100MG 20CPR RP (TRAMADOLO CLORIDRATO)	COMPRESSE RILASCIO MODIFICATO	Al bisogno
Rischio ambientale: Farmaco pericoloso per l'ambiente: Smaltire il farmaco negli appositi contenitori nei pressi delle farmacie rispettando le norme sulla raccolta differenziata. Non rilasciare il farmaco nell'ambiente o negli scarichi; **Possibili effetti con erbe:** Consultare il medico prima di assumere Valeriana;		

Figure 28. Environmental impact of drugs in the patient's documentation ("*Rischio ambientale*"). In this example, the information is available for levothyroxine, amoxicillin/clavulanic acid, acetaminophen and tramadol

4.1.2. Potentially nephrotoxic drugs

Exposure to nephrotoxic drugs is associated with the occurrence of acute kidney injury (AKI), which could progress in CKD and increase the risk of mortality, especially in critically ill patients. Approximately 30% of AKIs can be attribute directly or indirectly to drug use through one or more mechanisms of nephrotoxicity. From the review of scientific literature, the following mechanisms of renal toxicity associated with potentially nephrotoxic drugs have been identified:

- Altered intraglomerular hemodynamic: some drugs can cause vasoconstriction leading to renal impairment or interfere with the ability of the kidneys to regulate glomerular pressure and the glomerular filtration rate (GFR). Examples of drugs that can cause AKI through this mechanism of action are angiotensin-converting enzyme (ACE) inhibitors, diclofenac and cyclosporine.
- Tubular cell toxicity: some drugs such as aminoglycosides and antiretrovirals can interfere with tubular transport and mitochondrial function and increase the formation of free radicals and oxidative stress causing tubular cell toxicity.
- Inflammation at the level of glomerulus (glomerulonephritis), tubular cells and surrounding interstitium (acute or chronic interstitial nephritis): inflammatory changes are generally caused by immune mechanisms or allergic responses. Signs of nephritis include fibrosis, renal scarring, proteinuria and symptoms of hypersensitivity reaction. Drugs associated with renal inflammation are, for example, lithium, sulphonamides and tacrolimus.
- Crystal nephropathy and other forms of tubular obstruction: drugs such as antibiotics, antivirals and methotrexate can cause renal impairment due to the production of crystal that are insoluble in human urine. These crystals can precipitate in the distal tubular lumen causing obstruction of the urine flow and renal damage.
- Rhabdomyolysis: the release of myoglobin and creatine kinase into the plasma as a result of myocyte lysis can lead to direct renal toxicity, tubular obstruction and alterations in GFR. Examples of drugs associated with secondary renal injury caused by rhabdomyolysis are statins and methadone.
- Thrombotic microangiopathy: is characterized by the presence of platelet thrombi in the microcirculation caused by immune-mediate reactions or direct endothelial

toxicity. Drugs associated whit this mechanism of nephrotoxicity include cyclosporine, quinine and clopidogrel.

- Acute tubular necrosis: it involves damage to the tubular cells, which can lead to acute kidney failure. High doses of intravenous bisphosphonates have been associated with this mechanism of nephrotoxicity.
- Osmotic nephrosis: it is characterized by swelling of the renal proximal tubular cells due to the formation of vacuoles in the cytoplasm. It can be observed after parenteral infusion of high-osmolar solutions (i.e., mannitol, radiocontrast, intravenous immune-globulins).
- Renal syndrome associated with electrolyte alterations: hypomagnesemia or hypernatremia can cause proximal tubulopathy or Fanconi syndrome responsible for kidney damage. Vincristine, cyclophosphamide and cetuximab have been associated with renal syndrome.
- Pseudo AKI: caused by increased metabolic production of creatinine. It has been observed for drugs such as imatinib and clofibrate.

The final table implemented on NavFarma® consists of 305 records and 13 columns for a total of 301 different active ingredients or drug classes. Information initially reported in 18 columns was merged to comply with the parameters of the NavFarma® knowledge-base, which allows a limited number of columns to be read and some standard columns to be present:

1. Record identification number;
2. ATC code;
3. Active ingredient;
4. 5-level risk score;
5. Table type and pictogram (yellow pictogram for drugs with unknown, insignificant and low risk, red for drugs with moderate and high risk);
6. Tooltip text including a short sentence for both non-critical and critical patients. The definition of critical and non-critical patients and the nephrotoxic potential of drugs according to patient characteristics were defined in the studies of Stottlemyer *et al*. [116] and Gray *et al*. [117], the two main sources used for the creation of the table. The definition of critical patient is given in the descriptions

for healthcare professionals and is as follows: “The following are considered critical patients: patients referred to intensive care units or patients at high risk of drug-induced nephrotoxicity (e.g., >60 years of age, GFR<60 mL/min/1.73 m^2, hypovolemia, hypoalbuminemia, >1 nephrotoxic drug, high doses, diabetes, heart failure, obesity, hypotension, sepsis, genetic polymorphisms)”;

7. Description for healthcare professionals, including mechanism of nephrotoxicity, clinical recommendations and list of consulted sources;
8. Description for patients (blank field, patients are not expected to receive recommendations on this adverse event);
9. Minimum age (the information on potential nephrotoxicity appears for patients ≥18 years of age);
10. Maximum age (blank field, the information on potential nephrotoxicity appears for all adult patients);
11. Gender (blank field, the information on potential nephrotoxicity appears for patients of all genders);
12. Object (blank field, useful column for the NavFarma® developer);
13. Last update.

There are a total of 23 unique tooltip texts associated with the 5 categories of nephrotoxicity that change according to risk for critically ill patients, while the short text for non-critical patients remains fixed (Table 13). Description for healthcare professionals varies according to specific drugs.

Table 13. Unique tooltip text associated with the 5 nephrotoxicity categories

5-level risk score for non-critical patients	Tooltip texts in Italian language for both non-critical and critical patients
Unknown	- "**Pazienti critici e non**: rischio di nefrotossicità sconosciuto. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità sconosciuto. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità sconosciuto; **Pazienti critici**: rischio di nefrotossicità trascurabile. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale."
Insignificant	- "**Pazienti critici e non**: rischio di nefrotossicità trascurabile. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità trascurabile. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale."

Low	- "**Pazienti critici**: rischio di nefrotossicità trascurabile. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità trascurabile; **Pazienti critici**: rischio di nefrotossicità basso. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità trascurabile; **Pazienti critici**: rischio di nefrotossicità sconosciuto. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti critici e non**: rischio di nefrotossicità basso. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità basso. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti critici**: rischio di nefrotossicità basso. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità basso; **Pazienti critici**: rischio di nefrotossicità trascurabile. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità basso; **Pazienti critici**: rischio di nefrotossicità basso (casi rari). La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità basso; **Pazienti critici**: rischio di nefrotossicità moderato. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità basso; **Pazienti critici**: rischio di nefrotossicità sconosciuto. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale."
Moderate	- "**Pazienti critici e non**: rischio di nefrotossicità moderato. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità moderato. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità moderato; **Pazienti critici**: rischio di nefrotossicità basso (casi rari). La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità moderato; **Pazienti critici**: rischio di nefrotossicità basso. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità moderato; **Pazienti critici**: rischio di nefrotossicità elevato. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità moderato; **Pazienti critici**: rischio di nefrotossicità sconosciuto. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale."
High	- "**Pazienti critici e non**: rischio di nefrotossicità elevato. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale." - "**Pazienti non critici**: rischio di nefrotossicità elevato; **Pazienti critici**: rischio di nefrotossicità moderato. La presenza di >1 farmaco nefrotossico aumenta il rischio di danno renale."

Finally, active ingredients included in the table on potentially nephrotoxic drugs belong for the most part to the classes of antineoplastic agents – ATC L01 (48 out of 305 records), antibacterials for systemic use – J01 (42 records), antivirals for systemic use – J05 (23 records) and of agents acting on the renin-angiotensin system – C09 (18 records). The majority of drugs or drug classes have a moderate nephrotoxic potential (176 out of 305 records), followed by low potential (65 records), unknown potential (39), irrelevant potential (15) and high nephrotoxicity (10). Drugs at high risk of nephrotoxicity that should be given special attention when used by patients with risk factors (i.e., patients in intensive care units, >60 years of age, GFR <60 mL/min/1.73 m^2, taking >1 potentially nephrotoxic drug, high drug doses, diabetes, heart failure, obesity, hypotension, sepsis, specific genetic polymorphisms) are:

- **Amphotericin B** (ATC A07AA07 and J02AA01): toxicity of proximal tubular cells mediated by altered permeability causing acute tubular necrosis and malfunction. Possible manifestations are renal tubular acidosis, urine concentration defects and electrolyte disturbances. It can also cause AKI due to induced vasoconstriction. Acid formulations of amphotericin B are more toxic than lipid formulations.
- **Colistin** (A07AA10 and J01XB01): mechanism of renal toxicity not reported.
- **Tobramycin** (J01GB01): toxicity of proximal tubule cells mediated by impairment of mitochondrial function, interference with tubular transport, increased oxidative stress or free radical formation.
- **Gentamicin** (J01GB03): toxicity of proximal tubule cells mediated by impairment of mitochondrial function, interference with tubular transport, increased oxidative stress or free radical formation.
- **Amikacin** (J01GB06): toxicity of proximal tubule cells mediated by impairment of mitochondrial function, interference with tubular transport, increased oxidative stress or free radical formation.
- **Foscarnet** (J05AD01): possible crystal nephropathy (urinary flow obstruction and interstitial nephritis), tubular toxicity (impaired mitochondrial function, interference with tubular transport, increased oxidative stress) and acute tubular necrosis. It can also cause electrolyte abnormalities.

- **Cisplatin** (L01XA01): AKI due to chronic interstitial nephritis, tubular toxicity (accumulation in proximal tubular cells), acute tubular necrosis, renal syndrome associated with electrolyte disorders and distal renal tubular acidosis.
- **Lithium** (N05AN01): several mechanisms of nephrotoxicity, including chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis and nephrogenic diabetes insipidus.

4.1.3. Drugs with a known risk of long QT

The QT interval is the segment of the electrocardiogram (ECG) from the start of the Q wave to the end of the T wave (Figure 29) and it represents the electrical activity of the ventricles, that is the time in which ventricular depolarization and repolarization occur. [160]

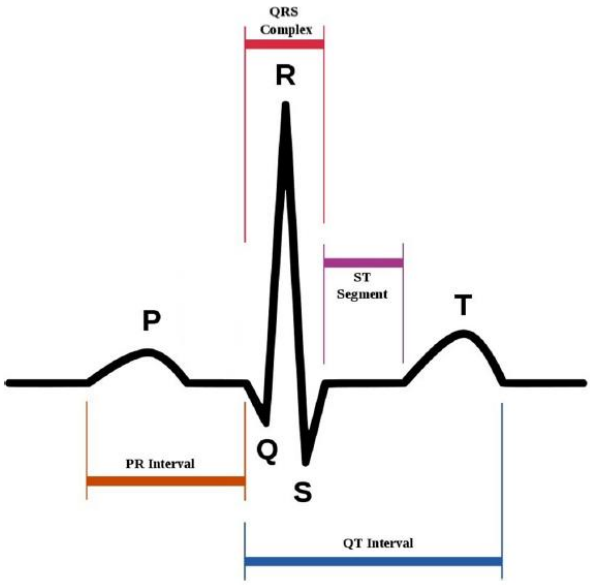


Figure 29. ECG. Source: De Vecchis R, *et al*. Eur J Clin Pharmacol 2018 [160]

The duration of the QT interval changes as the heart rate changes: it is shorter when the heart rate is high and it is longer when the heart rate is lower.

Prolongation of the QT interval, or long QT syndrome (LQTS), can increase the risk of dangerous ventricular arrhythmias, which can lead to syncope or sudden cardiac death.

Several drugs have been identified capable of prolonging the QT interval by affecting cardiac cell activity. The risk of arrhythmias caused by these drugs is generally dose-dependent and reversible when the drug is discontinued. Some patients are at increased risk of experiencing this adverse event, particularly in the presence of specific genetic predispositions, diseases or concomitant intake of specific drugs. Therefore, to prevent potentially fatal arrhythmias, it is critical to know the drugs associated with QT prolongation to enable proper monitoring and reduce the risk of serious adverse events, such as *torsade de pointe*. [160]

Table on drugs that may prolong the QT interval implemented on the NavFarma® knowledge-base consists of 397 records and 10 columns:

- Record identification number;
- Active ingredient;

- ATC code of the drug;
- 4-level risk score of the potential to prolong the QT interval;
- Table type;
- Tooltip short text;
- Description for healthcare professionals, including the mechanism of QT prolongation and the complete list of sources consulted;
- Text for patients (empty field, patients do not receive information on the possible deprescription of prescribed medications);
- Pictogram;
- Last update.

The tooltip text appears when the user places the cursor over the specific pictogram; each risk category corresponds to a short tooltip text in Italian language:

- **High risk**: "*Alto rischio di comparsa di sindrome del QT lungo e torsioni di punta*", i.e., the drug has been shown to cause long QT syndrome. The syndrome is manifested by palpitations, ventricular arrhythmias (including *torsade de pointes* and ventricular fibrillation), syncope, convulsions and, in severe cases, sudden cardiac death. This effect is caused by prolongation of the duration of the ventricular action potential by various mechanisms, including inhibition of the hERG potassium channel. Increased risk of QT prolongation may be attributed to electrolyte imbalances such as hypokalaemia, hypocalcaemia and hypomagnesemia.
- **Moderate risk**: "*Possibile comparsa di sindrome del QT lungo (rischio moderato)*", i.e., the drug could induce long QT syndrome, but at commonly used doses there is insufficient evidence that it causes severe ventricular arrhythmias. The syndrome may manifest as palpitations, ventricular arrhythmias and fainting. As before, the most common mechanism of action is related to hERG potassium channel inhibition.
- **Low risk**: "*Possibile comparsa di sindrome del QT lungo in presenza di fattori di rischio (rischio basso)*", i.e., the drug has been associated with long QT syndrome in patients with one or more risk factors, including advanced age (>75 years), female gender, smokers, drug overdose, history of myocardial infarction or ischemic heart disease, presence of arrhythmias, use of antiarrhythmic drugs, heart failure, hypertension,

electrolyte imbalances, simultaneous use of multiple QT-prolonging drugs and genetic factors such as congenital long QT syndrome.

- **Unknown risk**: "*Rischio incerto di comparsa di sindrome del QT lungo*". In this case, cases of patients with QT interval prolongation following drug use have been reported, but the evidence is limited and insufficient to demonstrate a cause-and-effect relationship between the adverse event and drug use.

Description for healthcare professionals comprehensively shows all the information extracted from the various sources; drugs sharing the same risk category have the same description. The descriptions can be viewed after clicking on the corresponding pictogram, which is red for high-risk drugs and yellow for all other cases.

QT-prolonging drugs classified as moderate risk are the majority and correspond to 169 drugs and 233 records. In fact, I would like to remember that a single active ingredient can have two or more ATC codes depending on its function and that all ATC codes correspond to a single record in the tables implemented for NavFarma®. The most frequent drug classes with moderate risk of prolonging the QT interval according to the ATC classification, level 2 are: antineoplastic agents (ATC L01, 69 records), psycholeptics (N05, 16 records), antibacterials for systemic use (J01, 12 records) and drugs for endocrine therapy and psychoanaleptics (L02 and N06 respectively, corresponding to 10 records each).

There are 74 drugs and 87 records categorized as low risk of QT interval prolongation: 12 records of psycholeptics (N05) and 10 records of psychoanaleptics (N06), for the most frequent.

A total of 61 drugs were classified as high risk of causing prolongation of the QT interval, corresponding to 67 different records. These belong mostly to psycholeptic drugs (N05, 15 records), antibacterials for systemic use (J01, 10 records) and drugs for cardiac therapy (C01, 9 records).

Finally, 10 drugs corresponding to 10 records were classified as unknown risk, and they belong to the classes of psycholeptic drugs (N05, 8 records), lipid modifying agents (C10, 1 record) and antihypertensives (C02, 1 record).

Overall, the drug classes (ATC level 2) included in the table that are most associated with prolongation of the QT interval are shown in Figure 30.

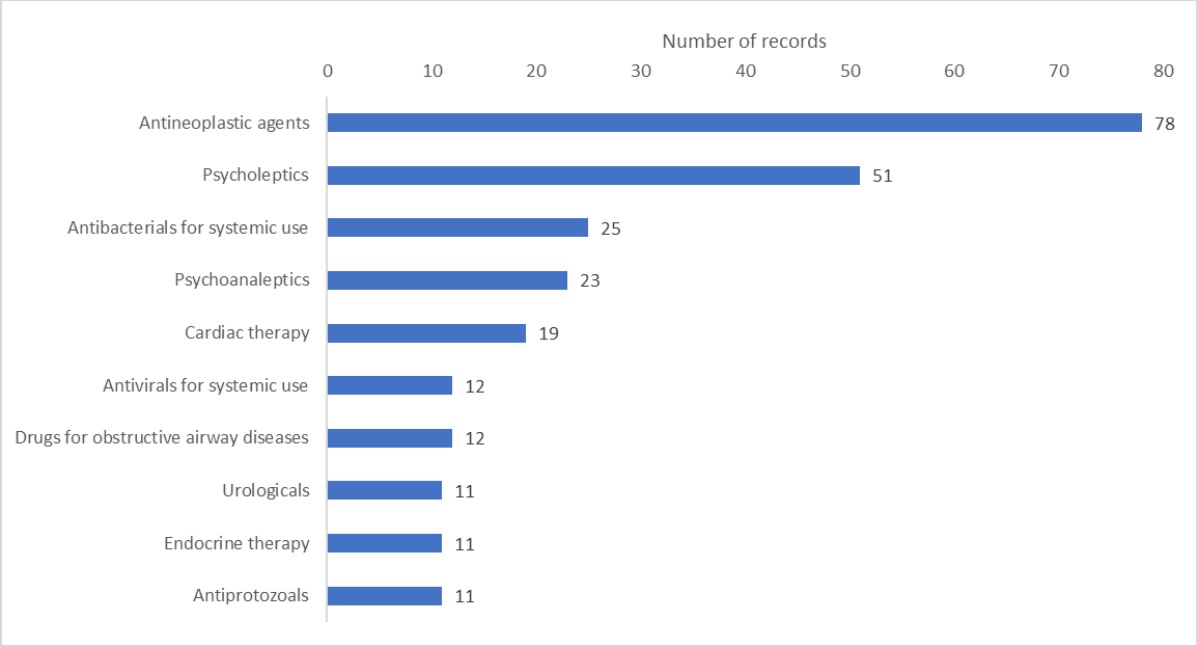


Figure 30. Drug classes according to the ATC classification, level 2 that most cause QT prolongation. Only drug classes with ≥10 records are shown in this figure

Some of these drugs are commonly used by older patients, a population already vulnerable due to comorbidities, physiological changes and polytherapy. For this reason, careful revision of pharmacological therapies with the support of tools capable of identifying potentially harmful drugs is essential. These include amiodarone (ATC C01BD01), azithromycin (J01FA10), haloperidol (N05AD01), risperidone (N05AX08) and citalopram (N06AB04), all of which are classified as being at high risk of causing QT interval prolongation, particularly in patients with risk factors.

4.1.4. Guidelines for deprescription and tapering dose

The final table implemented on NavFarma® includes 110 records and 11 columns, similarly to the other tables feeding the CDSS knowledge-base. Each record corresponds to a single active ingredient or drug class linked to an ATC code at level 5 (active ingredient) or level 2/3 (drug class).

Columns are:

- Record identification number;
- Active ingredient or drug class;
- ATC code;
- Table type and pictogram, which can be red or yellow;
- Tooltip text summarizing the conditions under which deprescription is recommended;
- Description for healthcare professionals, including information on why the drug/drug class should be deprescribe and in which cases, how to deprescribe, risks associated with the inappropriate use of the drug/drug class, deprescription priority and the full list of sources consulted;
- Text for patients (empty field);
- Minimum age (empty field);
- Maximum age (empty field);
- Gender (empty field);
- Last update.

In the table, drugs are categorized according to the priority of recommendation for deprescription, as reported in the sources consulted. This classification helps to quickly identify which drugs require immediate attention and which can be considered for longer-term review. Deprescription categories are:

- High priority: 49 drugs or drug classes are considered at high risk of harm to older or critically ill patients and their deprescription is highly recommended to avoid significant adverse effects.
- Medium priority: 44 drugs or drug classes with moderate risk, the deprescription of which is recommended in many circumstances but does not require immediate action.

- Low priority: 17 drugs or classes, which are considered low risk and can therefore be deprescribed without urgency after an assessment of the patient's characteristics.

Overall, the table includes 46 drug categories (for some classes the deprescription recommendations apply to the entire class, for others there are variable recommendations for different active ingredients in the class) and 9 active ingredients not included in the previous classes, as shown in Table 14.

Table 14. Drug categories and drugs included in the deprescription table

Drug categories	Drugs
5α-reductase inhibitors	Bethanechol
Antiacids (PPIs, H2 antagonists)	Calcium + vitamin D
Antiarrhythmics	Chloral hydrate
Antibiotics	Digoxin
Anticoagulants	Eflornithine
Antidementia medications	Ivabradine
Antidepressants	Liothyronine
Antiemetics	Ranolazine
Antiepileptics	Theophylline
Antihistamines	
Antihypertensives	
Antimalarials	
Antimycotics	
Antiplatelets	
Antipsychotics	
Antitussive	
Bisphosphonates	
Cannabis-based drugs	
Diuretics	
Drugs for urinary frequency and incontinence	
Ear medications	
Eye drops	
Gout medications	
Immunosuppressants	
Inhaled corticosteroids	
Intestinal antispasmodics	
Laxatives	
Lipid-lowering drugs	
Medications for urinary retention	
Mineral supplements	

Muscle relaxants
Nasal anticongestants
Non-insulin antidiabetics
Non-opioid analgesics
NSAIDs
Oestrogens with or without progestins
Opioids
Peripheral vasodilators
Prokinetics
Rubefacients
Sedative hypnotics (benzodiazepines, barbiturates, Z-drugs)
Systemic corticosteroids
Throat medications
Topical antimicrobial
Vasodilators
Vitamins

Abbreviations: PPIs, proton pump inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs

The recommendations included in the table are evidence-based and can help healthcare professionals to reduce or discontinue medications that are no longer needed or that may be harmful to the patient.

The following is a summary of selected recommendations for the most commonly used drug classes.

Antihypertensives and diuretics

The most common adverse effect in patients treated with antihypertensives is orthostatic hypotension, which is often asymptomatic and, therefore, undiagnosed. Hypotension may increase the risk of falls in older and frail patients.

Other adverse events vary depending on the class of antihypertensive, for example:

- Beta-blockers (e.g., atenolol, metoprolol): sinus bradycardia, exacerbation of acute heart failure, lethargy, sleep disturbance, blurred vision.
- Alpha-1 adrenergic blockers (e.g., prazosin, doxazosin): peripheral oedema, worsening of stress incontinence in women.
- Diuretics (e.g., hydrochlorothiazide, furosemide): hypokalaemia, hyponatraemia, hypomagnesemia, erectile dysfunction, decreased lithium excretion.

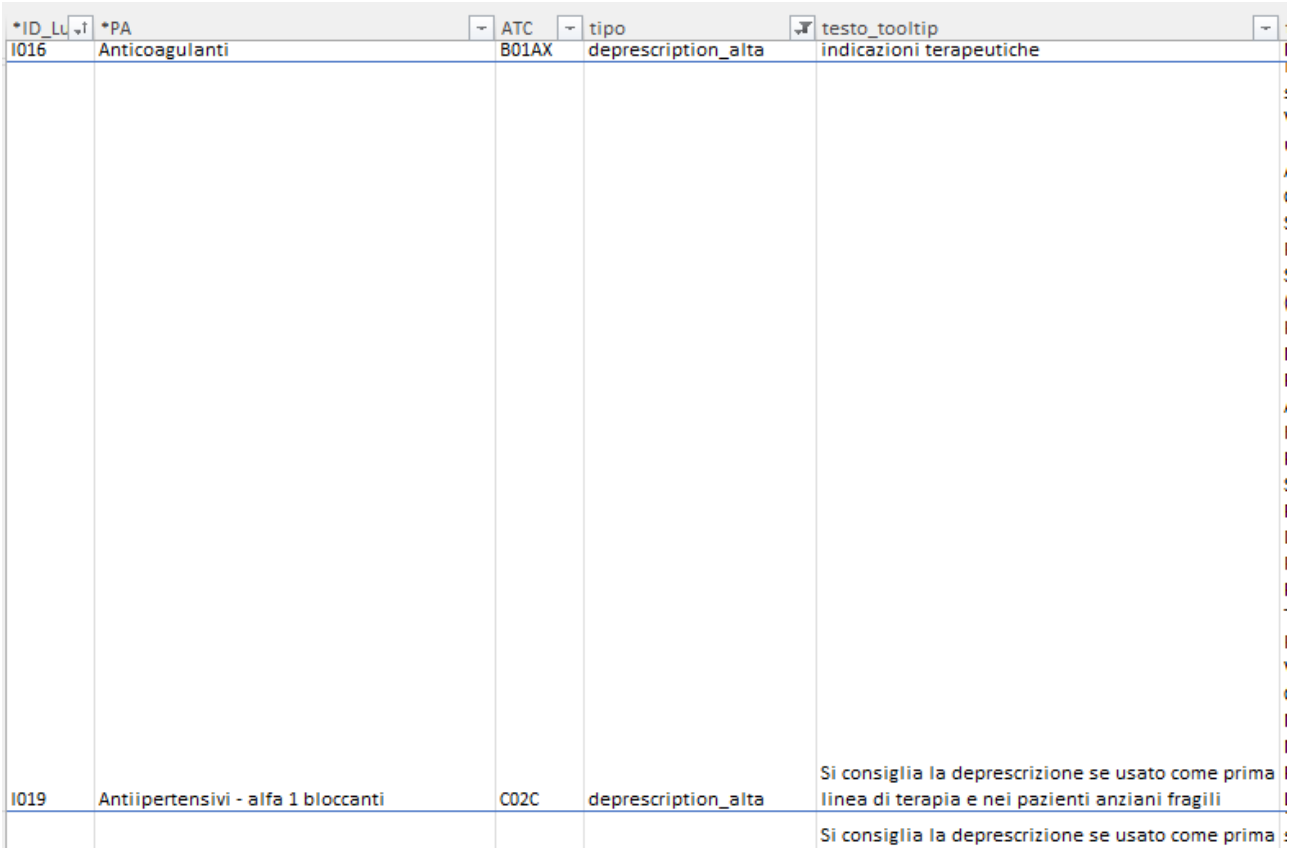
Patients most indicated for deprescription of antihypertensive drugs are subjects older than 85 years with comorbidities, frail or immobilized subjects, subjects with high risk of falls, patients diagnosed with orthostatic hypotension and patients with limited life expectancy.

Some studies conducted in favour of deprescribing antihypertensives reported an increased cardiovascular risk associated with very low systolic or diastolic arterial pressures in older patients following the use of antihypertensives.

Lifestyle modifications such as exercise, salt, sugar and alcohol restriction and weight loss can support the reduction and/or discontinuation of antihypertensives.

For successful deprescription, it is important to minimize the use of medications that may increase blood pressure; in addition, low or normotensive blood pressure levels while using antihypertensives and the use of only one antihypertensive drug are predictive factors for successful deprescription. [174]

Based on this evidence, the Excel table was compiled and implemented on NavFarma® (Figure 31).



*ID_LI	*PA	ATC	tipo	testo_tooltip
I016	Anticoagulanti	B01AX	deprescription_alta	indicazioni terapeutiche
I019	Antiipertensivi - alfa 1 bloccanti	C02C	deprescription_alta	Si consiglia la deprescrizione se usato come prima linea di terapia e nei pazienti anziani fragili
				Si consiglia la deprescrizione se usato come prima

Figure 31. Excerpt of the deprescription table implemented on NavFarma® for α-1 adrenergic blockers. The figure shows the tooltip text (description for healthcare professionals is too long to fit into a figure)

Complete text for healthcare professionals is:

"*I bloccanti alfa-1 (per es, prazosina, doxazosina, terazosina) presentano un alto rischio di ipotensione ortostatica, non raccomandati come trattamento antiipertensivo di prima linea. Altri antiipertensivi hanno un migliore rapporto rischio-beneficio. Nei pazienti fragili il controllo stringente della pressione non è essenziale. I farmaci alfa-bloccanti possono causare vasodilatazione, marcata ipotensione posturale, cadute e incidenti.*

Valutare il rapporto rischio/beneficio della terapia antiipertensiva, per esempio ipotensione ortostatica, effetti avversi sul SNC, rischio di cadute. Valutare la terapia compressiva o l'elevazione dell'arto in alternativa alla terapia antiipertensiva. Consigliare al paziente di seguire uno stile di vita adeguato.

ACE inibitori, bloccanti dei recettori dell'angiotensina II, calcio antagonisti e bloccanti alfa adrenergici non sono consigliati nei pazienti residenti in case di cura con demenza in stato avanzato/stadio finale.

Consiglio per la deprescrizione:

Se si assume più di un antiipertensivo, interromperne uno alla volta, mantenendo invariato il dosaggio degli altri.

Ricominciare il trattamento se la pressione diastolica supera 90 mm Hg e/o se la pressione sistolica supera 150 mm Hg (160 mm Hg in assenza di danno d'organo). Prima verificare l'aderenza del paziente al trattamento.

Sospendere gli alfa agonisti gradualmente per evitare ipertensione di rimbalzo. Se assunti quotidianamente per più di 3 o 4 settimane, ridurre la dose del 50% ogni 1 o 2 settimane. Una volta al 25% della dose originale e qualora non siano stati riscontrati sintomi da astinenza (dolore al petto, aumento della frequenza cardiaca, aumento della pressione sanguigna misurata per un massimo di 6 mesi, ansia, tremore), interrompere il farmaco. Se si verificano sintomi di astinenza, tornare a circa il 75% della dose precedentemente tollerata.

Rischio clinico:

Medio

Priorità di deprescrizione:

Alta"

PPIs

Several studies reported the inappropriate use of PPIs in hospitalized patients, who often continue therapy with this drug class after discharge. Australian researchers developed a set of suggestions for a proper PPI deprescribing strategy: [176]

- Convince clinicians of the importance and necessity of deprescribing;
- Use control groups;
- Identify inappropriate prescriptions;
- Explain the prescription method;
- Explain the side effects of inappropriate prescribing;
- Conduct prolonged follow-up of at least 24 months after deprescribing.

Some of the reasons why a stepwise PPI deprescription strategy should be used:

- Functional dyspepsia caused by overprescribing PPIs, especially in the long term;
- Absence of risk factors for gastric bleeding (gastroprotection not necessary);
- Enteric infections (*Clostridium difficile*, *Campylobacter*, *Salmonella*) with long-term use;
- Increased risk of fractures;
- Risk of bacterial peritonitis in patients with cirrhosis;
- Risk of hypomagnesemia;
- Increased risk of acute intestinal nephritis;
- Risk of vitamin B12 deficiency;
- Increased risk of pneumonia.

NavFarma®'s knowledge-base reports:

"*Gli inibitori di pompa protonica (IPP) possono causare perdite e fratture ossee con l'uso per più di un anno ad alte dosi, soprattutto negli anziani. Nei pazienti non in trattamento con FANS si consiglia la deprescrizione di IPP e di bloccanti H2.*

Fattori di rischio per il sanguinamento gastrointestinale che potrebbero richiedere l'uso di IPP/antagonisti H2 sono: età maggiore di 65 anni, trattamento con antiaggreganti, warfarin o altri anticoagulanti orali, storia di ulcera peptica o di sanguinamento gastrointestinale.

Interrompere gli IPP/antagonisti H2 quando non sono usati per la gastroprotezione nei pazienti senza sintomi di ulcera peptica, sanguinamento gastrointestinale o dispepsia per almeno un anno. L'uso prolungato può causare infezioni da Clostridium difficile.

Se l'uso di IPP è appropriato, prescrivere omeprazolo o lansoprazolo alla più bassa dose efficace. L'uso di IPP dovrebbe essere rivalutato dopo 4-8 settimane e interrotto se non più necessario. Per l'uso a lungo termine rivalutare la terapia annualmente.

Consiglio per la deprescrizione:

Gli IPP possono essere sospesi completamente senza scalare la dose, se necessario. Per evitare ipersecrezione da rimbalzo è possibile sospendere riducendo gradualmente la dose. Se usati quotidianamente per più di 3 o 4 settimane, ridurre la dose del 50% ogni 1 o 2 settimane. Una volta al 25% della dose originaria e se non sono stati osservati sintomi da astinenza, interrompere il farmaco. Se si verificano sintomi da astinenza, tornare a circa il 75% della dose precedentemente tollerata.

Rischio clinico:

Alto

Priorità di deprescrizione:

Alta"

Benzodiazepines

The Canadian Geriatrics Society, the Canadian Academy of Geriatric Psychiatry and the Beers criteria [39,179,181] recommend that benzodiazepines should not be used as first-line drugs in the treatment of insomnia, but only when nonpharmacological therapies have failed and, most importantly, they should be used for the shortest possible time. In fact, the efficacy of benzodiazepines has been shown to decline after four weeks of use, and their use in older patients carries significant risks such as falls, motor vehicle accidents, memory problems and daytime sedation. A systematic review on benzodiazepine deprescription showed that withdrawal symptoms are generally mild and do not include seizures. Expected benefits include:

- Improved vigilance;
- Reduced falls;
- Decreased sense of sedation during the day.

The main adverse events related to benzodiazepine use include physical dependence, memory impairment, functional impairment, anxiety, irritability, sweating, and gastrointestinal symptoms.

On NavFarma®:

"*Se il paziente è stabile sia dal punto di vista fisico e psicologico che personale, è motivato e ha il supporto sociale adeguato, si consiglia la deprescrizione delle benzodiazepine o Z-drugs. Con l'uso a lungo termine il rischio di eventi avversi, incluse le cadute, supera i benefici attesi. I farmaci sedativi possiedono proprietà anticolinergiche e andrebbero usati con cautela. L'uso di benzodiazepine è stato associato a un maggiore rischio di sviluppare polmonite. Uno studio ha suggerito che l'assunzione di benzodiazepine per più di 3 mesi, in particolare quelle con lunga emivita, aumenta il rischio di insorgenza di polmonite, ma le evidenze sono limitate.*

Nitrazepam e flurazepam hanno un'azione prolungata e possono dare origine a effetti residui il giorno successivo; le dosi ripetute tendono ad essere cumulative.

Consiglio per la deprescrizione:

La deprescrizione deve essere flessibile e la sospensione deve essere tollerabile per il paziente. La velocità di sospensione dipende da dose iniziale, durata di impiego e risposta clinica.

Se il farmaco è stato assunto per un breve periodo (da 2 a 4 settimane), si può generalmente sospendere in 2-4 settimane.

Se, invece, l'assunzione si è protratta per un periodo più lungo, la sospensione deve essere graduale per evitare confusione e psicosi. È possibile iniziare con uno switch a una dose equivalente di diazepam. Iniziare con una riduzione del 5-10% ogni 1 o 2 settimane oppure con un ottavo della dose ogni quindici giorni, monitorando eventuali sintomi da astinenza. I sintomi da astinenza (per es, perdita dell'appetito e di massa corporea, tremori, insonnia, sudorazione, tinnito, disturbi della percezione) possono iniziare entro 1 giorni dalla sospensione con le benzodiazepine a breve durata d'azione e entro 3 settimane con le benzodiazepine a lunga durata d'azione. Alcuni sintomi possono continuare per settimane e mesi dopo l'interruzione. Generalmente i sintomi si risolvono entro 6-18 mesi dall'ultima dose per i trattamenti di lunga durata. La sospensione può durare da 3 mesi a 1 anno o più.

Rischio clinico:

Medio

Priorità di deprescrizione:

Alta"

Antidepressants

"*Gli antidepressivi sono indicati per trattare episodi singoli di depressione per 6-9 mesi. Nel caso di episodi multipli il trattamento consigliato è di 2 anni; non vi sono evidenze per trattamenti di durata maggiore.*

Dosulepina è controindicata e non dovrebbe essere prescritta.

Valutare la deprescrizione degli antidepressivi nei pazienti con demenza avanzata/stadio finale e in caso di eventi avversi severi. Gli antidepressivi triciclici possono peggiorare la demenza, il glaucoma, la costipazione, la ritenzione urinaria; gli SSRI possono indurre iponatriemia clinicamente significativa.

Evitare la combinazione di antidepressivi triciclici con altri farmaci con attività anticolinergica (per es, clorpromazina, ossibutinina, clorfenamina) poiché può aumentare il rischio di decadimento cognitivo.

Gli antidepressivi triciclici non sono appropriati nei pazienti residenti in case di cura con demenza avanzata/stadio finale.

Consiglio per la deprescrizione:

Ridurre la dose di antidepressivi gradualmente per evitare sintomi da astinenza. Se assunti continuamente per 6 settimane o più, ridurre lentamente la dose nell'arco di 4 settimane.

Gli antidepressivi con breve emivita (ad es, paroxetina, venlafaxina) devono essere ridotti più lentamente.

La fluoxetina (lunga emivita) da 20 mg può essere interrotta immediatamente, mentre dosi più elevate devono essere interrotte nell'arco di 2 settimane.

Rischio clinico:

Medio

Priorità di deprescrizione:

Media"

NSAIDs

Figure 32 shows an example of how the recommendation on NSAID deprescription appear on the NavFarma® CDSS.

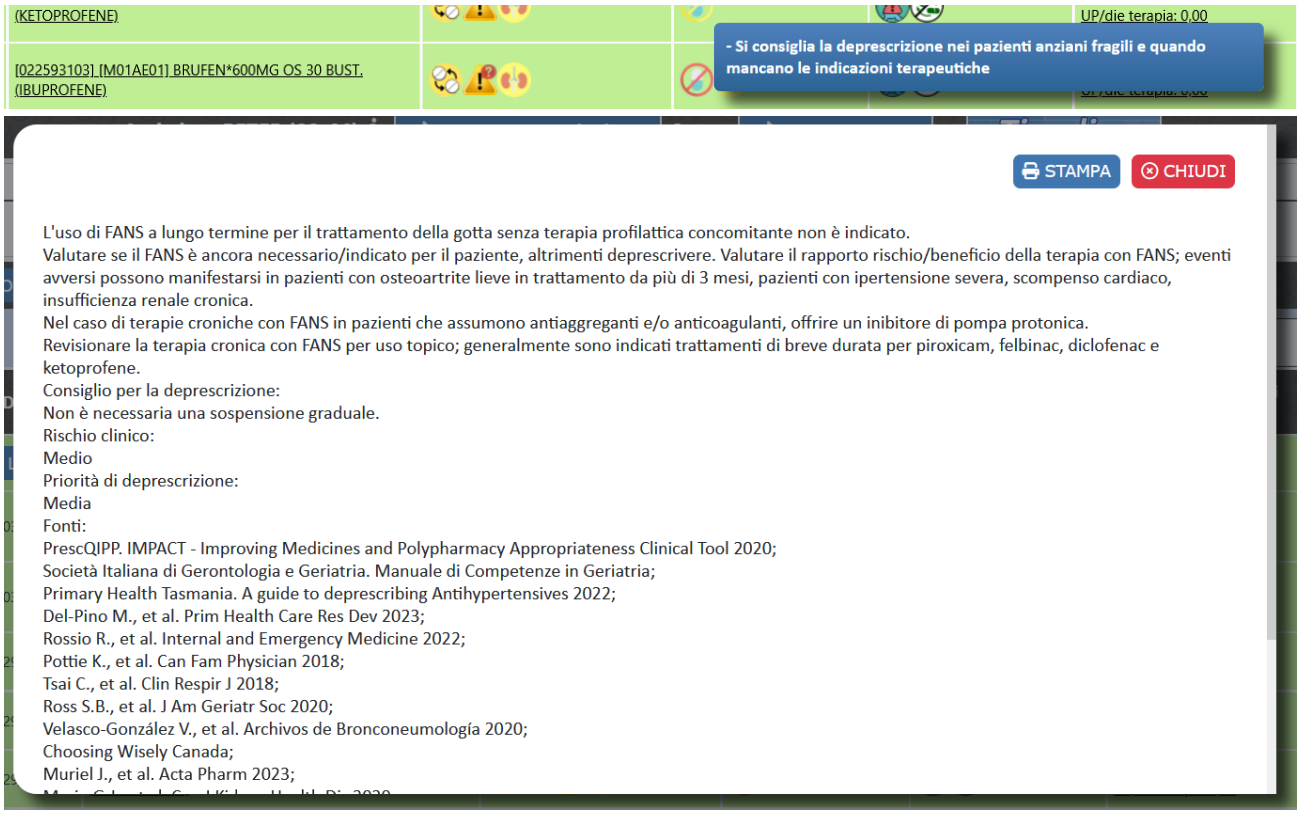


Figure 32. Deprescription of ibuprofen on NavFarma®. Top tooltip, bottom description for healthcare professionals

4.2. Pilot study to test the new version of NavFarma®

Approval to conduct the pilot study at the Mauriziano Hospital was obtained from the hospital General Director on April 5, 2024. The pilot study was a retrospective, observational study because patient data collected at baseline were analysed and no changes in drug treatment were made as a result of the researcher's analysis. The results of the analysis were shared with hospital pharmacists of the Mauriziano Hospital and were used by the Infologic company to improve its CDSS.

Anonymized data of 11 patients admitted to the internal medicine department in June 2024 and entered into NavFarma® by the hospital pharmacist in July 2024 were analysed. Characteristics of the study population during hospitalization (baseline) are shown in Table 15.

Table 15. Characteristics of the study population at baseline

Patient ID	Sex	Age in 2024	Reason for hospital admission	Diagnosis, n	Daily drugs, n	Drugs as needed, n
Patient 1	F	75	Pericardial disease	6	6	3
Patient 2	F	94	Left heart failure	6	9	2
Patient 3	F	92	Pneumonia	9	7	0
Patient 4	F	83	Sepsis	2	5	1
Patient 5	F	68	Poorly defined morbid condition	4	6	2
Patient 6	M	92	Acute cholecystitis	6	6	3
Patient 7	F	78	Infectious gastroenteritis	8	14	1
Patient 8	M	76	Bronchopneumonia	8	11	1
Patient 9	M	93	Respiratory failure	5	8	2
Patient 10	F	85	Infectious gastroenteritis	6	9	1
Patient 11	M	75	Pneumonia associated with SARS-CoV	9	5	4
Median [IQR]	-	**83 [75.5-92]**	-	**6 [5.5-8]**	**7 [6-9]**	**2 [1-2.5]**

Abbreviations: Patient ID, patient identification number; F/M, female/male; IQR, interquartile range

Most of the patients selected were women (7 out of 11), with a median age of 83 years. Patient were admitted to the internal medicine department for various reasons, including respiratory diseases (4 patients out of 11), diseases of the gastrointestinal tract (3 out of 11) and cardiovascular diseases (2 out of 11). A total of 43 different daily drugs (both hospital and home medications) were recorded on NavFarma®, the most frequent being pantoprazole

(6 patients out of 11), ceftriaxone (5 patients) and enoxaparin (5 patients). Twenty different drugs were used by selected patients as needed, primarily paracetamol (8 patients) and morphine (3 patients). The most common diseases in the population were heart diseases (7 patients), asthma and/or COPD (6 patients) and inflammatory diseases of the gastrointestinal tract (5 patients). These results highlight the heterogeneity of older polypharmacy patients admitted to the internal medicine department.

NavFarma® identified a total of 43 major DDIs in the study population, of which 39 were unique, corresponding to 30 different drugs. The drugs most involved in DDIs were trazodone (9 DDIs), amiodarone (6 DDIs) and digoxin (6 DDIs). Particularly:

- trazodone could interact with antipsychotics and with amiodarone increasing the risk of QT-interval prolongation;
- trazodone could interact with anticoagulants increasing the risk of bleeding;
- trazodone could interact with benzodiazepines, opioids and antidepressants increasing the risk of central nervous system depression and/or serotonergic syndrome;
- digoxin could interact with various drug classes increasing the risk of alterations of digoxin plasma levels, which could lead to digoxin toxicity or reduced efficacy;
- amiodarone could also interact with various drugs leading to potential side effects, such as increased risk of bleeding, hypotension and QT-interval prolongation.

According to the latest version of the Beers criteria [39] included in the NavFarma® knowledge-base, a total of 102 PIPs corresponding to 26 different drugs were identified by the software. Considering the latest version of the STOPP criteria [40], NavFarma® identified 204 PIPs, corresponding to 38 different drugs. Classifying PIPs according to their intrinsic characteristics (valid in most older patients or conditioned by the presence of specific patient conditions, as specified in the methods section), 44.1% of the Beers criteria (45 PIPs) and 11.8% of the STOPP criteria (24 PIPs) were **valid in most older patients**; the remaining PIPs were **conditioned**, respectively 55.9% of the Beers criteria (57 PIPs) and 88.2% of the

STOPP criteria (180 PIPs). Figure 33 summarizes PIPs identified by NavFarma® in the study population classified according to the above-mentioned characteristics.

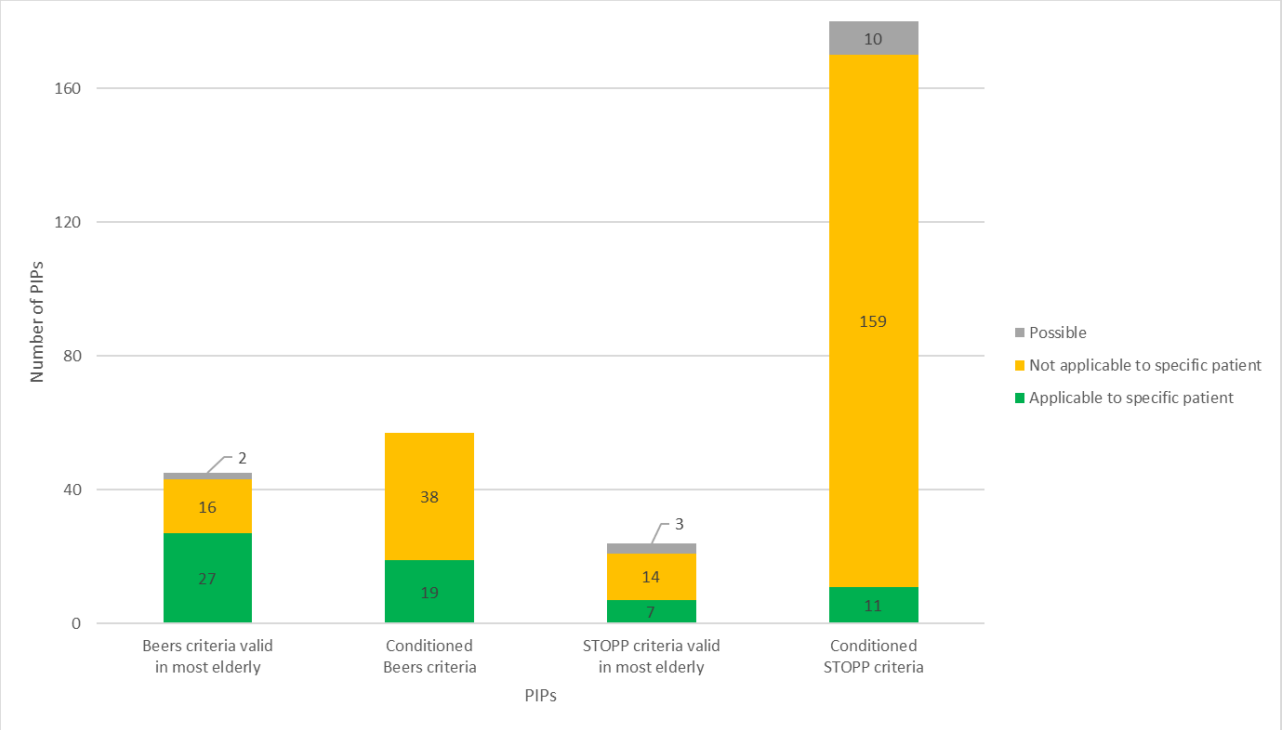


Figure 33. PIPs according to the Beers and the STOPP criteria identified by NavFarma® in the study population. PIPs valid in most elderly are valid in older patients regardless of the patient's previous characteristics. Conditioned PIPs are valid only in patients with specific clinical conditions. Applicable PIPs identify PIPs that may cause side effects in the patient; non-applicable PIPs are PIPs that do not apply to the specific patient; possible PIPs are PIPs for which applicability could not be assessed due to unavailable data.
Abbreviations: PIPs, potentially inappropriate prescriptions

Considering only **applicable** and **possible** PIPs (both valid in most patient and conditioned), 48 PIPs according to the Beers criteria (47.1% of the total Beers criteria) and 31 PIPs according to the STOPP criteria (15.2% of the total STOPP) were selected (Table 16).

Table 16. PIPs assessed as applicable or possible for the patients analyzed by the researcher on drug use

Drug	PIPs, n	Reasons for PIPs
PIPs according to the Beers criteria (*n*=48)		
Trazodone	7	- It may cause or worsen SIADH or hyponatremia in most elderly. - It may increase the risk of falls when taking other drugs active on the CNS.
Pantoprazole	6	- It may increase the risk of *C. difficile* infections, pneumonia, GI neoplasms, bone loss and fractures in most elderly.
Furosemide	4	- It may cause or worsen SIADH or hyponatremia in most elderly.
Paroxetine	4	- It may cause or worsen SIADH or hyponatremia in most elderly. - It may increase the risk of falls when taking other drugs active on the CNS. - Doses >6 mg/die may cause orthostatic hypotension or high anticholinergic effect.

Haloperidol	3	- It may cause or worsen SIADH or hyponatremia in most elderly. - It may increase the risk of falls when taking other drugs active on the CNS. - It may increase the risk of stroke, cognitive impairment and mortality in most elderly.
Digoxin	3	- Uncertain risk/benefit ratio in the treatment of heart failure. - Safer alternatives available in the treatment of atrial fibrillation.
Quetiapine	3	- It may cause or worsen SIADH or hyponatremia in most elderly. - It may increase the risk of falls when taking other drugs active on the CNS. - It may increase the risk of stroke, cognitive impairment and mortality in most elderly.
Alprazolam	2	- It may increase the risk of falls when taking other drugs active on the CNS. - It may increase the risk of cognitive impairment, delirium, falls and accidents in most elderly.
Levothyroxine	2	- It may cause possible cardiac issues in most elderly.
Mirtazapine	2	- It may cause or worsen SIADH or hyponatremia in most elderly. - It may increase the risk of falls when taking other drugs active on the CNS.
Morphine	2	- It may increase the risk of falls when taking other drugs active on the CNS.
Acetylsalicylic acid	1	- It may worsen existing ulcers or cause new or additional ulcers in most elderly.
Enoxaparin	1	- It may increase the risk of bleeding when CrCL <30 ml/min.
Fentanyl	1	- It may increase the risk of falls when taking other drugs active on the CNS.
Insulin	1	- It may increase the risk of hypoglycaemia when taking without concomitant use of basal or long-acting insulin.
Lacosamide	1	- It may increase the risk of falls when taking other drugs active on the CNS.
Lorazepam	1	- It may increase the risk of falls when taking other drugs active on the CNS.
Pregabalin	1	- It may cause adverse effects on the CNS when CrCl <60 ml/min.
Tramadol	1	- It may worsen delirium.
Warfarin	1	- It has a higher risk of bleeding than other oral anticoagulants in most elderly.
		PIPs according to the STOPP criteria (*n*=31)
Digoxin	4	- It may increase the risk of mortality in the treatment of atrial fibrillation for periods >3 months. - No evidence of benefit in the treatment of heart failure in patients with preserved systolic ventricular function.
Acetylsalicylic acid	2	- Lack of benefit with the combination of antiplatelet and anticoagulants in the treatment of stable coronary artery disease, cerebrovascular disease, peripheral arterial disease, atrial fibrillation, coronary stent, coronary stenosis.
Alprazolam	2	- It may increase the risk of sedation, confusion, falls, accidents when used for >4 week in most elderly. - It may increase the risk of addiction, falls, accidents when used for >1 week to treat insomnia.
Amiodarone	2	- It may increase the risk of bleeding in most elderly.
Bisoprolol	2	- It may mask hypoglycaemic symptoms in hypoglycaemic patients. - No evidence of benefit in the treatment of uncomplicated hypertension in monotherapy.
Fentanyl	2	- It may increase the risk of persistence of severe pain without concomitant use of short-acting opioids.

		- Daily use may increase the risk of stypsis without concomitant use of a laxatives.
Furosemide	2	- Safer alternatives available in the first-line treatment of hypertension without heart failure.
Pantoprazole	2	- High doses are potentially inappropriate for >8 weeks in the treatment of uncomplicated peptic ulcers.
Prednisone	2	- Systemic corticosteroids may increase the risk of unnecessary side effects in the treatment of COPD. - It may increase the risk of recurrence in patients with prior peptic ulcers or erosive oesophagitis without concomitant use of a PPI.
Haloperidol	1	- It may increase the risk of confusion, hypotension, falls, extra-pyramidal adverse effects when used as hypnotic in most elderly.
Apixaban	1	- It may increase the risk of bleeding in most elderly.
Atenolol	1	- No evidence of benefit in the treatment of uncomplicated hypertension in monotherapy.
Azithromycin	1	- It may increase the risk of bleeding in most elderly.
Ceftriaxone	1	- Lack of therapeutic indications for the treatment of asymptomatic bacteriuria.
Levosulpiride	1	- It may increase the risk of confusion, hypotension, falls, extra-pyramidal adverse effects when used as hypnotic in most elderly.
Levothyroxine	1	- No evidence of benefit in the treatment of hypothyroidism in older patients.
Metoprolol	1	- It may mask hypoglycaemic symptoms in hypoglycaemic patients.
Naloxone/ oxycodone	1	- Daily use may increase the risk of stypsis without concomitant use of a laxatives.
Paroxetine	1	- It may cause or worsen hyponatremia in patients at risk.
Quetiapine	1	- It may increase the risk of confusion, hypotension, falls, extra-pyramidal adverse effects when used as hypnotic in most elderly.

Abbreviations: PIPs, potentially inappropriate prescriptions; SIADH, syndrome of inappropriate antidiuretic hormone secretion; CNS, central nervous system; GI, gastrointestinal; CrCl, creatinine clearance; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor

All patients analysed had at least one drug with potential anticholinergic effects, one potentially nephrotoxic drug and one drug that may prolong the QT interval. Table 17 summarizes for each patient and for the overall population the NavFarma® alerts considered to review patients' baseline therapies.

Table 17. Summary of MRPs identified by NavFarma® and verified by the researcher on drug use in the therapies of the patients analyzed

ID	DDIs, n	PIPs (Beers criteria), n		PIPs (STOPP criteria), n		ACB score	Potentially nephrotoxic drugs, n	Potentially QT-prolonging drugs, n
		Val	*Cond*	*Val*	*Cond*			
P1	1	1	0	0	0	2	3	3
P2	8	4	3	2	0	5	2	5
P3	0	1	0	1	1	2	3	4
P4	0	1	0	0	2	1	3	2
P5	3	2	0	2	2	1	3	2
P6	5	1	2	0	2	3	7	5
P7	6	5	4	2	3	4	5	6
P8	6	3	0	1	3	3	7	5
P9	5	7	3	1	3	5	4	5
P10	3	4	2	0	4	5	3	4
P11	6	0	5	1	1	3	2	2
Median [IQR]	**5 [2-6]**	**2 [1-4]**	**2 [0-3]**	**1 [0-1.5]**	**2 [1-3]**	**3 [2-4.5]**	**3 [3-4.5]**	**4 [2.5-5]**

Abbreviations: ID, patient ID; DDI, drug-drug interactions; PIPs, potentially inappropriate prescriptions; val, valid in most elderly (applicable and possible); cond, conditioned (applicable and possible); ACB, anticholinergic cognitive burden; IQR, interquartile range

A total of 32 drugs, corresponding to 19 unique active ingredients, with potential anticholinergic effects were prescribed to the study population. Among these, only paroxetine is a definite anticholinergic (ACB score of 3), while all the other drugs are possible anticholinergics with an ACB score of 1. The most prescribed anticholinergic drugs were furosemide and trazodone, prescribed to 4 patients out of 11, and digoxin and morphine, prescribed to 3 patients. The use of drugs with anticholinergic effect, especially in older patients, requires special attention as they could increase the risk of severe side effects such as mental confusion, cognitive impairment, delirium and falls. [41]

Potentially nephrotoxic drugs identified were 42, corresponding to 18 unique active ingredients. The majority (35 out of 42) have a low risk of inducing renal damage, while the remainder have a moderate risk. Despite this, almost all patients (9 out of 11) had 3 or more different potentially nephrotoxic drugs, which when added together increase the risk of renal damage. [116,117] The most prescribed ones were paracetamol (low risk, 8 patients), pantoprazole (low risk, 6 patients) and ceftriaxone (moderate risk, 5 patients).

Finally, 43 potentially QT-prolonging drugs were identified, for a total of 21 different active ingredients. As for potentially nephrotoxic drugs, the majority have a low risk (28 out of 43), while only 10 and 5 have a moderate and a high risk, respectively; however, 8 patients out of 11 presented 3 or more drugs that may prolong the QT interval, leading to potentially

additive effects on cardiac rhythm that may cause even severe arrhythmias. [134] The potentially QT-prolonging drugs to pay most attention to in this population are pantoprazole (low risk, prescribed to 6 patients), ceftriaxone (moderate risk, prescribed to 5 patients) and furosemide (low risk, prescribed to 4 patients).

From these data, it can be deduced that pharmacological therapies of older polypharmacy patients admitted to the internal medicine department present numerous PIPs and other MRPs that may worsen the patient's condition. Therefore, this represents a patient population that would benefit from medication review before discharge. The most critical drugs identified in the study population were:

- trazodone (24 total alerts), which is inappropriate according to the Beers criteria and has possible anticholinergic effects. Trazodone is an antidepressant with moderate sedative action which makes it suitable for use in older patients suffering from delirium, agitation or insomnia. [226] However, the concomitant use of other drugs active on the central nervous system should be limited or avoided to reduce the risk of side effects.
- digoxin and furosemide (22 total alerts each), which are inappropriate according to both the Beers and the STOPP criteria, are possible anticholinergics and only furosemide presents a low risk of nephrotoxicity. These drugs are primarily used to treat symptoms of heart failure. Diuretics and ACE inhibitors may represent safer alternatives to digoxin as it interacts with several drug classes increasing the risk of digoxin toxicity, while a safer alternative to furosemide may be spironolactone. [227]
- pantoprazole (20 total alerts), which is inappropriate according to the Beers and the STOPP criteria, is potentially nephrotoxic and may prolong the QT interval. PPIs should be deprescribed after 12 months in older patients with no symptoms of peptic ulcer, gastrointestinal bleeding or dyspepsia, except in high-risk patients. If appropriate, the lowest effective dose of omeprazole or lansoprazole should be used, and the therapy should be reassessed annually. [172]

At the time of the pilot study, classifying PIPs, both valid in most elderly and conditioned, into applicable and non-applicable to the specific patient represented a time-consuming activity performed by the hospital pharmacist or the researcher on drug use. In fact, at the time of the pilot study, NavFarma® only provided the total PIPs for each drug entered into

the patient's therapy with the corresponding description; it was up to the NavFarma® user reading the descriptions to assess the applicability of PIPs for the patient based on the presence or absence of specific conditions, such as diseases, dosage or duration limits, co-prescriptions with other drugs, altered blood values or frailty.

Therefore, in addition to testing the updated knowledge-base, the pilot study served to design a comprehensive but concise therapy review report. The study made it possible to identify key data needed for the evaluation of PIPs. In addition, the study provided a basis for the development and implementation of a tool aimed at automating the evaluation process of MRPs. This tool was designed to reduce reviewing time and simplify the steps required for an accurate therapy review.

Starting from manually prepared reports for each patient enrolled in the pilot study, a report template was developed, automatically filled in by NavFarma® with the selected information and editable by the consultant for medication review. On the next page is the manually prepared report for the first patient enrolled in the pilot study.

Paziente 1 Medicina Interna Mauriziano (donna, 75 anni)

Diagnosi (6)

Malattia pericardica	Ricoveri per **addensamento polmonare**
Psoriasi	**Tromboflebite**
Dispnea	Pregressa tiroidectomia
SARS-Coronavirus	Pregressa ernioplastica

Terapia farmacologica (6 PA giornalieri, 3 al bisogno)

P.A.	Posologia
PARACETAMOLO	Giornaliera
AMOXICILLINA/ACIDO CLAVULANICO	Giornaliera
BECLOMETASONE DIPROPRIONATO/FORMOTEROLO	Giornaliera
LEVOTIROXINA SODICA	Giornaliera
TRAMADOLO CLORIDRATO	Al bisogno
METOCLOPRAMIDE CLORIDRATO	Al bisogno
PARACETAMOLO	Al bisogno

Interazioni farmacologiche maggiori e farmaci potenzialmente inappropriati nell'anziano

Segnalazione	Farmaco/i	Descrizione	Commento
Interazioni	METOCLOPRAMIDE – TRAMADOLO	Aumento del rischio di depressione del SNC	Uso **al bisogno**. Non assumere METOCLOPRAMIDE e TRAMADOLO in concomitanza
Beers non condizionati da caratteristiche del paziente	LEVOTIROXINA SODICA	Possibili problemi cardiaci	Applicabile
	TRAMADOLO CLORIDRATO	Può esacerbare o causare sindrome da inappropriata secrezione dell'ormone antidiuretico (SIADH) o iponatremia	Non applicabile (uso **al bisogno**)
	METOCLOPRAMIDE CLORIDRATO	Può causare effetti extrapiramidali, compresa la discinesia tardiva	Non applicabile (uso **al bisogno**)
Beers condizionati	TRAMADOLO CLORIDRATO	Applicabile solo se CrCl < 30 ml/min. Effetti avversi sul SNC	Non applicabile
	TRAMADOLO CLORIDRATO	Peggioramento del delirium	Non applicabile
	TRAMADOLO CLORIDRATO	Aumenta il rischio di cadute e fratture se assunto insieme ad altri farmaci attivi sul SNC	Non applicabile (uso **al bisogno**)
	METOCLOPRAMIDE CLORIDRATO	Applicabile solo in caso di malattia di Parkinson	Non applicabile
STOPP non condizionati	TRAMADOLO CLORIDRATO	L'uso giornaliero di oppioidi senza uso di un lassativo concomitante è potenzialmente inappropriato	Non applicabile (uso **al bisogno**)
STOPP condizionati	AMOXICILLINA/ACIDO CLAVULANICO	Solo in caso di batteriuria asintomatica. Nessuna indicazione terapeutica	Non applicabile
	TRAMADOLO CLORIDRATO	Inappropriato nei pazienti con cadute ricorrenti	Non applicabile
	TRAMADOLO CLORIDRATO	Inappropriati come prima linea nel trattamento del dolore lieve	Non applicabile (uso **al bisogno**)
	TRAMADOLO CLORIDRATO	L'impiego di oppioidi a lunga durata d'azione senza oppioidi a	Non applicabile (uso **al bisogno**)

		breve durata d'azione per il trattamento del dolore moderato o grave è potenzialmente inappropriato	
	LEVOTIROXINA SODICA	Solo in caso di ipotiroidismo. Nessuna evidenza di beneficio	Non applicabile
	METOCLOPRAMIDE CLORIDRATO	Solo in caso di malattia di Parkinson	Non applicabile
	TRAMADOLO CLORIDRATO	Mancanza di prove di efficacia per il trattamento di osteoartrite	Non applicabile
	PARACETAMOLO	Solo per dosi >/= 3 g/die nei pazienti con scarso stato nutrizionale, malattia epatica cronica. Rischio di epatotossicità	Non applicabile
	TRAMADOLO CLORIDRATO	Inappropriato nei pazienti con stipsi cronica	Non applicabile

1 interazione farmacologica maggiore
1 criterio di Beers non condizionato
0 criteri di STOPP

ACB score: **2** (metoclopramide, tramadolo **al bisogno**)
Nefrotossicità: amoxicillina (rischio basso); paracetamolo (rischio basso); metoclopramide (rischio basso)
Rischio prolungamento intervallo QT: amoxicillina (rischio moderato); tramadolo (rischio moderato); metoclopramide (rischio basso)

La terapia risulta appropriata. Prestare attenzione all'uso di tramadolo e metoclopramide al bisogno, soprattutto se assunti nella stessa giornata.

This report was prepared by manually checking all the alerts shown by NavFarma® in the patient's therapy and by copying the most relevant information into a Microsoft Word document to verify the alerts. Finally, MRPs valid for the specific patient were counted and a brief suggestion for appropriate therapy management was written.

Reports were shared with hospital pharmacists and informatics of the Infologic company with the aim of co-designing an automatic report template to be implemented on NavFarma®. For this reason, a new feature was added to the software: the counselling tab including the editable medication review report (Figure 34).

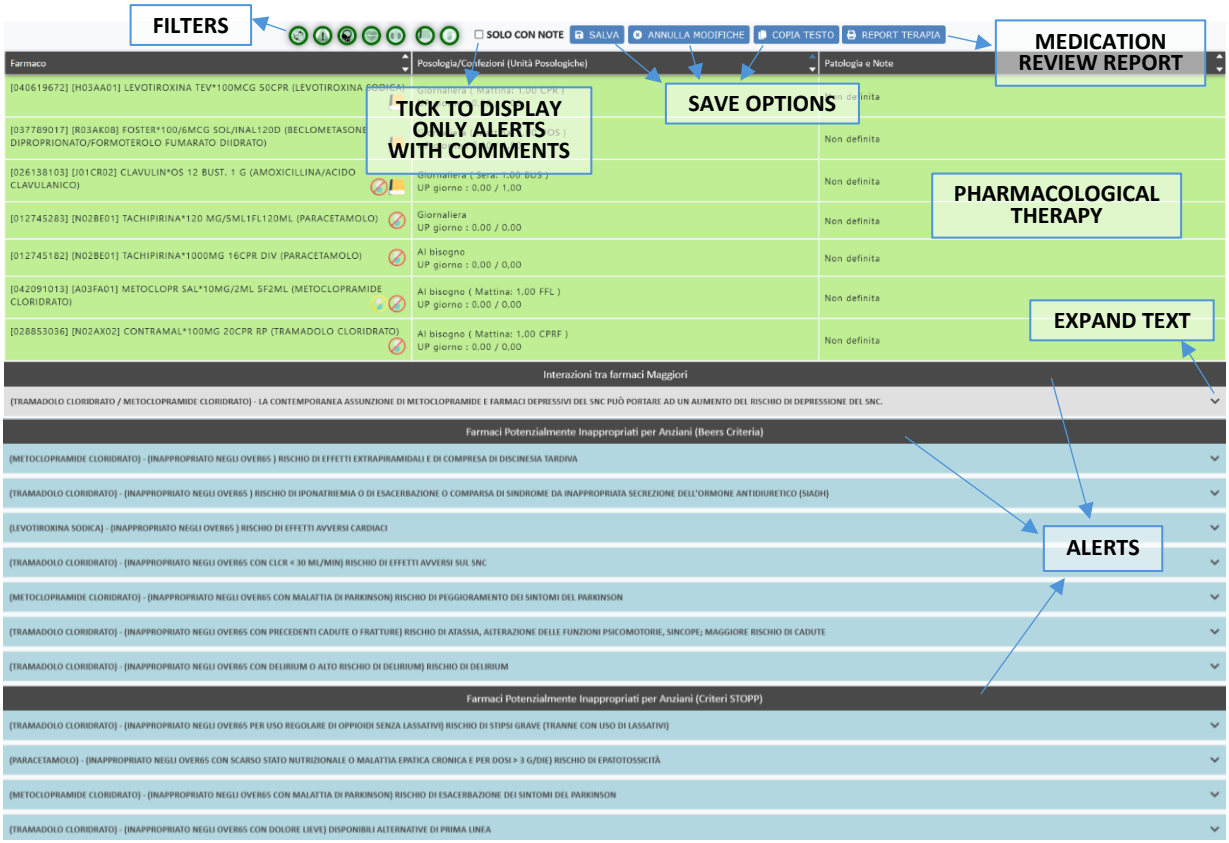


Figure 34. Part of the counselling tab implemented into NavFarma® from September 2024 related to Patient 1 of the pilot study

This tool includes filters to select which alerts and respective risks to display from those considered useful to perform medication review: drug-drug interactions, PIPs in older patients (a choice of EU(7)-PIM list and Beers, STOPP and STOPPFrail criteria), ACB score, QT-prolonging drugs, potentially nephrotoxic drugs, guidelines and recommendations for deprescribing. Alerts are divided based on their type and for each alert it is possible to expand the text to read the full description and write free comments. It is also possible to display only alerts with written comments to reduce alert fatigue. Moreover, the most useful feature of this tool is the possibility of downloading the preset medication review report in pdf or editable format. On the next page is the report for Patient 1 enrolled in the pilot study produced by NavFarma®. Users can use the free comments or open the editable version of the report (Microsoft Word) to fill in the column with notes and verify the CDSS-detected alerts and medication-related problem counts.

Report terapia farmacologica

Data report: 28/11/2024

Cognome e Nome: Paziente 1 MI Mauriziano (F, 75 anni)
Reparto: Studio Struttura: FPB

Diagnosi registrate (7): SARS-Coronavirus associato; Pericardite acuta; Tromboflebite superficiale; Psoriasi e affezioni similari; Dispnea e anomalie respiratorie; Intervento chirurgico; Intervento chirurgico;

Terapia farmacologica (4 medicinali cronici):
Medicinali cronici = Posologia (Giornaliera, A giorni alterni, Settimanale, Ogni x giorni)

- LEVOTIROXINA SODICA 100MCG 50CPR (Giornaliera)
- BECLOMETASONE DIPROPRIONATO/FORMOTEROLO FUMARATO DIIDRATO 100/6MCG SOL/INAL120D (Giornaliera)
- AMOXICILLINA/ACIDO CLAVULANICO OS 12 BUST. 1 G (Giornaliera)
- PARACETAMOLO 120 MG/5ML1FL120ML (Giornaliera)
- PARACETAMOLO 1000MG 16CPR DIV (Al bisogno)
- METOCLOPRAMIDE CLORIDRATO 10MG/2ML 5F2ML (Al bisogno)
- TRAMADOLO CLORIDRATO 100MG 20CPR RP (Al bisogno)

Interazioni farmacologiche e farmaci potenzialmente inappropriati (PIP) negli anziani

Segnalazione	Farmaci	Descrizione	Commento
Interazione **Maggiore**	TRAMADOLO CLORIDRATO - METOCLOPRAMIDE CLORIDRATO	La contemporanea assunzione di METOCLOPRAMIDE e FARMACI DEPRESSIVI DEL SNC può portare ad un aumento del rischio di depressione del SNC.	

Segnalazione	PA	Descrizione	Commento
BEERS Non condizionati	METOCLOPRAMIDE CLORIDRATO	(Inappropriato negli over65) Rischio di effetti extrapiramidali e di comparsa di discinesia tardiva	~~PIP Applicabile;~~ Uso al bisogno
BEERS Non condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65) Rischio di iponatriemia o di esacerbazione o comparsa di sindrome da inappropriata secrezione dell'ormone antidiuretico (SIADH)	~~PIP Applicabile;~~ Uso al bisogno
BEERS Non condizionati	LEVOTIROXINA SODICA	(Inappropriato negli over65) Rischio di effetti avversi cardiaci	PIP Applicabile;
BEERS Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con ClCr < 30 ml/min) Rischio di effetti avversi sul SNC	
BEERS Condizionati	METOCLOPRAMIDE CLORIDRATO	(Inappropriato negli over65 con malattia di Parkinson) Rischio di peggioramento dei sintomi del Parkinson	
BEERS Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con precedenti cadute o fratture) Rischio di atassia, alterazione delle funzioni psicomotorie, sincope; maggiore rischio di cadute	

BEERS Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con delirium o alto rischio di delirium) Rischio di delirium	
STOPP Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 per uso regolare di oppioidi senza lassativi) Rischio di stipsi grave (tranne con uso di lassativi)	
STOPP Condizionati	PARACETAMOLO	(Inappropriato negli over65 con scarso stato nutrizionale o malattia epatica cronica e per dosi > 3 g/die) Rischio di epatotossicità	
STOPP Condizionati	METOCLOPRAMIDE CLORIDRATO	(Inappropriato negli over65 con malattia di Parkinson) Rischio di esacerbazione dei sintomi del Parkinson	
STOPP Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con dolore lieve) Disponibili alternative di prima linea	
STOPP Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con stipsi) Rischio di esacerbazione della stipsi	
STOPP Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con osteoartrite) Rapporto rischio/benefici sfavorevole per l'uso a lungo termine	
STOPP Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con cadute o fratture ricorrenti) Rischio di ridotta percezione da parte degli organi di senso	
STOPP Condizionati	TRAMADOLO CLORIDRATO	(Inappropriato negli over65 con dolore moderato o grave) Rischio di persistenza del dolore grave (tranne in caso di associazione di oppioidi a lunga e breve durata d'azione)	
STOPP Condizionati	LEVOTIROXINA SODICA	(Inappropriato negli over65 con ipotiroidismo subclinico - i.e. T4 libero normale, TSH elevato ma < 10 mU/L) Nessuna evidenza di beneficio, rischio di tireotossicosi iatrogena	
STOPP Condizionati	AMOXICILLINA/ACIDO CLAVULANICO	(Inappropriato negli over65 con bacteriuria asintomatica) Mancanza di indicazione terapeutica	
STOPP Condizionati	PARACETAMOLO	(Inappropriato negli over65 con scarso stato nutrizionale o malattia epatica cronica e per dosi > 3 g/die) Rischio di epatotossicità	

Interazioni farmaco-farmaco e PIP:
Nessuna Interazione Controindicata Da Riportare
1 interazioni farmacologiche di tipo Maggiore
Beers applicabili (7): di cui 3 non condizionati e 4 condizionati
STOPP applicabili (11): di cui 1 non condizionati e 10 condizionati

ACB score (2):
Definizione effetti anticolinergici: elevati (3 punti); (possibili 2 punti); (moderati 1 punto)
METOCLOPRAMIDE CLORIDRATO (Moderati)
TRAMADOLO CLORIDRATO (Moderati)

Rischio prolungamento intervallo QT (3):

TRAMADOLO CLORIDRATO (moderato)
AMOXICILLINA/ACIDO CLAVULANICO (moderato)
METOCLOPRAMIDE CLORIDRATO (basso)

Rischio Nefrotossicità (4):
PARACETAMOLO (basso)
METOCLOPRAMIDE CLORIDRATO (basso)
AMOXICILLINA/ACIDO CLAVULANICO (basso)
PARACETAMOLO (basso)

Proposta per ottimizzare la terapia: La terapia risulta appropriata. Prestare attenzione all'uso di tramadolo e metoclopramide al bisogno, soprattutto se assunti nella stessa giornata.

There are some important differences between the manually prepared report and the report generated automatically by the system. First, all diagnosis are counted in the preset report, including previous surgeries that would otherwise not be counted; secondly, short descriptions of each PIP have been rewritten to clearly state the condition and the possible risk associated with inappropriate drug use; third, non-conditioned PIPs are automatically labelled as valid for the patient, although this is not always true (i.e., use as needed in Patient 1); finally, all PIPs in the table are counted, so it is up to the consultant to correct the counts after verifying applicability of PIPs.

Despite these limitations, this tool represents a major step forward in improving the CDSS as it reduces the time needed to perform medication reviews, provides all relevant information on one screen and allows customisation of the output. Moreover, filters for choosing which alerts to display have also been implemented in the therapies tab to allow users to reduce alert fatigue (Figure 35). Indeed, previous studies [5,6] identified up to 90% of low-specific or non-relevant alerts in CDSSs. The high number of alerts and warning has been recognized as one of the most frequently mentioned problems of CDSSs, which could result in alert fatigue. This phenomenon has been described as ignoring or overriding CDSS warnings due to their excessive amount, including those that could be potentially clinically relevant. This could lead to decreased effectiveness of the CDSS and reduced compliance by healthcare professionals with the system.

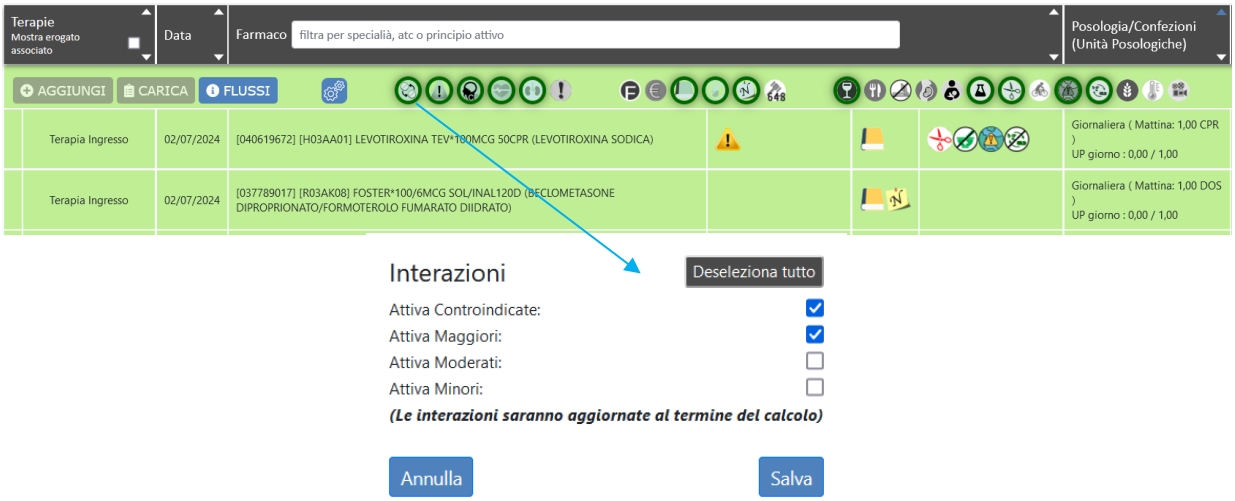


Figure 35. Filters on alerts implemented in the therapy tab of NavFarma®. By clicking on the alert icon, it is possible to choose which alerts to display; only selected alerts/icons (green circle and ticked boxes) will be display in the drug record

After testing the new features, the updated version of NavFarma® was made available to Infologic customers and webinars were organized on October 18th and November 26th, 2024, to illustrate the updated knowledge-base and new tools. During the webinars, I explained and showed to participants how the counselling tab works and how to use the preset report to perform medication review. Forty-four webinar invitations were sent to NavFarma® users, including hospital pharmacists and clinicians: 13 users participated to the first webinar, while 21 to the second one.

Ultimately, a short anonymous questionnaire was sent to the participants to the webinars to investigate their attitude towards the NavFarma® knowledge-base and usability in order to further improve the system. Nineteen out of 20 participants answered the questionnaire about NavFarma®. All respondents were hospital pharmacists; 2 stated that they have used NavFarma® in the past, 4 that they have been using NavFarma® for less than a year, 4 that have been using NavFarma® for more than a year and 9 declared they never used NavFarma®. The reasons for using NavFarma® include: therapy recognition and reconciliation (5 responses), assessment of prescription appropriateness and support in the choice of drugs (4 responses), identification of possible DDIs (4 responses), deprescription (2 responses), pharmacovigilance (1 response) and 3 undefined responses.

All alerts display by NavFarma® were considered useful or very useful by hospital pharmacists; some alerts also received negative ratings by 3 or more respondents (alerts considered not very useful or not useful):

- STOPPFrail criteria (3 responses);

- EU(7)-PIM list (3 responses);
- Drug-lab interactions (3 responses);
- ACB score (3 responses);
- Recommendations from clinical guidelines to treat specific diseases (3 responses);
- Video showing how to use specific medication device (4 responses);
- Presence of allergens (3 responses);
- Link to medication leaflet (5 responses);
- AIFA notes (5 responses);
- Low 648 (5 responses);
- Medication price (5 responses);
- Doping medications (5 responses);
- Storage temperature (5 responses);
- Potential pollutants to the water environment (5 responses).

Alerts to be printed in the documentations to be delivered to patients of major interest were interactions between drugs and food or beverage (18 responses), drug-herb interactions (15 responses), medications that may or may not be crushed (13 responses) and storage temperature (12 responses).

Overall, most users are satisfied with NavFarma® and believe that alerts and pictograms are complete and easy to understand. Only 4 respondents stated that NavFarma® is not easy to use and are not satisfied. Suggestions on how to improve NavFarma® include the inclusion of an active link to the bibliographic sources used to write the information, greater immediacy and evidence of the most relevant functions, including broken down by job profile, reduced number of alerts, proposed alternatives for splitable or non-crushable medications and export to Microsoft Word of the full description about DDIs.

4.3. DUR

Drug dispensing data of the ASL TO4 Territorial Pharmaceutical Services were collected in pseudonymized form to allow data to be collected at different times during the Ph.D. The ASL TO4 has periodically transferred monthly rough datasets to the DSTF after replacing the patients' social security number with a unique anonymous numeric code. Data cleansing was carried out at the DSTF and it involved removing records with missing or ambiguous data, standardizing the type of data reported in each column of the monthly datasets and merging them into annual dispensing datasets. Since the data collected covered a long-time interval, during which several IT companies succeeded each other in managing the ASL TO4 data, cleaning the datasets took quite a long time. This was necessary to be able to merge datasets with different types of information. Therefore, not all information is present for every month; for example, the province of residence of the patient or the code of the prescriber were not always available. Only the final clean datasets were retained by the DSTF as stipulated in the research agreement between the ASL TO4 and the DSTF for research purposes. The number of records before and after data cleaning are shown in Table 18.

Table 18. Collection of drug dispensing data (class A medications)[ii] of the ASL TO4

	2018	**2019**	**2020**	**2021**	**2022**	**2023 (until September 30)**
Total number of records	6,087,709	5,881,672	5,636,532	5,426,583	5,321,995	4,128,710
Number of drug-related records	5,598,394	5,550,127	5,219,903	5,200,334	5,223,424	4,106,012
Number of records after cleanup (%)	5,596,322 (91.9)	5,541,715 (94.2)	5,163,539 (91.6)	5,199,358 (95.8)	5,221,895 (98.1)	4,104,995 (99.4)
Number of unique individuals	366,238	370,865	322,430	339,848	356,430	340,939

Data from the AUSL VdA were transferred to the DSTF in the form of anonymized annual datasets; therefore, it will not be possible to collect additional data using the same key for transcoding patients' social security number. Data cleaning included the removal of records

[ii] Class A medications consist in all medications considered essential to ensure a good quality of life for citizens (e.g., drugs to treat chronic diseases, certain vaccines) that are reimbursed in full or in part by the Italian NHS.

associated with individuals not residing in the Valle d'Aosta Region. Table 19 summarizes dispensing data of drugs dispensed by community pharmacies of the AUSL VdA.

Table 19. Collection of drug dispensing data (class A medications) of the AUSL VdA

	2016	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Number of drug-related records	1,027,554	1,040,771	1,047,959	1,036,086	1,001,549	1,023,648	968,643
Number of records after cleanup (%)	994,608 (96.7)	978,465 (94.0)	985,372 (94.0)	1,015,389 (98.0)	973,466 (97.2)	994,371 (97.1)	934,454 (96.5)
Number of unique individuals	79,122	78,142	78,789	78,484	72,354	71,303	74,476

As specified in the method section, dispensing data of drugs dispensed by hospital pharmacies of the AUSL VdA, laboratory data obtained from healthcare facilities affiliated with the AUSL VdA and data on hospital admissions in the Valle d'Aosta Region were also collected. Drug dispensing data from hospital pharmacists of the AUSL VdA (class H medications)[iii] accounted for 89,394 records related to 11,044 individuals in the period between 01/01/2018 – 31/12/2022. Laboratory data were available for 84,355 unique individuals (878,819 records) in a period of 4 years (01/01/2018 – 31/12/2021), while data on hospital admissions from 01/01/2016 to 31/12/2021 had 20,013 records for 10,275 individuals.

[iii] Class H medications consist in medications usable only in hospitals or dispensed by hospital pharmacies to patients assisted by the hospital. Class H medications are completely free for the citizen as they are reimbursed by the Italian NHS.

4.3.1. Analysis on the use of antidiabetic drugs in the ASL TO4

Part of the results described below are included in scientific publications of which I am first author published during the Ph.D. programme, which are cited below:

- Armando LG, *et al*. Use of antidiabetic drugs in naïve diabetic patients of the ASLTO4 (Piedmont, Italy). Abstracts no. ESPACOMP-22-P33 from the 26th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Berlin, Germany, 17–19 November 2022. *Int J Clin Pharm* **2023**. doi: 10.1007/s11096-023-01537-5.
- Armando LG, *et al*. Assessing medication adherence and persistence to antidiabetic drugs in naïve patients from Piedmont (ASLTO4, Italy). Abstracts no. ESPACOMP-22-P34 from the 26th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Berlin, Germany, 17–19 November 2022. *Int J Clin Pharm* **2023**. doi: 10.1007/s11096-023-01537-5.
- Armando LG, *et al*. Describing treatment intensifications in naïve diabetic patients of the ASLTO4 (Piedmont Region, Italy). Abstracts no. ESPACOMP-23-P2 from the Abstracts of the 27th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Budapest, Hungary, 30 November–1 December 2023. *Int J Clin Pharm* **2024**; 46:328–353. doi: 10.1007/s11096-023-01688-5.
- Armando LG, *et al*. Assessing Therapeutic Choices and Adherence to Antidiabetic Therapy in Naïve Patients: A Retrospective Observational Study in a Local Health Authority of the Piedmont Region (Italy). *Healthcare* **2023**; 11:1655. doi: 10.3390/healthcare11111655.
- Armando LG, *et al*. Evaluation of the impact of regulatory measures that modify the prescription mode of antidiabetic drugs on the use of this drug class in adults living in the ASL TO4 (Piedmont, Italy). Poster presented at the 28th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Naples, Italy, 21-22 November 2024.

Antidiabetic drugs (ATC A10) were chosen by hospital pharmacists of the ASL TO4 as the main topic of interest because they represent the drug class with the highest expenditure for the ASL TO4. During January – December 2020, the total cost for antidiabetic drug expenditure was €5,792,174 for the ASL TO4 (*per capita* expenditure of €11.8); followed by antithrombotic drugs with an expenditure of €5,423,512 and by drugs for obstructive airway

disorders with €1,423,184. In fact, some medications reimbursed by the Italian NHS are purchased directly by ASL on behalf of community pharmacies, which then dispense them to citizens provided with a regular prescription: this distribution model is called "*distribuzione per conto*" (DPC) and concerns novel and expensive medications. It is promoted by health policies as it allows governing pharmaceutical spending reimbursed by the Italian NHS through regional tenders to purchase medications at a lower price than community pharmacies. Pharmaceutical expenditure of medications dispensed through DPC has increased in recent years not only for the ASL TO4 but also at the regional and individual ASL levels. This increase is accompanied by an increase in the number of packages dispensed, in part due to new medications being added to the DPC distribution channel, or from the shift regarding certain categories of medications from classical reimbursed distribution to DPC distribution (e.g., low molecular weight heparins). As for the ASL TO4, expenditure on antidiabetic drugs increased by 3.9%, from €5,792,174 in 2020 to €6,016,427 in 2021, while total expenditure on DPC drugs increased by 13.0% in 2020, ranking fourth in Piedmont (€17,463,709 *vs* regional expenditure of €145,811,740). Table 20 shows the latest available data for the Piedmont Region on DPC antidiabetic drug expenditure: ASL TO4 expenditure involves 72.0% oral antidiabetic drugs and 28.0% insulins. [228]

Table 20. Expenditure of antidiabetic drugs dispended by DPC during July 2020 – June 2021 for the Piedmont Region (total and by ASL) [228]

ASL	Expenditure (€)	Packages, n	Population, n	*Per capita* expenditure (€)
PIEDMONT REGION	**42,779,194.86**	**1,048,988**	**4,311,217**	**9.92**
ASL CITTÀ DI TORINO	8,943,133.62	215,060	855,545	10.45
ASL TORINO 4[a]	6,016,426.67	142,875	507,649	11.85
ASL TORINO 3	5,547,361.74	133,904	577,654	9.60
ASL ALESSANDRIA	4,299,757.45	109,531	446,506	9.63
ASL NOVARA	3,744,394.71	92,837	332,847	11.25
ASL CUNEO 1	3,183,059.47	79,409	403,582	7.89
ASL TORINO 5	3,069,375.18	77,766	299,791	10.24
ASL ASTI	1,891,660.54	48,582	202,538	9.34
ASL BIELLA	1,862,843.55	47,649	176,132	10.58
ASL CUNEO 2	1,637,409.90	37,780	164,785	9.94
ASL VERBANO CUSIO OSSOLA	1,313,437.27	34,132	171,896	7.64
ASL VERCELLI	1,270,334.76	29,463	172,293	7.37

[a] ASL TO4

Other reasons supporting the choice of this drug class as a research topic are related to the introduction of updated guidelines for the treatment of diabetes in July 2021 [229] and the publication of an AIFA note ("*Nota 100*") [230] allowing the prescription of inhibitors of

sodium-glucose transporter-2 (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and inhibitors of dipeptidyl peptidase-4 (DPP-4i) by GPs in January 2022.

First, drug dispensing data from community pharmacies of the ASL TO4 were analysed to describe how GPs of the ASL TO4 treat adult naïve patients with the first dispensation of an antidiabetic drug in 2019; patients died during the study period were excluded from the analysis. Figure 36 summarises the inclusion and exclusion criteria used to select the study population. Patient initiating antidiabetic therapy with metformin were selected to investigate therapy intensifications.

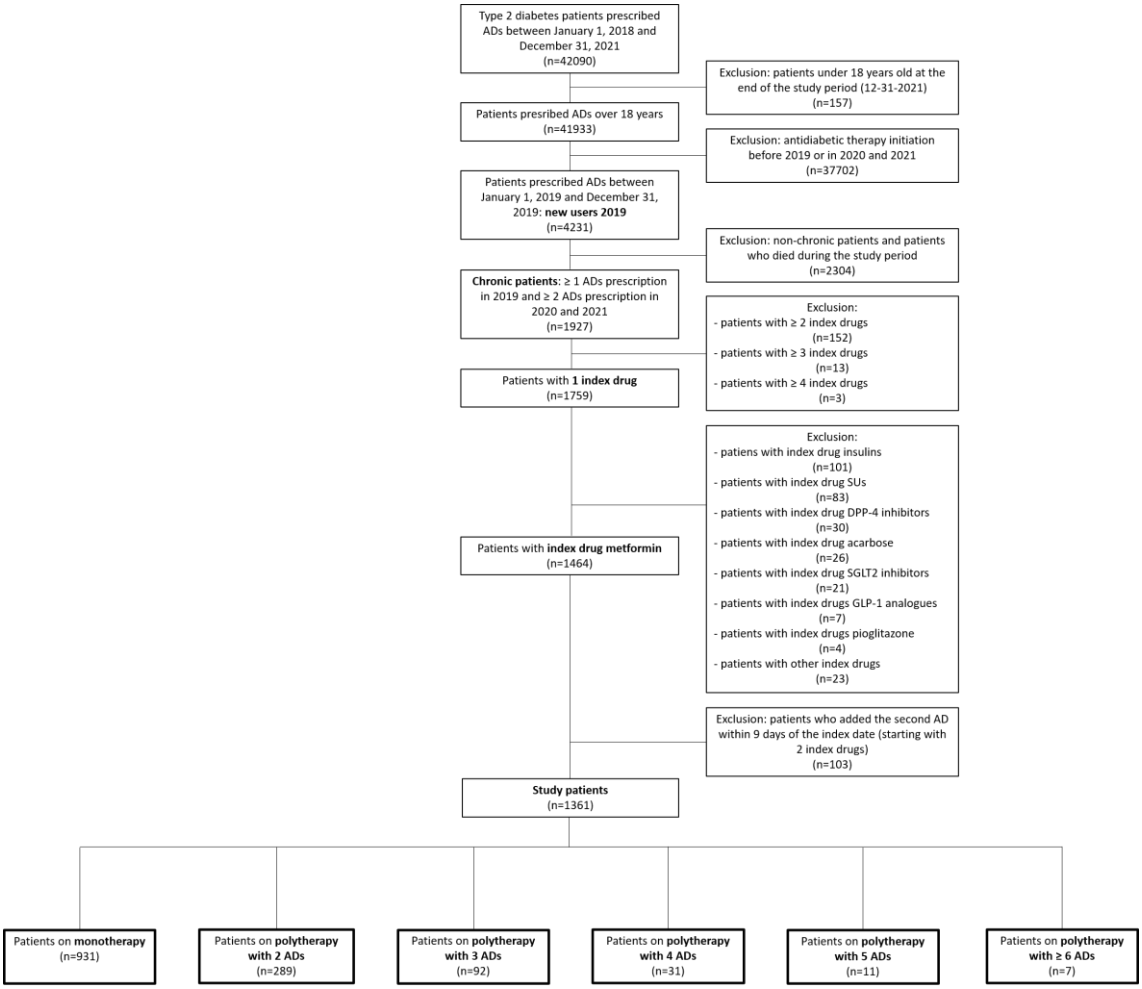


Figure 36. Flow-chart for selecting the study population. Abbreviations: AD, antidiabetic drug; SU, sulfonylureas; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose co-transporter 2; GLP-1, glucagon-like peptide-1. Source: Armando LG, *et al*. Healthcare 2023 [210]

A total of 1361 chronic patients who initiated antidiabetic therapy with metformin were identified. These patients were divided into 5 groups based on the number of antidiabetic

drugs dispensed during the study period (study period: 01/01/2019 – 31/12/2021). Their general characteristics are summarized in Table 21.

Table 21. General characteristics of the study population. Source: Armando LG, *et al*. Healthcare 2023 [201]

	1 AD	**2 ADs**	**3 ADs**	**4 ADs**	**≥5 ADs**
Patients, n (%)	931 (68.4)	289 (21.2)	92 (6.8)	31 (2.3)	18 (1.3)
Males	488 (52.4)	176 (60.9)	54 (58.7)	18 (58.1)	10 (55.6)
Females	443 (47.6)	114 (39.1)	38 (41.3)	13 (41.9)	8 (44.4)
Age, median [IQR]	71.0 [62.0-78.0]	65.0 [57.0-74.0]	64.5 [54.2-73.0]	64.5 [54.2-73.0]	62.0 [53.0-72.0]
Males	69.0 [62.0-75.0]	65.0 [56.0-73.0]	62.0 [53.0-70.0]	62.0 [53.0-70.0]	58.0 [53.0-73.0]
Females	72.0 [62.0-80.0]	67.0 [60.0-75.2]	66.0 [60.0-74.0]	66.0 [60.0-74.0]	64.0 [59.0-69.0]
Drugs of other classes co-prescribed during the study period, median [IQR]	10.0 [6.0-15.0]	11.0 [7.0-17.0]	9.0 [6.0-15.0]	12.0 [6.5-18.5]	14.0 [7.7-17.5]
Males	9.0 [5.0-15.0]	10.0 [5.7-15.0]	9.0 [5.0-10.0]	9.5 [7.0-17.0]	15.0 [13.0-22.5]
Females	12.0 [8.0-17.0]	13.0 [8.0-19.0]	9.5 [7.0-16.7]	16.0 [6.0-22.0]	9.0 [6.0-16.0]

Abbreviations: AD, antidiabetic drug; IQR, interquartile range

Median age decreases significantly (p<0.01, one way ANOVA test) as the number of different antidiabetic drugs dispensed to patients increases; this result may indicate that for older patients, GPs seem to follow established therapies, while toward younger patients they introduce adjustments in antidiabetic therapy more frequently, increasing the number of different drugs dispensed.

To better characterize this population, number and type of drugs other than antidiabetics dispensed to patients during the study period were analysed. Figure 37 shows the frequency of patients in each group with dispensations of other drug classes co-prescribed during the study period; drugs were classified according to the 14 ATC groups at level 1 (ATCL1), excluding ATC A10 – drugs used in diabetes.

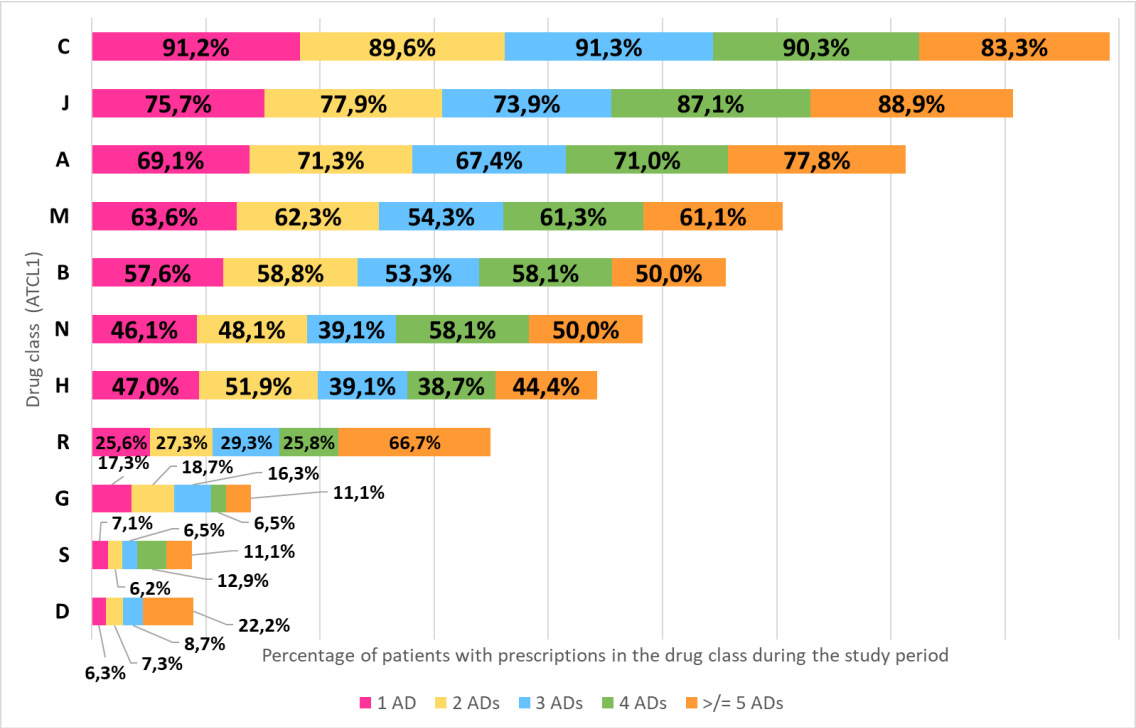


Figure 37. Frequency of patients in each group (different colors) with co-prescriptions for drugs other than antidiabetics during the study period according to their ATCL1. Only drug groups at ATCL1 with ≥10% prevalence in at least one group were considered. Source: Armando LG, *et al*. Healthcare 2023. [201]
Abbreviations: AD, antidiabetic drug; C, cardiovascular system; J, antiinfectives for systemic use; A, alimentary tract and metabolism; B, blood and blood forming organs; N, nervous system; H, systemic hormonal preparations; R, respiratory system; G, genito-urinary system and sex hormones; S, sensory organs; D, dermatologicals

No statistically significant differences were observed among the 5 groups. Drugs most commonly co-prescribed together with antidiabetics belong to the ATC group C (cardiovascular system drugs) for all groups except for the group with ≥5 antidiabetic drugs (orange in Figure 37), for which co-prescriptions of anti-infectives prevail (ATC group J). Next, we find co-prescriptions of anti-infective drugs (or of cardiovascular system drugs for patients with ≥5 antidiabetic drugs) and gastrointestinal system drugs (ATC group A). The same investigation was repeated with the co-dispensed drugs classified according to their ATCL2 to identify comorbidities according to the Rx-Risk Comorbidity Index as described by Pratt *et al*. [231] Comorbidities were then classified as diabetes-concordant or diabetes-discordant according to the definition provided by Piette *et al*. [232] Table 22 shows the medical conditions included in the adapted Rx-Risk Index.

Table 22. Frequency of patients in each group with comorbidities according to the adapted version of the Rx-Risk Comorbidity Index. The index was adapted for our study to use the ATCL2 to map the diseases. Only comorbidities with ≥10% prevalence in at least one subgroup were considered. Source: Armando LG, *et al*. Healthcare 2023 [201]

Drug classes (ATCL2)	Related medical conditions	Patients with prescriptions in the drug class during the study period (%)				
		1 AD	2 ADs	3 ADs	4 ADs	≥5 ADs
DM-concordant conditions						
C01, C04, C05, C07, C08, B01	Cardiovascular/cerebrovascular diseases and heart diseases	100.0	100.0	100.0	100.0	100.0
C02, C03, C09	Hypertension	100.0	100.0	94.6	100.0	77.8
C10	Hyperlipidemia	62.5	69.6	80.4	64.5	61.1
M04	Hyperuricemia/Gout	18.0	20.4	13.0	16.1	11.1
DM-discordant conditions						
J01-J07	Infectious diseases	83.8	87.5	88.0	100.0	100.0
A02	Acid related disorders	57.1	60.2	54.3	67.7	77.8
M01-M03, M09	Inflammatory/Rheumatic disorders	56.6	52.6	43.5	48.4	55.6
H02	Corticosteroid-responsive diseases	40.7	45.7	33.7	32.3	44.4
A08-A09, A11-A16	Nutrition-related diseases	36.5	32.9	29.3	29.0	33.3
N02	Pain, including migraine	29.9	29.4	23.9	41.9	33.3
N06, N07	Depression and other mental disorders	21.4	21.1	20.7	19.4	27.8
R03	Chronic obstructive airways diseases	19.9	20.8	23.9	22.6	61.1
A03-A04, A06- A07	Gastrointestinal disorders and nausea	19.9	19.4	18.5	22.6	50.0
B03	Anemia	17.7	17.3	9.8	6.5	11.1
G01-G04	Diseases of the genito-urinary system, including benign prostatic hypertrophy	17.4	19.0	16.3	6.5	11.1
H03	Thyroid disorders	12.5	13.5	7.6	9.7	11.1
R01-R02, R05-R07	Respiratory diseases	10.2	9.7	10.9	3.2	11.1
N03	Epilepsy	9.7	13.5	5.4	29.0	27.8
D01-D11	Dermatological diseases, including psoriasis	7.3	8.3	9.8	0.0	22.2
S01, S03	Eye disorders, including glaucoma	7.1	6.2	6.5	12.9	11.1
N05	Psychotic illnesses	3.3	5.5	3.3	6.5	11.1

Abbreviations: AD, antidiabetic drug; C01, cardiac therapy; C04, peripheral vasodilators; C05, vasoprotectives; C07, beta blocking agents; C08, calcium channel blockers; B01, antithrombotic agents; C02, antihypertensives; C03, diuretics; C09, agents acting on the renin-angiotensin system; C10, lipid modifying agents; M04, antigout preparations; J01, antibacterials for systemic use; J07, vaccines; A02, drugs for acid related disorders; M01, anti-inflammatory and antirheumatic products; M03, muscle relaxants; M09, other drugs for disorders of the muscolo-skeletal system; H02, corticosteroid for systemic use; A08, antiobesity preparations; A09, digestives, including enzymes; A11, vitamins; A16, other alimentary tract and metabolism products; N02, analgesics; N06, psychoanaleptics; N07, other nervous system drugs; A03, drugs for functional gastrointestinal disorders; A04, antiemetics and antinauseants; A06, drugs for constipation; A07, antidiarrheals, intestinal anti-inflammatory/anti-infective agents; R03, drugs for obstructive airway diseases; B03, antianemic preparations; G01, gynecological antiinfectives and antiseptics; G04, urologicals; H03, thyroid therapy; R01, nasal preparations; R02, throat preparations; R05, cough and cold preparations; R07, other respiratory system products; N03, antiepileptics; D01, antifungals for dermatological use; D11, other dermatological preparations; S01, ophthalmologicals; S03, ophthalmological and otological preparations; N05, psycholeptics

All patients in the 5 groups had concomitant conditions associated with the use of drugs to treat cardiovascular and/or cerebrovascular diseases (ATC C01, C04-C08, B01), while antihypertensives (ATC C02, C03, C09) were prescribed to most patients during the study period. These results are compatible with the characteristics of diabetes mellitus, which is often associated with hypertension and cardiovascular complications. [233-235] Moreover, it was observed a high proportion of patients with dispensations of antiinfectives (ATC J01-J07), which can be explained by the fact that no limit was placed on the number of concurrent dispensations, so acute illnesses were also included. The number of patients with a given comorbidity was comparable in the 5 groups, with the exception of chronic obstructive airways diseases (ATC R03), gastrointestinal disorders (ATC A03, A04, A06, A07), epilepsy (ATC N03) and dermatological diseases (ATC D01-D11), for which a higher prevalence was observed in the group of patients with ≥5 antidiabetic drugs. This may indicate that patients who adjusted their antidiabetic therapy more frequently during the study period (≥5 different antidiabetic drugs) typically received more prescriptions for drugs of different classes by their GP, which may be associated with a higher number of acute or chronic comorbidities.

More than half of the study population (931 patients, 68.4%) remained on metformin monotherapy throughout the study period, while 31.6% of patients (430 out of 1361) added one or more antidiabetic drugs to the initial therapy with metformin; therefore, therapy intensifications were evaluated for these patients. Median time to first intensification was 171.0 days (IQR 34.0-553.0), longer for the 2-antidiabetic drug group (251.0 days, IQR 53.0-614.0) and shorter for the ≥5-antidiabetic drug group (36.0 days, IQR 24.0-111.0). Table 23 shows the frequencies of antidiabetic drug classes used to intensify metformin monotherapy for the sample analysed.

Table 23. Intensifications of metformin monotherapy in naïve chronic diabetic patients. Any change of antidiabetic drug class dispensed during the study period was considered as an intensification; consecutive dispensations of drugs belonging to the same antidiabetic drug class were not considered as therapy intensifications. Source: Armando LG, *et al*. Healthcare 2023 [201]

Drug class with which therapy was intensified	Patients, n (%)
1 intensification (n=430, 100.0%)	
SGLT-2 inhibitors	**111 (25.8)**
Sulfonylureas	**79 (18.4)**
Combinations of oral antidiabetics	**64 (14.9)**
Insulins	55 (12.8)
GLP-1 analogues	54 (12.6)
DPP-4 inhibitors	41 (9.5)
Repaglinide	17 (4.0)
Pioglitazone	6 (1.4)
Acarbose	3 (0.7)
2 intensifications (n=141, 32.8%)	
Insulins	**35 (24.8)**
Combinations of oral antidiabetics	**28 (19.9)**
SGLT-2 inhibitors	**19 (13.5)**
GLP-1 analogues	18 (12.8)
Sulfonylureas	12 (8.5)
DPP-4 inhibitors	12 (8.5)
Switch to a different active ingredient from a drug class previously used	11 (7.8)
Pioglitazone	4 (2.8)
Repaglinide	1 (0.7)
Acarbose	1 (0.7)
3 intensifications (n=49, 11.4%)	
GLP-1 analogues	**11 (22.4)**
Switch to a different active ingredient from a drug class previously used	**10 (20.4)**
Insulins	**10 (20.4)**
Sulfonylureas	5 (10.2)
SGLT-2 inhibitors	5 (10.2)
Combinations of oral antidiabetics	4 (8.2)
DPP-4 inhibitors	2 (4.1)
Repaglinide	1 (2.0)
Pioglitazone	1 (2.0)
≥4 intensifications (n=20, 4.6%)	
Insulins	**7 (35.0)**
Switch to a different active ingredient from a drug class previously used	**6 (30.0)**
Combinations of oral antidiabetics	**3 (15.0)**
SGLT-2 inhibitors	2 (10.0)
DPP-4 inhibitors	1 (5.0)
GLP-1 analogues	1 (5.0)

Abbreviations: SGLT-2, sodium-glucose co-transporter 2; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase 4

Seventy-eight different combinations of two or more different antidiabetic drug classes used to intensify metformin monotherapy were identified. The most frequent were combinations of two antidiabetic drug classes:

- Metformin + SGLT-2i (82 patients, 19.1%);
- Metformin + sulfonylurea (59 patients, 13.7%);
- Metformin + combination of oral antidiabetic drugs (48 patients, 11.2%);
- Metformin + GLP-1 RA (32 patients, 7.4%);
- Metformin + insulin (11 patients, 2.6%).

Switching or adding SGLT-2i to metformin is considered appropriate as second-line therapy according to the guidelines to treat type 2 diabetes mellitus [236], particularly in subjects with previous cardiovascular events. On the contrary, the use of sulfonylureas alone or in combination with other antidiabetic drugs has been associated with increased body weight and increased risk of hypoglycaemia; therefore, they should be avoided or limited to patients who cannot be treated with safer drugs. [237] The following figures (Figures 38-41) represent the alluvial diagrams of therapy intensifications for the 5 patient groups analysed.

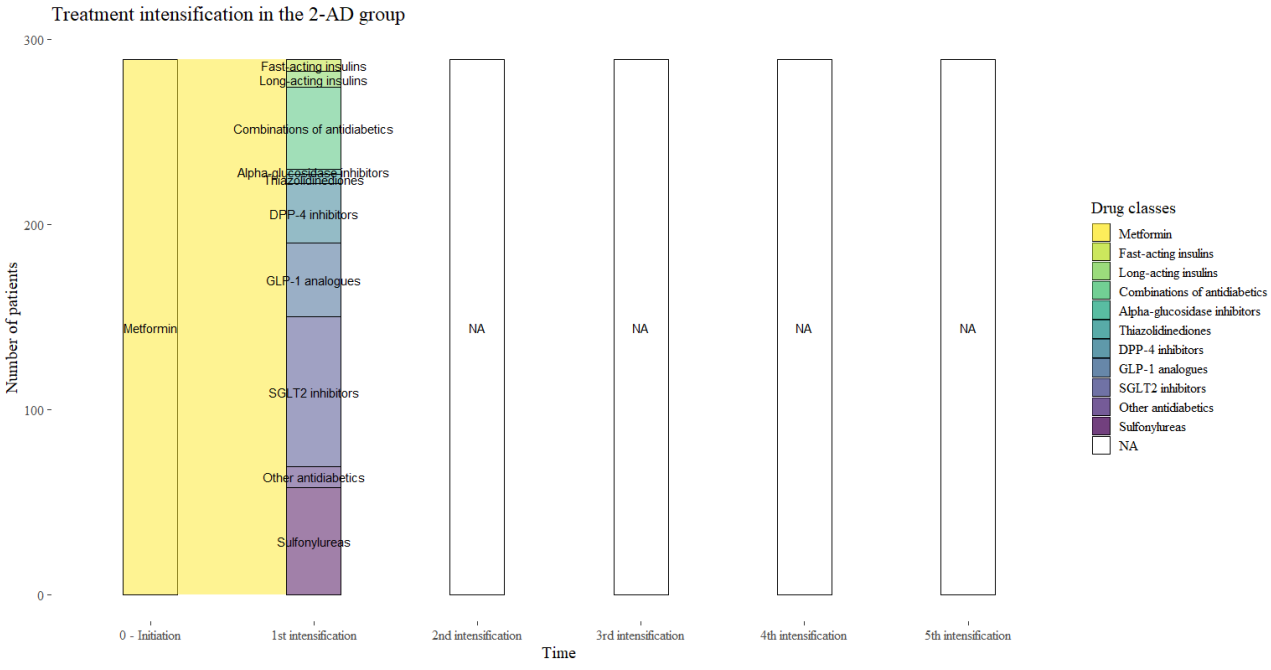


Figure 38. First intensification of therapy in the 2-antidiabetic drugs (AD) group.

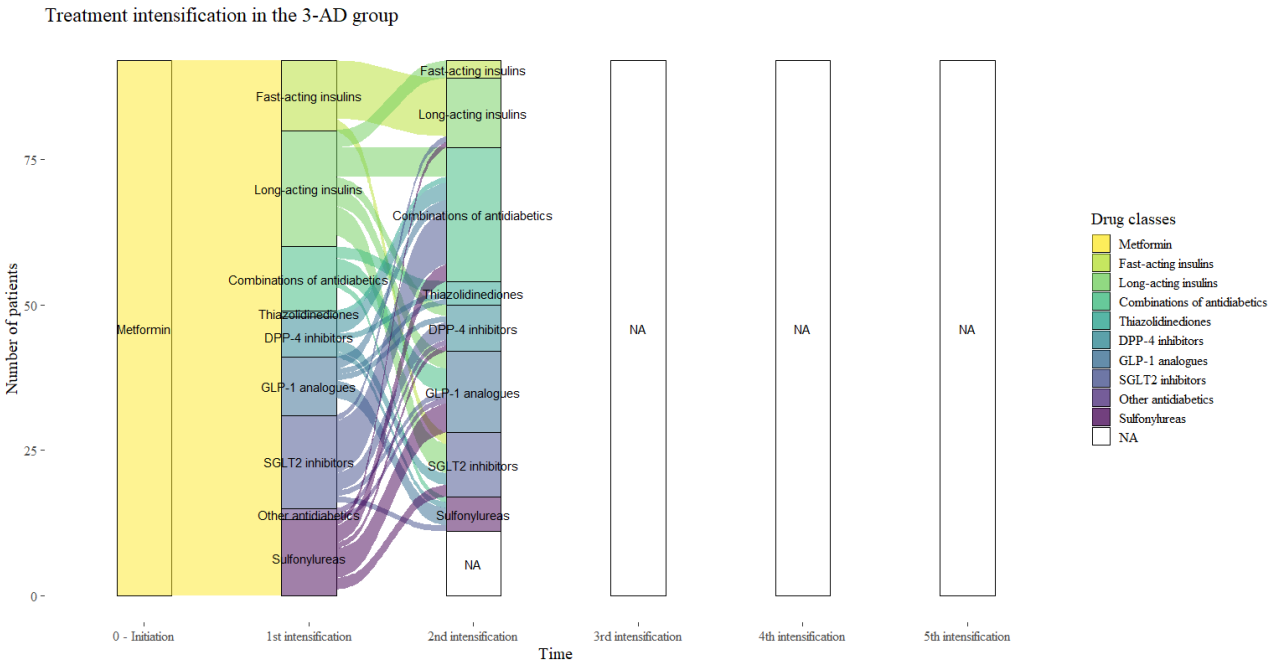


Figure 39. First and second intensification of therapy in the 3-antidiabetic drugs (AD) group. NA are patients who intensified antidiabetic therapy by switching to a different active ingredient of a drug class already used.

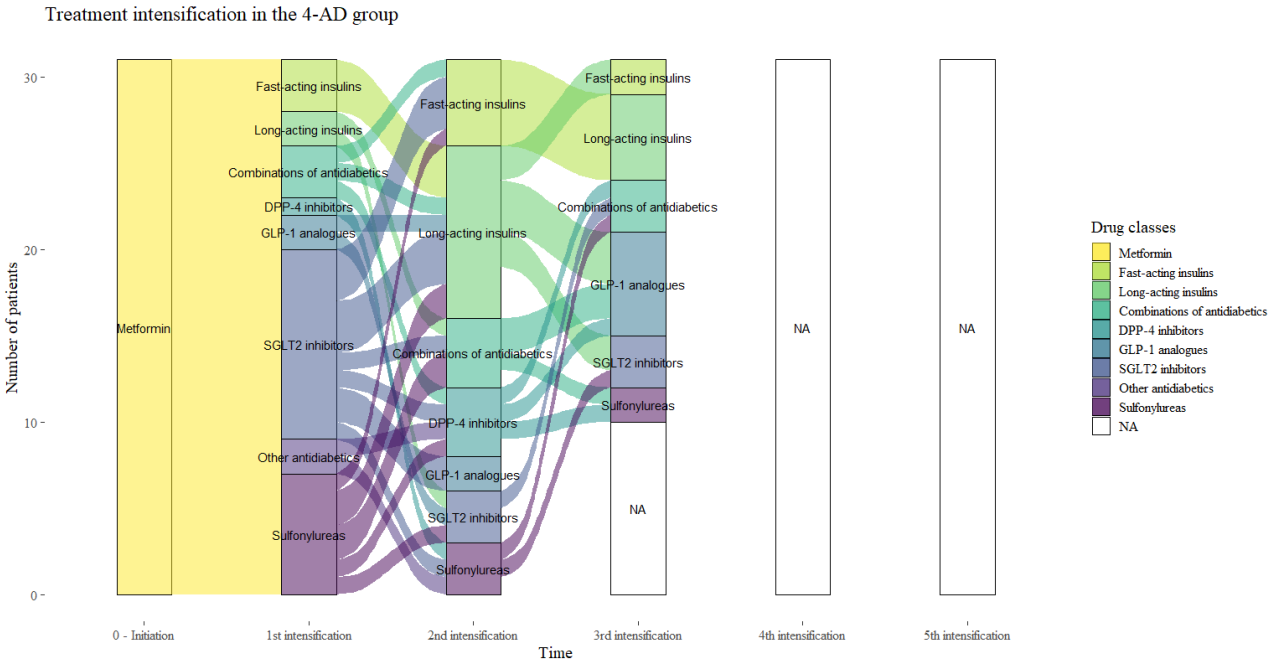


Figure 40. First, second and third intensification of therapy in the 4-antidiabetic drugs (AD) group. NA are patients who intensified antidiabetic therapy by switching to a different active ingredient of a drug class already used.

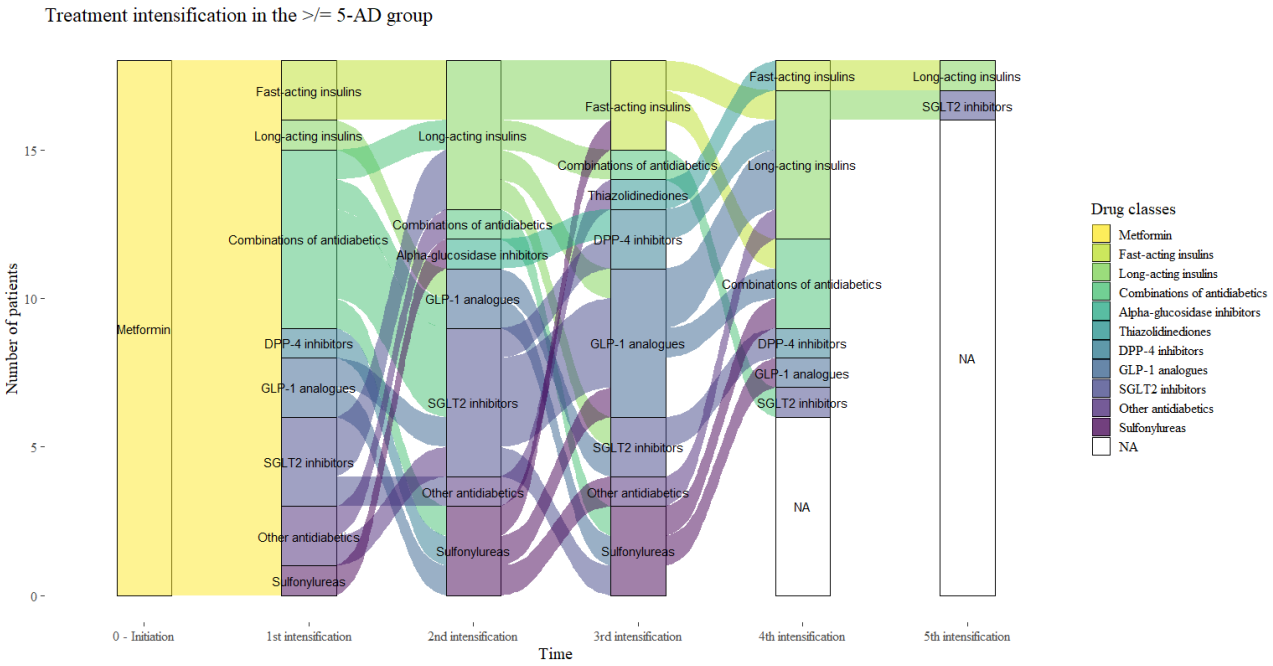


Figure 41. First, second, third, fourth and fifth intensification of therapy in the ≥5-antidiabetic drug (AD) group. NA 4th intensification are patients who intensified antidiabetic therapy by switching to a different active ingredient of a drug class already used. NA 5th intensification are patients with only 4 intensifications

For more details about the analysis on intensifications of antidiabetic therapy in a population of naïve patients of the ASL TO4, please refer to the related article published by the research group I am part of in the Healthcare journal in 2023. [201]

Secondly, drug dispensing data were used to measure medication adherence and persistence to antidiabetic therapy in the five group of patients included in the analysis. Medication adherence was measured as the continuous multiple-interval measure of medication availability (CMA) during the follow-up (follow-up: period between first and last dispensation in the study period for each patient) using the AdhereR package [238,239] that leverages the R programming language. Persistence was considered as the number of days a patient remains on treatment with the study drug without interruptions of more than a predefined gap: persistence values measured after one year from therapy initiation were compared with a 60- and 90-day gap. The ratio of the total amount of active ingredient dispensed to the DDD was used to measure the duration of each dispensation.

Adherence to overall antidiabetic therapy varies notably between the monotherapy group and patients with more than one antidiabetic drug: indeed, median CMA was 46.0% for patients on metformin monotherapy, while it ranged from 60.0% to 63.0% for the other groups. No differences were observed between males and females and between patients

over and under 70 years of age. Patients were than stratified according to their CMA value into adherent (CMA ≥80%), partially adherent (40% ≤ CMA < 80%) and non-adherent (CMA <40%). The percentage of partially adherent patients was the highest in all groups. As shown in Figure 42, as the complexity of antidiabetic therapy increases, the percentage of adherent patients increases and that of non-adherent patients decreases, with the exception of the last subgroup (≥5 antidiabetic drugs).

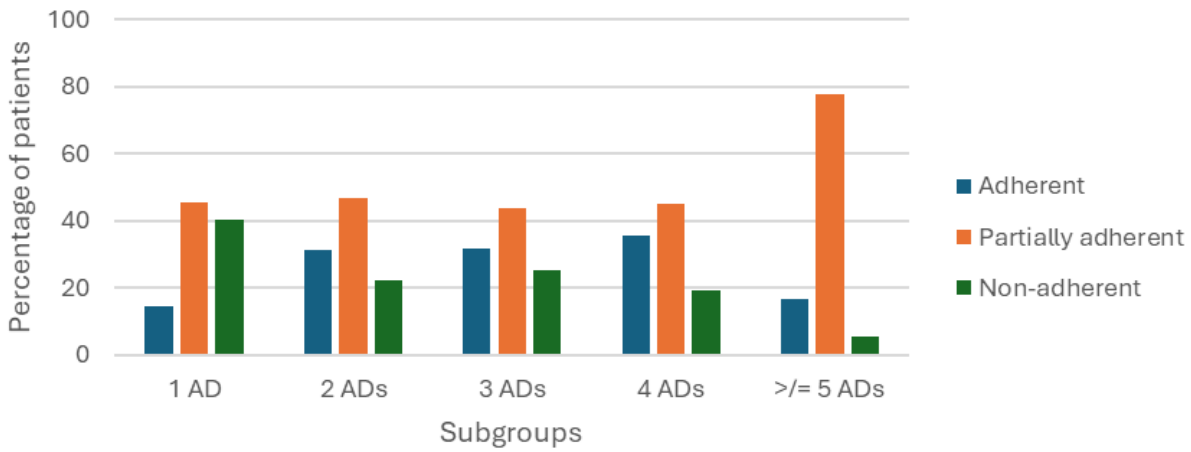


Figure 42. Results of medication adherence analysis for naïve diabetic patients of the ASL TO4

Persistence to overall antidiabetic therapy was measured one year after the index date for the five groups of patients separately. Table 24 shows the results of persistence analysis.

Table 24. Discontinuation rate to antidiabetic therapy (percentage of patients discontinuing therapy for a period longer than the allowed gap) and median time to discontinuation to antidiabetic therapy (follow-up: 1 year from the index date)

	1 AD	2 ADs	3 ADs	4 ADs	≥5 ADs
Allowed gap: 60 days					
Discontinuation rate at 1-year [95% CI]	56.2 [53.0-59.4]	48.4 [42.7-54.2]	57.6 [47.5-67.7]	48.4 [30.8-66.0]	44.4 [21.5-67.4]
Time to discontinuation (days), median [IQR]	256.0 [77.5-365.0]	365.0 [91.0-365.0]	294.0 [104.2-365.0]	365.0 [84.5-365.0]	365.0 [127.8-365.0]
Allowed gap: 90 days					
Discontinuation rate at 1-year [95% CI]	36.3 [33.2-39.4]	37.7 [32.1-43.3]	38.0 [28.1-48.0]	38.7 [21.6-55.9]	33.3 [11.6-55.1]
Time to discontinuation (days), median [IQR]	365.0 [184.5-281.9]	365.0 [172.0-365.0]	365.0 [156.5-365.0]	365.0 [147.5-365.0]	365.0 [265.0-365.0]

Abbreviations: AD, antidiabetic drug; CI, confidence interval; IQR, interquartile range

The percentage of patients discontinuing antidiabetic therapy one year after the index date is significantly reduced by extending the width of the admitted gap. However, a high proportion of naïve patients discontinue antidiabetic therapy temporarily or permanently approximately 1 year from the index date, regardless of both the complexity of antidiabetic therapy and the allowed gap between dispensations. Patients with ≥5 antidiabetic drugs show the highest persistence. Considering the overall population, statistically significant differences were observed between males and females (p=0.05, log-rank test), between patient older and younger than 70 years of age (p<0.05) and between patients with and without therapy intensifications (p<0.0001, Figure 43).

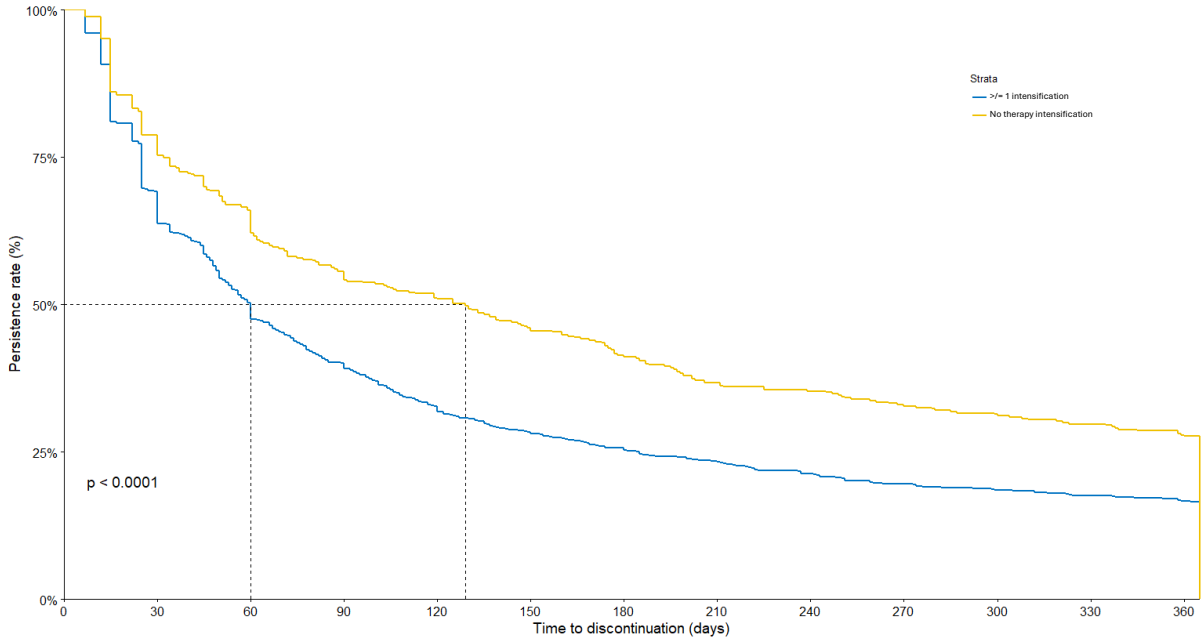


Figure 43. Kaplan-Meier curves of persistence to antidiabetic therapy one year after index date for enrolled patients with or without therapy intensifications during the study period

Finally, drug dispensing data collected from the ASL TO4 in the period 01/06/2020 – 30/09/2023 were used to investigate the impact of the introduction of the "*Nota 100*" [240] by the AIFA in 2022. Notes by the AIFA regulate the prescription of medications reimbursed by the Italian NHS to patients with specific conditions. Particularly, the "*Nota 100*" was published in the Italian *Gazzetta Ufficiale* on January 21, 2022, allowing for GPs to autonomously prescribe SGLT-2i, GLP-1 RA and DPP-4i to their patients diagnosed with type 2 diabetes mellitus without intermediation by the diabetologist. The implementation of the "*Nota 100*" is supported by numerous evidence demonstrating the benefits of SGLT-2i, GLP-1 RA and DPP-4i in reducing glycated haemoglobin (HbA1c). [230] In addition, several

randomized clinical trials [241-243] demonstrated relevant benefits for SGLT-2i and GLP-1 RA in terms of reduction of both major cardiovascular events and mortality in patients with established cardiovascular disease or multiple risk factors. SGLT-2i demonstrated a greater effect on the reduction of hospitalizations for heart failure, while GLP-1 RA appear to have relevant effects on reducing the incidence of strokes. Moreover, there are evidence [244,245] documenting a positive effect of SGLT-2i and, to a lesser extent, of GLP-1 RA on the progression of renal damage. Regarding DPP-4i, the results of randomized clinical trials [246] indicate no benefit on renal and cardiovascular outcomes; however, given their good tolerability profile, manageability and ease of use, they should be considered as second-choice drugs for patients with CKD or at risk of cardiovascular disease. [230] Although different guidelines [247-251] or the treatment of type 2 diabetes mellitus classify diabetic patients variably according to specific characteristics, they all agree that SGLT-2i or GLP-1 RA should be considered as first- or second-choice therapy, alone or in combination with metformin for patients with or at risk of atherosclerotic cardiovascular disease (ASCVD).

Dispensations of A10 drugs were analysed for 39,469 patients aged ≥18 years with at least one dispensation of a study drug during the study period. Table 25 shows the general characteristics of the selected population.

Table 25. General characteristics of patients using antidiabetic drugs during 01/06/2020 – 30/09/2023 living in the ASL TO4. Underlined drugs are included in the "*Nota 100*"

A10 drug	Patients, n (%)	Males, n (%)	Median age [IQR]
Metformin	29,106 (73.7)	16,084 (55.3)	70.0 [63.0-77.0]
Insulins	17,008 (43.1)	9286 (54.6)	71.0 [61.0-78.0]
SGLT-2 inhibitors	9330 (23.6)	5812 (62.3)	67.0 [60.0-73.0]
GLP-1 analogues	6719 (17.0)	3979 (59.2)	66.0 [58.0-73.0]
Sulfonylureas	6615 (16.8)	3591 (54.3)	73.0 [67.0-80.0]
Metformin + SGLT-2 inhibitors	3400 (8.6)	2183 (64.2)	65.0 [58.0-71.0]
DPP-4 inhibitors	3383 (8.6)	1731 (51.2)	78.0 [72.0-83.0]
Metformin + DPP-4 inhibitors	2021 (5.1)	1151 (57.0)	73.0 [67.0-79.0]
DPP-4 inhibitors + SGLT-2 inhibitors	1604 (4.1)	916 (57.1)	68.0 [61.0-74.0]
Repaglinide	1052 (2.7)	563 (53.5)	78.0 [70.0-84.0]
Acarbose	733 (1.9)	360 (49.1)	73.0 [67.0-80.0]
Pioglitazone	695 (1.8)	418 (60.1)	72.0 [65.0-79.0]
Metformin + pioglitazone	542 (1.4)	356 (65.7)	71.0 [64.0-76.0]
Metformin + sulfonylureas	504 (1.3)	270 (53.6)	77.0 [71.0-83.0]
Pioglitazone + DPP-4 inhibitors	115 (0.3)	58 (50.4)	74.0 [68.0-79.0]
Sulfonylureas + pioglitazone	24 (0.1)	16 (66.7)	73.0 [68.0-80.0]

Metformin was prescribed to nearly twice as many patients as other A10 drug classes (73.7%), while insulins were prescribed to almost half of the study population (43.1%).

Dispensations of SGLT-2i, GLP-1 RA and sulfonylureas had similar frequencies of use, with 23.6%, 17.0% and 16.8% of patients using these classes, respectively. Other A10 drug classes were prescribed to less than 10% of the population. For all drug classes, the proportion of men (except for acarbose) and individuals with 65 years or older prevail. Patients received an average of 2 different A10 drug classes in the study period, ranging from 1 to 10. These results confirm the extensive use of sulfonylureas in the ASL TO4 observed by the previous analysis.

Weekly prevalence of users of antidiabetic drugs was the outcome of this analysis, as defined in the methods section of this dissertation. The DDD was used as prescribed daily dose and a grace period of 1.5 times the duration of the dispensation was adopted to consider the variable prescription duration of all antidiabetic drugs on the Italian market. The study period was divided into two segments: pre-intervention (from June 1, 2020 to the introduction of the "*Nota 100*" on January 21, 2022 – 19 weeks) and post-intervention (from January 21, 2022 to September 30, 2023 – 19 weeks); ARIMA model was used to predict the weekly prevalence of antidiabetic users in absence of the "*Nota 100*" (counterfactual), compared with observed values. The results of the comparison are shown in Figures 44 and 45.

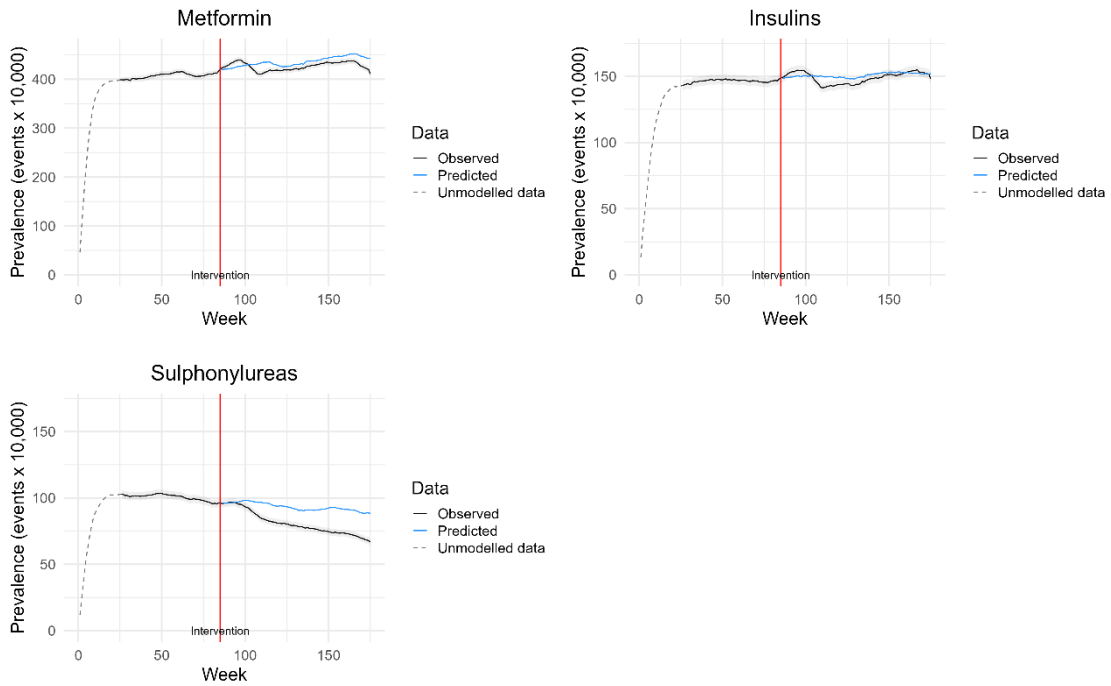


Figure 44. Weekly prevalence of users of the most commonly used antidiabetic drugs not included in the "*Nota 100*". The first 25 weeks of the study period (gray dashed line) were not considered for prediction. The blue lines and the black lines represent the predicted and the observed values, respectively. The red line represents the date of the intervention (January 21, 2022). 95% CI (gray area) was measured for the observed values using the Clopper-Pearson method

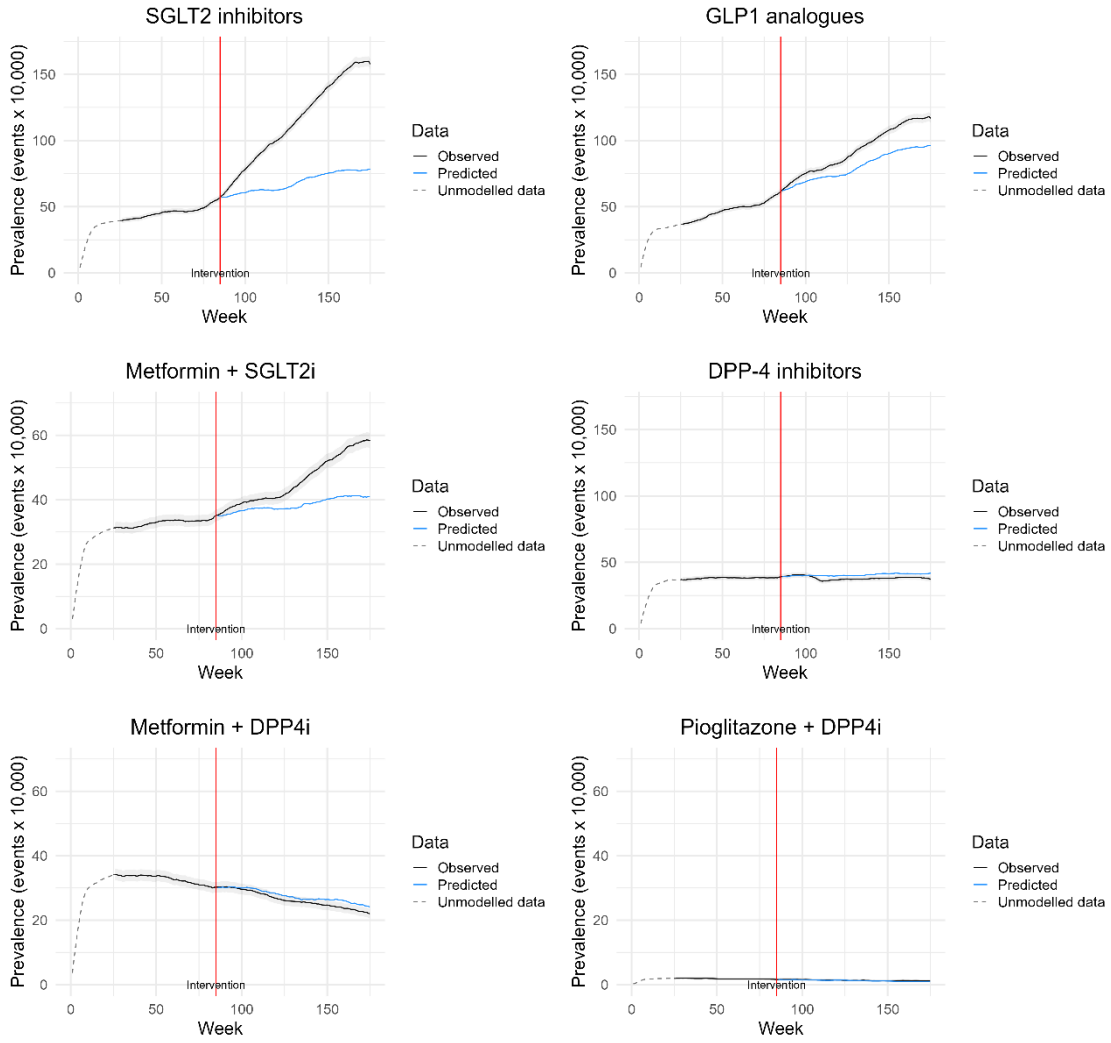


Figure 45. Weekly prevalence of users of the drug classes included in the "*Nota 100*". The first 25 weeks of the study period (gray dashed line) were not considered for prediction. The blue lines and the black lines represent the predicted and the observed values, respectively. The red line represents the date of the intervention (January 21, 2022). 95% CI (gray area) was measured for the observed values using the Clopper-Pearson method

As expected, ITS analysis showed a consistent increase in the use of SGLT-2i and GLP-1 RA, accompanied by a slight decrease in the use of metformin and insulins; particularly, insulins remain the only pharmacological therapy available to treat type 1 diabetes mellitus, so their prevalence of use has not declined dramatically. Prevalence of use of sulfonylureas decreased but not as consistently as expected, while contrary to expectation, the use of DPP-4i did not increase after the introduction of the "*Nota 100*". Sulfonylureas have been used for many decades, having a well-established efficacy and safety profile that make them an established option for many GPs. This long history of use could contribute to therapeutic inertia, which indicates the tendency of GPs not to modify or intensify a therapy out of routine despite evidence of new and safer alternatives. [252,253] The low use of DPP-4i could

be justified by the intrinsic characteristics of this drug class. Specifically, their glucose-lowering efficacy is moderate compared to SGLT-2i and GLP-1 RA; additionally, they lack the cardiovascular and renal benefits demonstrated by other drug classes, as well as the effect on body weight reduction, that are crucial for many diabetic patients. These elements may contribute to the limited success of DPP-4i among patients.

From the ITS analysis, no changes in the prevalence of use of other antidiabetic drug classes were observed before and after the introduction of the "*Nota 100*": this could mean that the drug classes included in the "*Nota 100*" are prescribed in addition to existing antidiabetic therapy rather than as a replacement.

A summary of these results has been included in a briefing paper for GPs of the ASL TO4 including recommendations on the appropriate prescription of antidiabetic drugs. The results of the paper were presented by Prof. Clara Cena and the undersigned from January 2025 in meetings organized between GPs of the ASL TO4 and hospital pharmacists of the Territorial Pharmaceutical Services of the ASL TO4.

4.3.2. Analysis on the use of lipid-lowering drugs in the AUSL VdA

Lipid-lowering drugs (ATC C10) were chosen as a topic of investigation because hospital pharmacists of the Valle d'Aosta Region found a consistently underutilisation of these drug class compared to other Italian regions. According to the national report on medicines use in Italy of 2022 by the OsMed [60], Valle d'Aosta is the Italian region with the lowest prevalence of use of lipid-lowering drugs (9.7% *vs* a national value of 14.4%), a value comparable to one observed in the autonomous provinces of Trento and Bolzano (Figure 46). Other reasons of interest lie in the facts that the use of lipid-lowering drugs is constantly increasing over the last nine years and that statins represent the drug class with the higher *per capita* expenditure and consumption in 2022. [60] Therefore, a research agreement between the AUSL VdA and the DSTF was put in place to investigate the use of lipid-lowering drugs in the Valle d'Aosta Region and to support hospital pharmacists in the identification of areas of intervention to improve the prescription of these drugs by physicians.

Regione	Prevalenza d'uso (%)			Età mediana
	maschi	femmine	totale	
Piemonte	13,5	12,5	13,0	72
Valle d'Aosta	10,4	9,1	9,7	72
Lombardia	13,4	12,3	12,9	71
PA Bolzano	9,9	8,9	9,4	73
PA Trento	12,4	11,5	11,9	72
Veneto	13,9	12,4	13,2	72
Friuli VG	14,1	13,1	13,6	73
Liguria	13,7	13,2	13,5	73
Emilia R.	14,6	14,5	14,5	71
Toscana	14,1	13,5	13,8	73
Umbria	14,6	14,1	14,3	72
Marche	16,4	16,2	16,3	72
Lazio	14,6	14,9	14,7	71
Abruzzo	14,7	14,6	14,6	70
Molise	14,3	14,4	14,4	71
Campania	15,9	16,5	16,2	68
Puglia	16,0	16,6	16,3	70
Basilicata	15,5	16,1	15,8	70
Calabria	15,5	15,8	15,7	69
Sicilia	15,6	16,5	16,1	70
Sardegna	14,8	16,4	15,6	71
Italia	**14,5**	**14,3**	**14,4**	**71**

Figure 46. Exposure to class A hypolipidemic drugs by region [60]

First, a prevalence of users of lipid-lowering drugs of 9.8% was found in 2022 in the population of the Valle d'Aosta Region. This result covers both class A and class H lipid-lowering drugs and confirms OsMed data. Annual prevalences of C10 users are shown in

Figure 47. An increase in prevalence can be observed over the study period, with the exception of 2020 where prevalence drops slightly from previous years; this could be explained by the restrictive measures introduced during the Covid-19 pandemic.

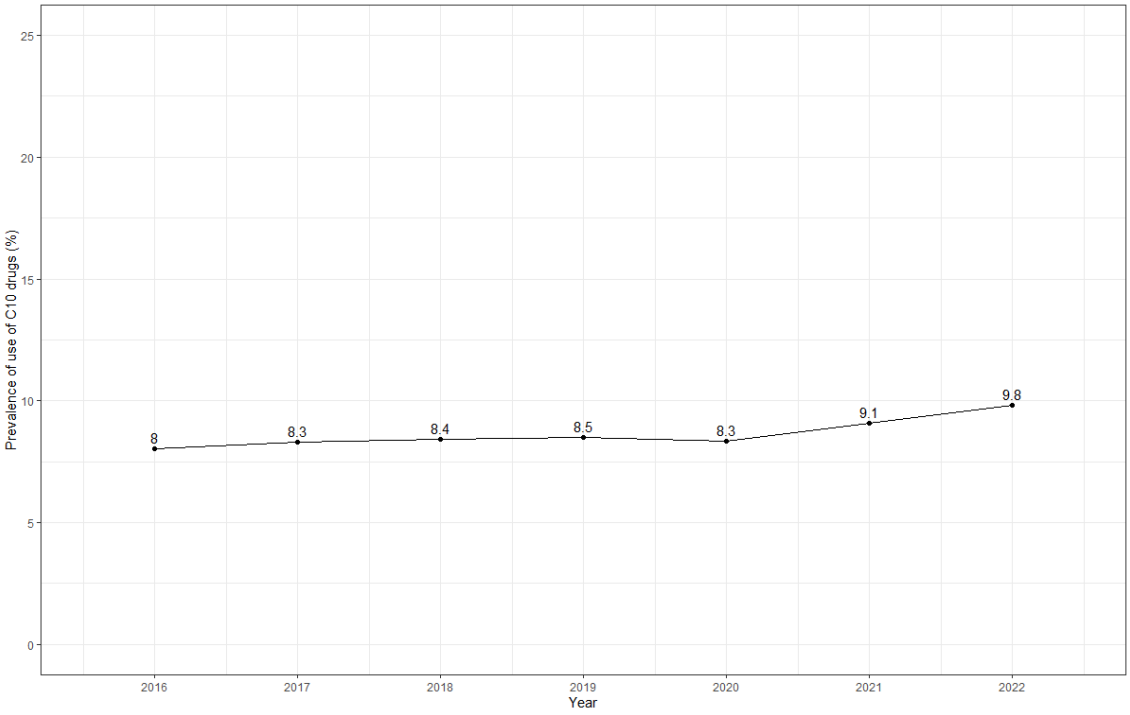


Figure 47. Annual prevalence of use of lipid-lowering drugs in the Valle d'Aosta Region. Data on the general population of the Valle d'Aosta Region was extrapolated from the *Istituto Nazionale di Statistica* (Istat) [254]

During the study period, a total of 403,211 dispensations of both class A and class H C10 medications and 18,915 unique subjects were recorded. Given the large amount of data collected, during the months of the Ph.D. general analyses of hypolipidemic drug use were conducted by selecting populations of patients with defined characteristics, in order to gain an overview of the use of this class of drugs in the Valle d'Aosta Region and to decide which analyses to investigate in depth for publications in scientific journals.

Since high blood lipid levels, particularly cholesterol bound to low-density lipoproteins (C-LDL), are a leading cause of cerebro and cardiovascular ischemic diseases worldwide, a population of patients at high risk of cardiovascular events were selected to investigate the appropriateness of use of lipid-lowering drugs:

- Patients with hospitalizations for cardio- or cerebrovascular events (*primary cardiovascular disease*) or with previous cardio- or cerebrovascular events (*secondary cardiovascular disease*). Cardio- or cerebrovascular events related to

hypercholesterolemia were selected from the SDO database by filtering for the following diagnoses, as reported by Rodriguez *et al*. [255] and by Sarraju *et al*. [256]: *acute myocardial infarction*, *other acute and subacute forms of ischemic heart disease*, *old myocardial infarction*, *angina pectoris*, *other forms of chronic ischemic heart disease* (**ICD-9 410-414**), *occlusion and stenosis of precerebral arteries*, *occlusion of cerebral arteries*, *transient cerebral ischemia*, *acute but ill-defined cerebrovascular disease*, *other and ill-defined cerebrovascular disease* (**433-437**), *atherosclerosis* (**440**).

- Patients with *diabetes mellitus* (filter for **ICD-9=250** from the SDO database).
- Patients with *chronic kidney disease (CKD) stage 3/4* (filter for **ICD-9=5853-5454** from the SDO database).

These patient populations at high risk of cardiovascular events were identified by hospital pharmacists of the AUSL VdA as the groups of greatest interest in evaluating the use of lipid-lowering drugs.

All these patients were hospitalized during the study period, therefore, we can consider their condition more or less critical. As stated by the guidelines of the National Institute of Health and Care Excellence (NICE) [257], patients with previous cardio- or cerebrovascular events should be treated with lipid-lowering drugs for secondary prevention of cardiovascular diseases, particularly with atorvastatin 80 mg for the initial treatment (the highest commercially available dose). Several guidelines [258,259] identify patients with type 1/2 diabetes mellitus or stage 3/4 CKD, with or without other cardiovascular risk factors, at moderate to very-high risk of ASCVD: therefore, these patients should be offered a low-dose statin or other hypolipidemic treatment according to the severity of their clinical condition. For these categories of patients, C-LDL values considered unsafe if not treated with hypolipidemic drugs are: [259]

- Secondary prevention of ASCVD (<u>very-high risk</u>): drug intervention recommended when C-LDL ≥70 mg/dl;
- Primary prevention of ASCVD with diabetes mellitus (<u>moderate to very-high risk</u> based on duration of diabetes and presence of organ damage): drug intervention recommended when C-LDL ≥190 mg/dl (moderate risk);
- Primary prevention of ASCVD with CKD (<u>high to very-high risk</u> based on glomerular filtration rate): drug intervention recommended when C-LDL ≥116 mg/dl (high risk).

Target C-LDL values are **<55 mg/dl** for patients at very-high risk, **<70 mg/dl** for patients at high risk and **<100 mg/dl** for patients at moderate risk. [259]

Figure 48 shows a flow-chart for the selection of the study populations. In order not to leave out data of potential interest to the AUSL VdA, analyses were conducted at various levels of the selected populations, up to consider study samples for which the most information was available (medications dispensed, hospitalizations, results of cholesterol measurements) so that more in-depth analyses could be conducted.

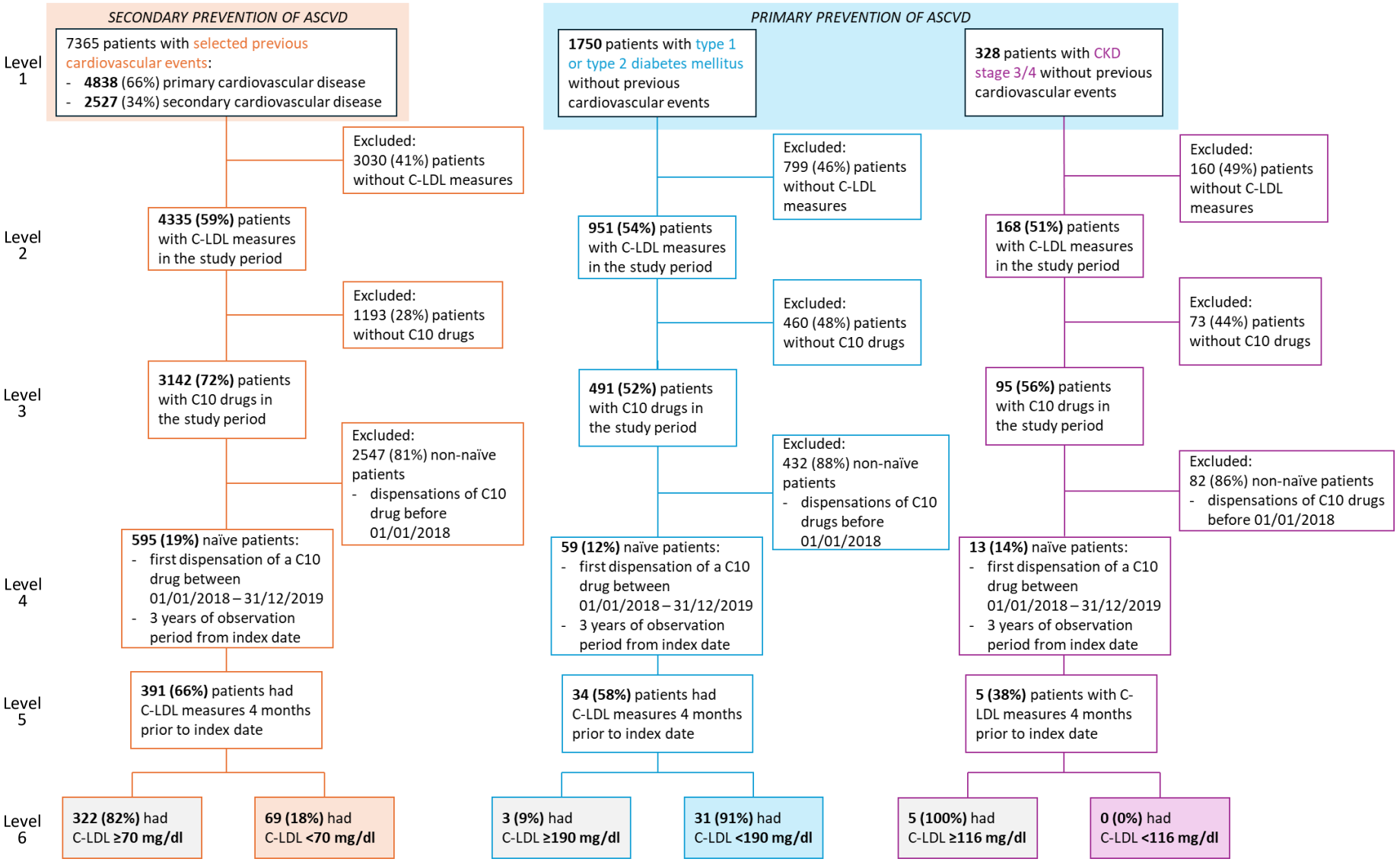


Figure 48. Flow-chart for the selection of the study populations. Since it is not possible to extrapolate the conditions of the patients enrolled in a retrospective study conducted with data collected for administrative purposes, the highest C-LDL threshold was selected for each risk category.

Abbreviations: CKD, chronic kidney disease

As shown in Figure 48, only 57.8% (5454 out of 9443) of patients with cardiovascular risk factors had at least one C-LDL measurement recorded during the study period (level 2 of Figure 48). Of these, 667 (12.2%) were patients naïve to hypolipidemic treatment (level 4): they represent three study samples for whom the use of C10 drugs, adherence and persistence to treatment was assessed.

Before reporting the results for the three study samples, it is worth commenting on the group of patients with previous cardiovascular events but without any dispensation of C10 drugs during the study period (patients excluded from further analysis). This topic is of particular interest to the AUSL VdA both to better understand the low consumption of lipid-lowering drugs in the Valle d'Aosta Region and to promote educational interventions to improve prescriptive appropriateness among prescribers. Specifically, among the 7365 patients with hospitalizations for selected primary and secondary cardiovascular diseases (first box on the left of Figure 48), 43.8% (3226 patients, including 1902 with a primary cardiovascular disease and 1324 with secondary cardiovascular diseases) was discharged and did not subsequently receive dispensations of lipid-lowering drugs during the study period. Annual data of discharged patients divided by primary cardiovascular disease (i.e., the reason for hospitalization) and secondary cardiovascular disease (i.e., previous event) are shown in Table 26.

Table 26. Discharged patients with selected cardiovascular diseases (level 1 of Figure 48)

Year	**Primary cardiovascular disease**			**Secondary cardiovascular disease**		
	Discharged patients, n	Discharged patients without C10 drugs, n (%)	Deceased patients among those without C10 drugs, n (%)	Discharged patients, n	Discharged patients without C10 drugs, n (%)	Deceased patients among those without C10 drugs, n (%)
2016	964	402 (41.7)	114 (28.4)	540	298 (55.2)	107 (35.9)
2017	927	394 (42.5)	132 (33.5)	526	279 (53.0)	142 (50.9)
2018	928	373 (40.2)	182 (48.8)	501	245 (48.9)	140 (57.1)
2019	1034	401 (38.8)	182 (45.4)	498	242 (48.6)	131 (54.1)
2020	858	280 (32.6)	226 (80.7)	406	191 (47.0)	145 (75.9)
2021	938	265 (28.2)	164 (61.9)	484	231 (47.7)	136 (58.9)
2022	NA	NA	117	NA	NA	109
2023 (until May 31)	NA	NA	37	NA	NA	23
Total	**4838**	**1902 (39.3)**	**1154 (23.8)**	**2527**	**1324 (52.4)**	**933 (36.9)**

Abbreviations: NA, not available

The median age of untreated discharged patients was 88 years [IQR 81-94], and the most frequent cardiovascular diseases were other and ill-defined cerebrovascular disease (49.0%), occlusion of cerebral arteries (17.6%) and other ischemic chronic heart disease (13.4%). C-LDL measurements conducted in healthcare facilities in the Valle d'Aosta Region were available for 1193 patients (37.0%, Figure 48 between level 2 and level 3): the last recorded value of C-LDL was observed for these patients, and it was found that 96.2% of them (1148 patients) had C-LDL values above the identified target of <55 mg/dl. Despite this, these patients do not appear to be treated with class A and/or class H lipid-lowering drugs dispensed in the Valle d'Aosta Region. Some possible explanations:

- Hospitalization and discharge for cardiovascular diseases occurred toward the end of the study period, so these patients were not yet in fact on secondary prevention.
- Patients died during or after hospitalization. With the data available to us (month and year of death, data updated to May 31, 2023), we know that 64.7% (2087 patients) of discharged patients without dispensations of C10 drugs during the study period died (Table 26 and Figure 49). We explained the higher number of patients with primary cardiovascular diseases who died in 2020 due to Covid-19. In fact, it is possible that in 2020 patients with cardiovascular diseases and Covid-19 were discharged by recording Covid-19 as the cause of hospitalization rather than the cardiovascular disease; therefore, records of primary cardiovascular diseases are lower in 2020, while the number of deaths is higher. This trend is less pronounced for the group of patients with secondary cardiovascular diseases since Covid-19 is already included among the reasons for hospitalization of these patients.
- Selected cardio- or cerebrovascular diseases could increase the risk of ASCVD-related diseases but with higher C-LDL targets.
- Age over 80 years or reduced life expectancy for whom statins are not indicated.
- Patients get their medications in different ways, for example, they may have purchased class C medications or out of the Valle d'Aosta Region (data not available).
- Patients had blood tests in healthcare facilities not affiliated with the AUSL VdA (data not available).

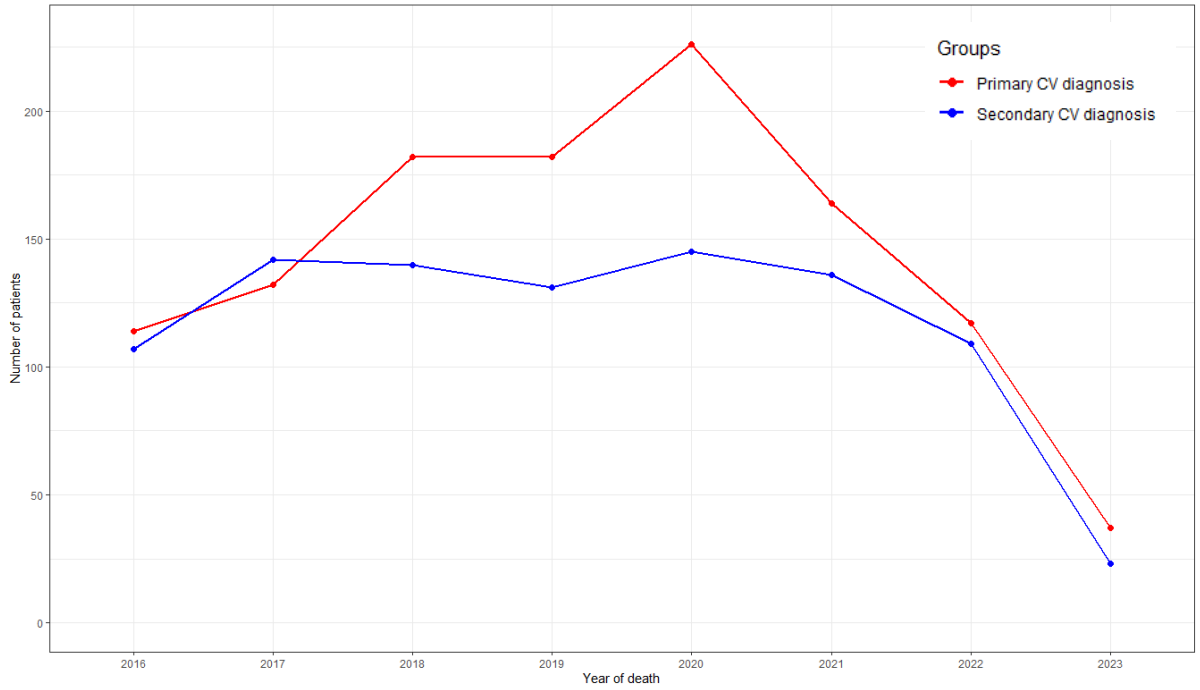


Figure 49. Discharged patients with primary or secondary cardiovascular diseases without lipid-lowering drugs who died during the study period.
Abbreviations: CV, cardiovascular

Despite these elements and despite the presence of guidelines to prevent further ASCVD, a large proportion of patients with previous cardiovascular events remain untreated with lipid-lowering drugs; this finding was shared with hospital pharmacists of the AUSL VdA who will promote countermeasures to better understand this scenario.

The three study samples consisted in patients naïve to hypolipidemic treatment, enrolled in 2018 and 2019, with risk factors for ASCVD-related diseases (level 4 of the flowchart in Figure 48): 595 patients with selected cardio- or cerebrovascular diseases, 59 patients with diabetes mellitus and 13 patients with CKD. Patients were followed for 3 years starting from index dates (observation period). General characteristics of the study population are reported in Table 27.

Table 27. General characteristics of the study population (level 4 of Figure 48)

	ASCVD-related diseases	Diabetes mellitus	CKD stage 3/4
Patients, n (%)	595	59	13[a]
Males	398 (66.9)	32 (54.2)	9 (69.2)
Females	197 (33.1)	27 (45.8)	4 (30.8)
Median age at enrolment (2018) [IQR]	66 [58-75]	64 [58-74]	66 [50-75]
Males	65 [58-75]	66 [60-69]	66 [50-69]
Females	69 [62-76]	63 [57-78]	78 [56-78]
Index C10 drug, n (%)			
Atorvastatin	409 (68.7)	26 (44.1)	4 (30.8)
Omega-3 triglycerides	65 (10.9)	10 (16.9)	4 (30.8)
Simvastatin	47 (7.9)	7 (11.9)	2 (15.4)
Rosuvastatin	25 (4.2)	7 (11.9)	2 (15.4)
Lovastatin	15 (2.5)	3 (5.1)	1 (7.7)
Ezetimibe	11 (1.8)	0 (0.0)	0 (0.0)
Simvastatin/ezetimibe	9 (1.5)	0 (0.0)	0 (0.0)
Rosuvastatin/ezetimibe	7 (1.2)	0 (0.0)	0 (0.0)
Pravastatin	3 (0.5)	1 (1.7)	0 (0.0)
Gemfibrozil	2 (0.3)	0 (0.0)	0 (0.0)
Fenofibrate	1 (0.2)	4 (6.8)	0 (0.0)
Evolocumab	1 (0.2)	0 (0.0)	0 (0.0)
Cholestyramine	0 (0.0)	1 (1.7)	0 (0.0)
Alirocumab	0 (0.0)	0 (0.0)	0 (0.0)
Number of different C10 drugs in the observation period, n (%)			
1	318 (53.4)	47 (79.7)	11 (84.6)
2	169 (28.4)	9 (15.2)	1 (7.7)
3	79 (13.3)	2 (3.4)	1 (7.7)
≥4	29 (4.9)	1 (1.7)	0 (0.0)

[a] In the group of patients with CKD, 4 patients out of 13 also had diabetes and were included in both groups. Therefore, the total number of unique patients in the study population is 663.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; IQR, interquartile range

In the group of patients with ASCVD-related diseases, both patients hospitalized for cardio- or cerebrovascular events (primary cardiovascular disease) and patients hospitalized for different reasons but with previous cardio- or cerebrovascular events (secondary cardiovascular disease) were considered: these were, respectively, 517 patients with primary ASCVD-related diseases and 78 with secondary ASCVD-related diseases. Table 28 shows the frequency of ASCVD-related diseases detected in the study sample. The most frequent diagnosis was other forms of chronic ischemic heart disease for both groups, while the second most frequent diagnosis was acute myocardial infarction for primary cardiovascular diseases and occlusion and stenosis of precerebral arteries for secondary cardiovascular diseases. During the study period, the median number of hospitalizations for primary

cardiovascular diseases was 2, ranged from 1 to 10; the median duration of hospitalization for primary cardiovascular diseases was 6 days, ranged from 0 to 74 days.

Table 28. Frequency of primary and secondary cardiovascular diseases (level 4 of Figure 48, only patients with previous ASCVD-related diseases)

	Total, n (%) (n=595)	**Primary ASCVD-related disease, n (%)** (n=517)	**Secondary ASCVD-related disease, n (%)** (n=78)
Other forms of chronic ischemic heart disease	320 (53.8)	291 (56.3)	29 (37.2)
Acute myocardial infarction	264 (44.4)	259 (50.1)	5 (6.4)
Other acute and subacute forms of ischemic heart disease	69 (11.6)	65 (12.6)	4 (5.1)
Occlusion of cerebral arteries	65 (10.9)	59 (11.4)	6 (7.7)
Atherosclerosis	50 (8.4)	39 (7.5)	11 (14.1)
Old myocardial infarction	49 (8.2)	48 (9.3)	1 (1.3)
Other and ill-defined cerebrovascular disease	36 (6.1)	23 (4.4)	13 (16.7)
Transient cerebral ischemia	29 (4.9)	26 (5.0)	3 (3.8)
Occlusion and stenosis of precerebral arteries	29 (4.9)	15 (2.9)	14 (17.9)
Angina pectoris	28 (4.7)	27 (5.2)	1 (1.3)
Acute but ill-defined cerebrovascular disease	9 (1.5)	9 (1.7)	0 (0.0)

For the group of patients with primary ASCVD-related diseases (n=517), the date of the first hospitalization for a cardio- or cerebrovascular event was investigated compared with the index date (Figure 50). Dates of diagnoses were not available for patients with secondary ASCVD-related disease, who were therefore excluded from the following assessment.

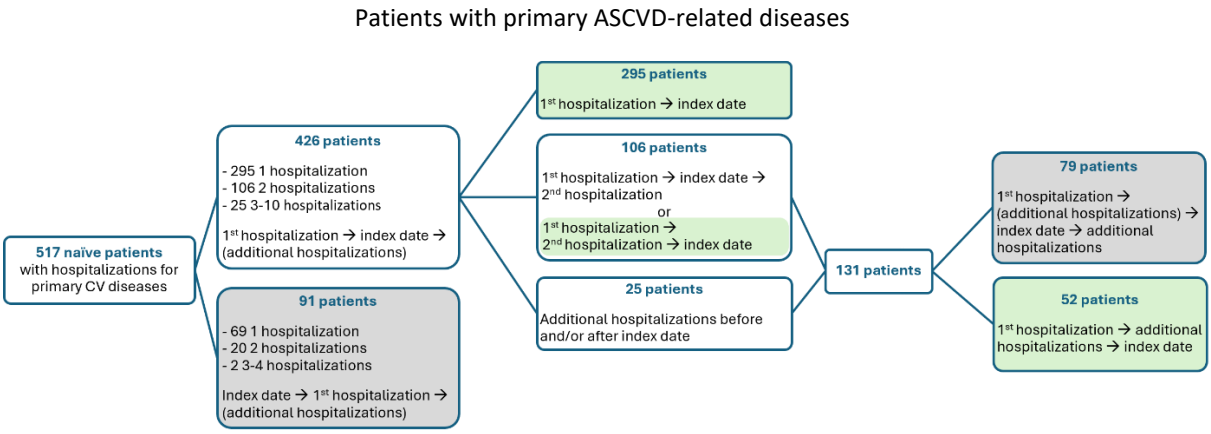


Figure 50. Patterns of hospitalization dates and index dates for naïve patients with primary cardiovascular diagnosis. Green boxes include patients for whom hypolipidemic therapy was found to be effective (no subsequent cardiovascular events). Gray boxes include patients for whom the likelihood of experiencing an additional cardiovascular event after the index date was assessed through Kaplan-Meier curves.
Abbreviations: CV, cardiovascular

As shown in Figure 50, it was found that 426 patients (82.4%) had the first dispensation of a lipid-lowering drug after the first hospitalization for a cardio- or cerebrovascular event, with a median number of days between the discharge and the index date of 81.0 days [IQR 26-182; range 2-1350]; these patients were on secondary prevention of ASCVD from the beginning of the observation period. The majority of them (295 out of 426 patients, 69.2%) had no other hospitalizations for cardio- or cerebrovascular events after the index date. One quarter of them (106 patients, 24.9%) had two hospitalizations for an ASCVD-related disease during the observation period, while 5.9% (25 patients) had 3 to 10 hospitalizations for an ASCVD-related disease during the observation period. For the latter, hospitalizations after the first hospitalization for cardio- or cerebrovascular causes may have occurred before and/or after index date. Specifically, 79 patients out of 131 (60.3%) have had additional cardio- or cerebrovascular hospitalizations after the index date; for these patients, the likelihood of having an additional ASCVD-related event after initiation of lipid-lowering drugs was assessed through Kaplan-Meier survival analysis.

The remaining 91 patients (17.6%) had dispensations of lipid-lowering drugs from 3 to 1348 days before the first hospitalization for an ASCVD-related event (median days between index date and first hospitalization 469.0 [IQR 195-734]); as far as we know, these patients were not on secondary prevention of ASCVD at the beginning of the observation period, but we cannot draw any other conclusions with the data available to us. The likelihood of having a cardio- or cerebrovascular event after initiation of lipid-lowering treatment was also evaluated for these patients.

Kaplan-Meier curves for the 79 and 91 patients with additional ASCVD-related events after the index date for a lipid-lowering drug are shown in Figure 51: 50.0% of patients in secondary prevention of ASCVD at the beginning of the observation period are likely to experience an additional cardiovascular event 229.0 days [IQR 47-511] after starting hypolipidemic therapy. The other group of patients have a median time to first cardio- or cerebrovascular event of 447.0 days [IQR 146-673], with a statistically significant difference from the first group ($p<0.05$, log-rank test). These patients were considered to be in primary prevention of ASCVD at the beginning of the observation period (they were in secondary prevention of ASCVD starting from the first hospitalization), possibly due to excessive blood cholesterol levels.

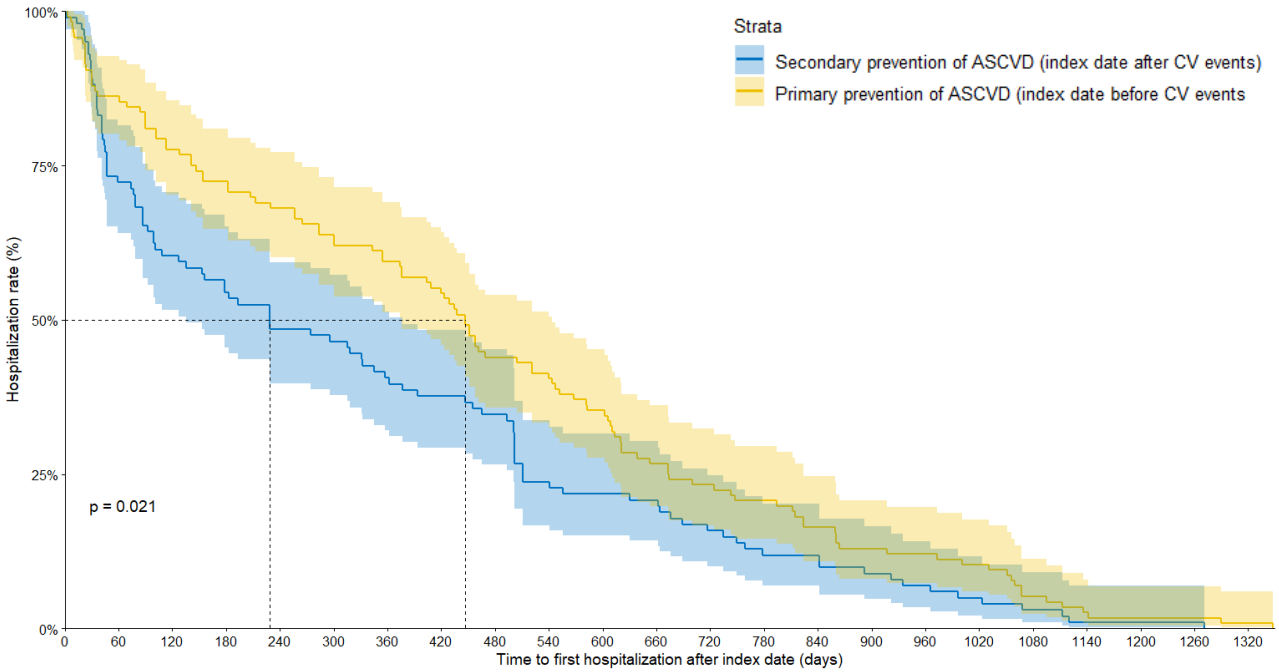


Figure 51. Kaplan-Meier curves of the time between the initiation of hypolipidemic therapy and a cardiovascular event. The yellow curve represents patients on primary prevention of ASCVD (index date before first hospitalization for cardiovascular causes, n=91 patients); the blue curve represents patients on secondary prevention of ASCVD (index date after first hospitalization for cardiovascular causes, n=79 patients).
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular

The following are the results of medication adherence and persistence of the three study samples including naïve patients with risk factors associated with ASCVD (level 4 of Figure 48):

1. selected primary or secondary cardio- or cerebrovascular diseases (n=595);
2. diabetes mellitus without hospitalizations for cardiovascular events (n=59);
3. CKD stage 3/4 without hospitalizations for cardiovascular events (n=13).

Medication adherence values were measured for the overall hypolipidemic therapy with the equation below (Equation 1).

$$MPR = \frac{Number\ of\ days\ covered\ by\ the\ dispensed\ therapy}{Observation\ period\ -\ duration\ of\ hospitalizations} \times 100$$

Equation 1. Medication adherence as the percentage MPR – "medication possession ratio". Number of days covered by the therapy was measured by dividing the dose of active ingredient dispensed by the daily dose to be taken: *1 unit/die* for statins and/or ezetimibe; *1 unit/14 days* for PCSK9 inhibitors; *DDD* for other lipid-lowering drugs. A grace period of 1.5 times the duration of the last dispensing event was considered to create the treatment events. Observation period was 3 years from the index date. Deceased patients were included in the analysis

Median adherence was twice as large for the group of patients with primary cardiovascular diseases, while it was similar for the other groups. Table 29 shows the median adherence values, as well as the percentages of adherent, partially adherent and non-adherent patients in the three study samples. Except for the first group, the proportion of non-adherent patients prevails in all groups with more than half of the patients.

Table 29. Results of adherence and persistence to hypolipidemic therapy (level 4 of Figure 48)

	ASCVD-related diseases		**Diabetes mellitus** (n=59)	**CKD stage 3/4** (n=13)
	Primary diagnosis (n=517)	*Secondary diagnosis* (n=78)		
Adherence to C10 drugs at 3 years, median [IQR]	**66.2 [24-100]**	**26.6 [8-72]**	**30.9 [6-76]**	**33.2 [5-97]**
MPR ≥80%: Adherent patients, n (%)	211 (40.8)	18 (23.1)	13 (22.0)	4 (30.8)
40% ≥ MPR > 79%: Partially adherent patients, n (%)	120 (23.2)	13 (16.7)	14 (23.7)	2 (15.4)
MPR <40%: Non-adherent patients, n (%)	186 (36.0)	47 (60.3)	32 (54.2)	7 (53.8)
Persistence to C10 drugs at 3 years, median time to discontinuation [IQR] (days)	**392.0 [88-1095]**	**170.5 [60-674]**	**112.0 [35-508]**	**112.0 [30-554]**
Persistent patients, n (%)	148 (28.6)	12 (15.4)	5 (8.5)	2 (15.4)
Non-persistent patients, n (%)	369 (71.4)	66 (84.6)	54 (91.5)	11 (84.6)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; IQR, interquartile range; MPR, medication possession ratio

Going into more detail about these study samples, it was found that the most commonly used hypolipidemic class is statins (596 out of 663 patients, 89.9%), followed by omega-3 triglycerides (132 patients, 19.9%), statin + ezetimibe (125, 18.8%) and ezetimibe (52, 7.8%). These were also the drug class with the highest adherence to therapy 3 years after index date, as shown in Figure 52.

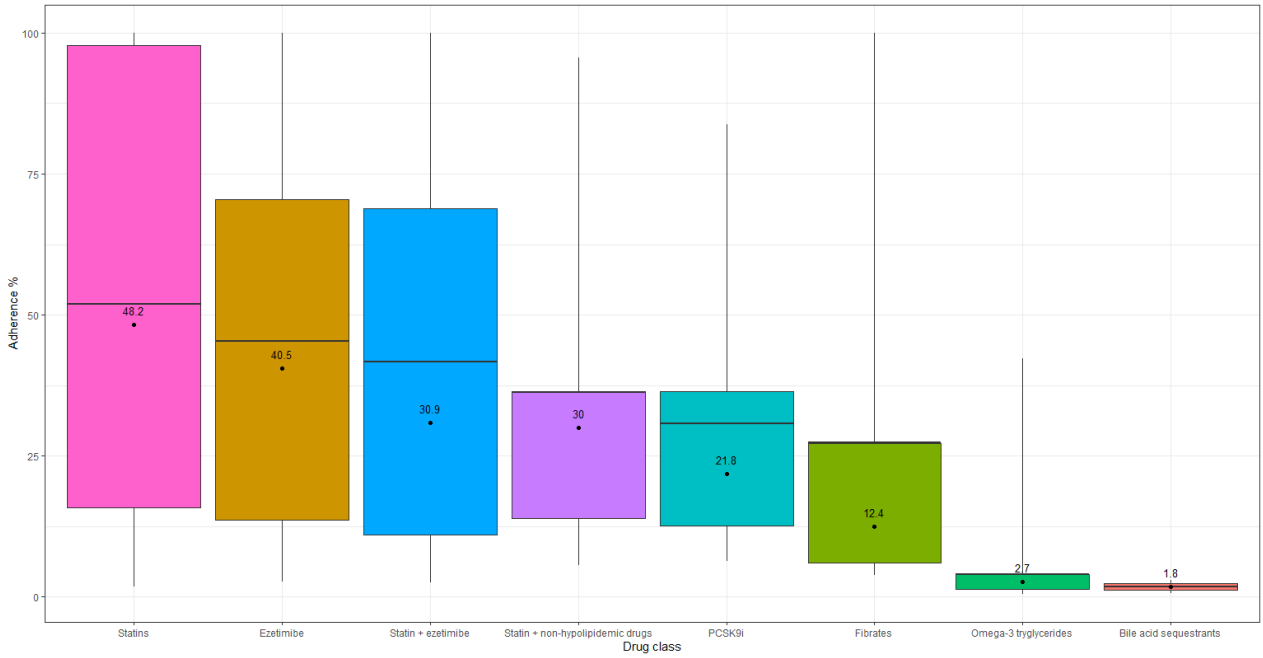


Figure 52. Box plots with means (horizontal black lines), medians (black points), IQR (colored boxes) and range (vertical black lines) for each drug class analyzed

Persistence was assessed using the Kaplan-Meier survival analysis; median time to discontinuation to overall hypolipidemic therapy and percentages of persistent and non-persistent patients are shown in Table 29. As shown in Figure 53, patients with previous cardio- or cerebrovascular diseases were significantly more persistent than patients with diabetes mellitus and CKD (p<0.0001, log-rank test). Males were significantly more persistent to overall hypolipidemic therapy compared to females (p<0.05, log-rank test), with a median time to discontinuation of 359.0 days *vs* 230.0 days.

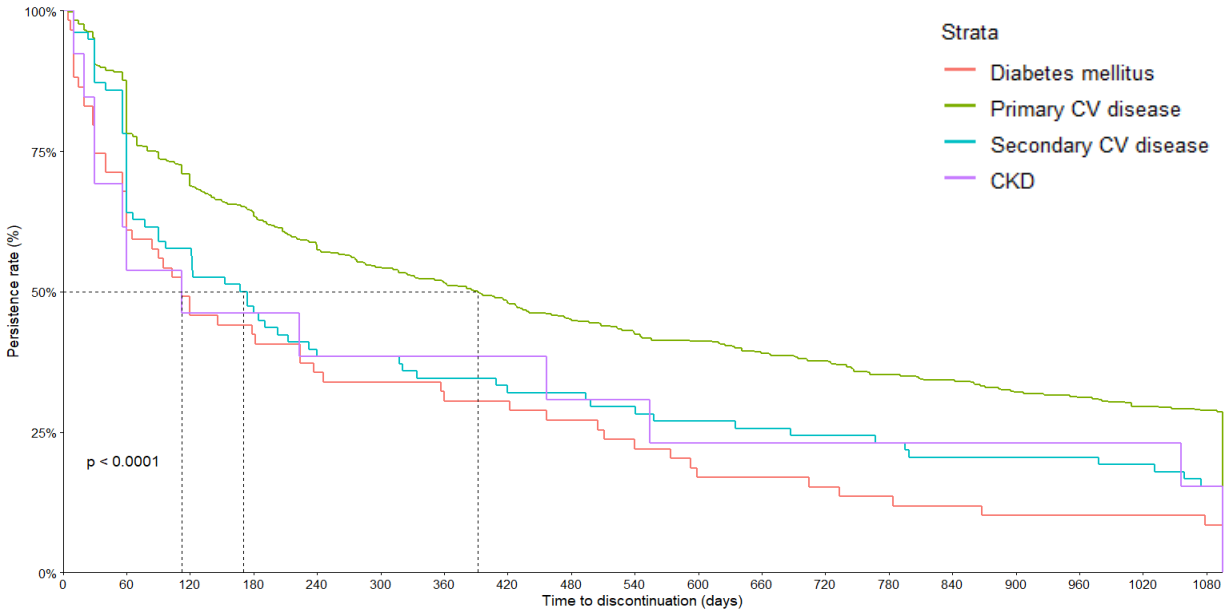


Figure 53. Persistence to hypolipidemic therapy at 3 years from the index date.
Abbreviations: CV, cardiovascular; CKD, chronic kidney disease

Finally, persistence was measured over the observation period by dividing patients according to the index drug used (level 4 of Figure 48, all patients with cardiovascular risk factors together). As shown in Table 30, most patients initiated hypolipidemic therapy with atorvastatin (439 out of 663 patients, 66.2%), followed by omega-3 triglycerides (8.1%) and simvastatin (7.8%). Lipid-lowering drugs with the highest proportion of persistent patients were ezetimibe and rosuvastatin/ezetimibe, with nearly half of patients still in treatment with the index drug at 3 years (Figure 54). Possible causes of non-persistence to the index drug are switch with another active ingredient, hospitalization, delay in supply, perception of well-being and poor understanding of the importance of treatment, ADRs, complex polytherapy regimen, death. As for deceased patients, they represent 15.2% of the study population (101 out of 663 patients):

- 69 patients with primary ASCVD-related diseases (13.3%) died during the study period with a median time from index date of approximately 2.1 years (we only know the month and year of death);
- 22 patients with secondary ASCVD-related diseases (28.2%) died with a median time from index date of 1.7 years;
- 6 patients with diabetes mellitus (10.2%) died with a median time from index date of 2.7 years;

- 4 patients with CKD stage 3/4 (30.8%) died with a median time from index date of 2.1 years.

Since we do not know the causes of death, we can only speculate on advanced age, worsening condition and presence of comorbidity as possible causes.

Table 30. Frequency, persistence and time to discontinuation to index drugs (level 4 of Figure 48)

Index drug	Patients, n (%)	Persistent patients, n (%)	Time to discontinuation, median [IQR]
Atorvastatin	439 (66.2)	124 (28.2)	430.5 [120-1095]
Omega-3 triglycerides	54 (8.1)	5 (9.1)	20.0 [10-122]
Simvastatin	52 (7.8)	8 (17.0)	112.0 [56-554]
Rosuvastatin	39 (5.9)	6 (15.0)	176.0 [56-731]
Ezetimibe	21 (3.2)	**10 (47.6)**	987.0 [123-1095]
Lovastatin	19 (2.9)	2 (10.5)	180.0 [60-452]
Rosuvastatin/ezetimibe	15 (2.3)	**6 (40.0)**	641.0 [166-1095]
Simvastatin/ezetimibe	11 (1.7)	3 (27.3)	207.0 [113-1001]
Pravastatin	4 (0.6)	1 (25.0)	44.0 [26-319]
Fenofibrate	4 (0.6)	1 (25.0)	236.0 [100-544]
Gemfibrozil	2 (0.3)	0 (0.0)	50.0 [40-60]
Fluvastatin	1 (0.2)	0 (0.0)	266.0 [266-266]
Evolocumab	1 (0.2)	0 (0.0)	791.0 [791-791]
Cholestyramine	1 (0.2)	0 (0.0)	7.0 [7-7]

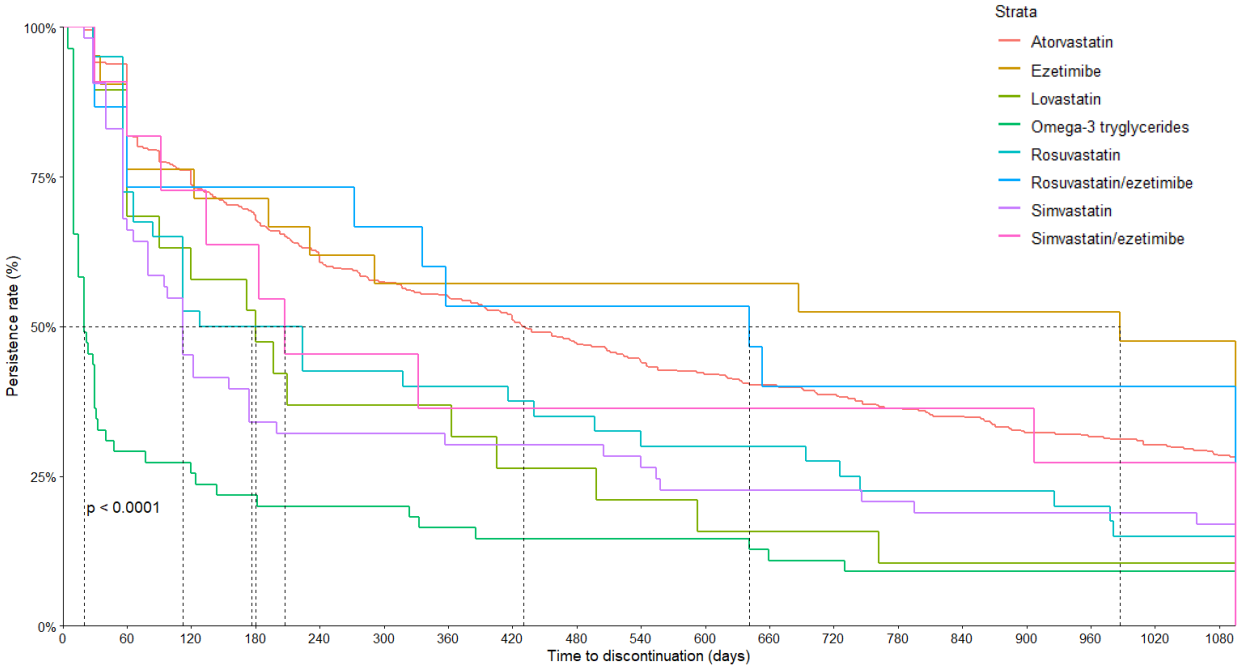


Figure 54. Persistence to hypolipidemic index drugs 3 years after index date

Finally, patients with C-LDL measures 4 months before index date, 6 months after index date (±1 month), 1 year after index date (±1 month) and 2 and 3 years after index date (± 4 months) were selected to investigate trends in blood cholesterol levels in patients persistent and not-persistent to hypolipidemic therapy (level 5 of Figure 48, only patients with ASCVD-related events). Outcomes of patients with diabetes mellitus and CKD were not reported because the number of patients was less than 10 for each period considered. Figure 55 shows the results of this evaluation for patients with primary and secondary cardio- or cerebrovascular diseases. At 6 months after initiation of treatment with lipid-lowering drugs, a significant drop in C-LDL values is observed, which then remains almost unchanged at 1, 2 and 3 years. Persistent (or adherent) patients generally show lower C-LDL values.

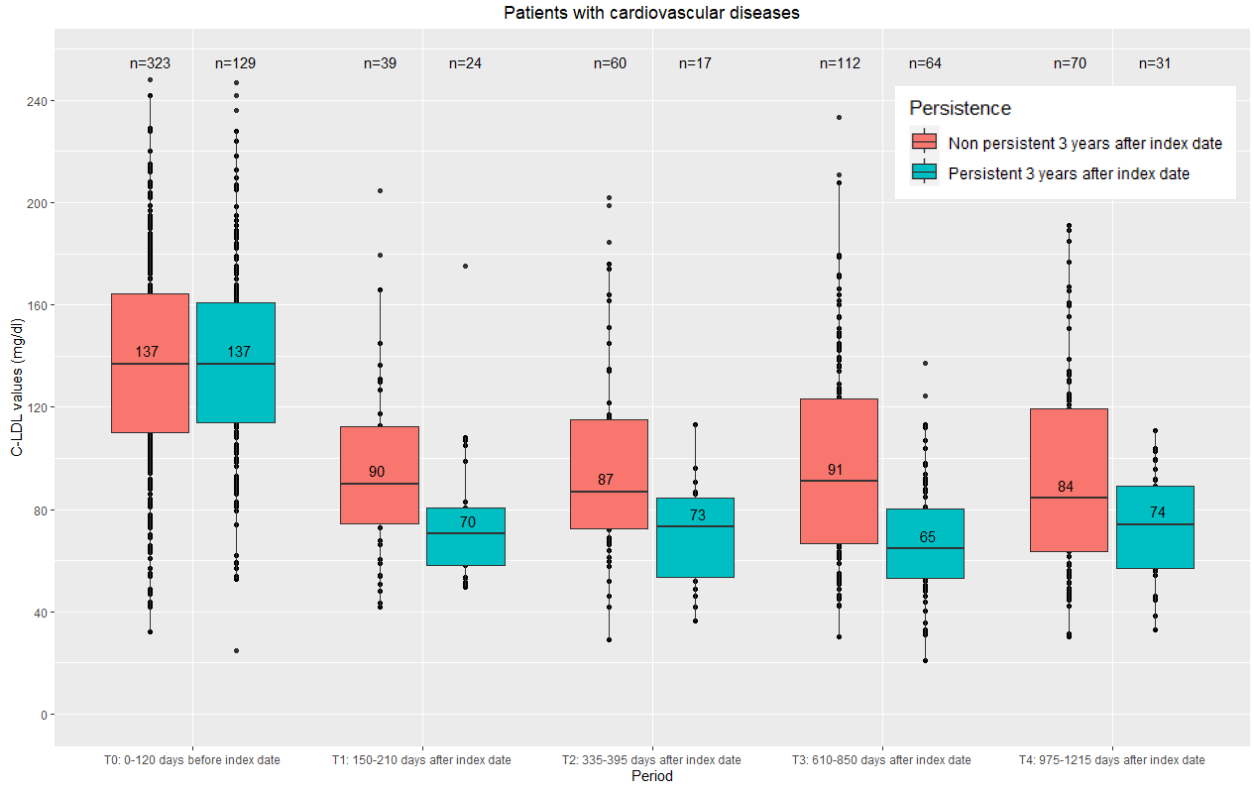


Figure 55. Box plots showing median C-LDL values (horizontal black lines) measured at selected time periods (T0-T4) for persistent and non-persistent patients

Considering all available C-LDL measures before and after the index date, differences were observed in the proportion of patients above and below a predefined target depending on the sample considered (Table 31). Target C-LDL values are: [259]

- <55 mg/dl for patients with ASCVD-related diseases (very-high risk of ASCVD);
- <100 mg/dl for patients with diabetes mellitus (moderate risk);

- <70 mg/dl for patients with CKD (high risk).

Since the risk category may vary depending on the patient's condition, the lowest category was selected for each study sample. In all groups there is an increase in the number of patients below target following hypolipidemic therapy. With the exception of patients with CKD (who are very limited in number), in the other groups, adherent patients reach the target more often after initiation of therapy than partially or non-adherent patients.

Table 31. Proportion of patients in the three study samples with C-LDL measures above and below the targets identified by the ESC/EAS 2019 guidelines [259]

Study samples[a]	**Patients with C-LDL measures before index date**		**Patients with C-LDL measures after index date**		**Δ% of patients below the target before and after C10 therapy**
	C-LDL > target, n (%)	C-LDL ≤ target, n (%)	C-LDL > target, n (%)	C-LDL ≤ target, n (%)	
ASCVD-related diseases: Target C-LDL <55 mg/dl	**512 (92.1)**	**44 (7.9)**	**413 (78.1)**	**116 (21.9)**	**+14.0**
Adherent	202 (36.3)	22 (4.0)	163 (30.8)	72 (13.6)	+9.7
Partially adherent	114 (20.5)	12 (2.2)	96 (18.1)	27 (5.1)	+2.9
Non-adherent	196 (35.3)	10 (1.8)	154 (29.1)	17 (3.2)	+1.4
Diabetes mellitus: Target C-LDL <100 mg/dl	**33 (76.7)**	**10 (23.3)**	**19 (38.0)**	**31 (62.0)**	**+38.7**
Adherent	9 (20.9)	1 (2.3)	2 (4.0)	9 (18.0)	+15.7
Partially adherent	7 (16.3)	3 (7.0)	2 (4.0)	9 (18.0)	+11.0
Non-adherent	17 (39.5)	6 (14.0)	15 (30.0)	13 (26.0)	+12.0
CKD stage 3/4: Target C-LDL <70 mg/dl	**5 (83.3)**	**1 (16.7)**	**7 (70.0)**	**3 (30.0)**	**+13.3**
Adherent	2 (33.3)	1 (16.7)	1 (10.0)	2 (20.0)	+3.3
Partially adherent	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	+0.0
Non-adherent	3 (50.0)	0 (0.0)	5 (50.0)	10 (10.0)	+10.0

[a] Not all patients enrolled had C-LDL measures before and after the index date: 556 patients with cardiovascular diseases had C-LDL measures before the index date and 529 after; 43 patients with diabetes mellitus had C-LDL measures before and 50 after; 6 patients with CKD had C-LDL measures before and 10 after (these numbers were used to calculate the percentages in Table 31). All available C-LDL values (even more than one per patient before and/or after index date) were considered for this analysis.
Abbreviations: CKD, chronic kidney disease

Median C-LDL values decrease from 128.0 mg/dl before index date to 80.5 mg/dl after index date for patients with cardio- or cerebrovascular diseases; from 142.5 mg/dl to 90.2 mg/dl for patients with diabetes and from 143.1 mg/dl to 100.9 mg/dl for patients with CKD. Figure 56 shows these data divided by adherent, partially adherent and non-adherent patients. Despite the decreasing trend, the median C-LDL values after initiation of hypolipidemic therapy are suboptimal, especially for adherent and less adherent patients with previous cardiovascular events.

This analysis identified poorly adherent or persistent patients who did not meet desirable C-LDL targets and identifying a population who could, ideally, be referred for educational interventions by GPs of the AUSL VdA.

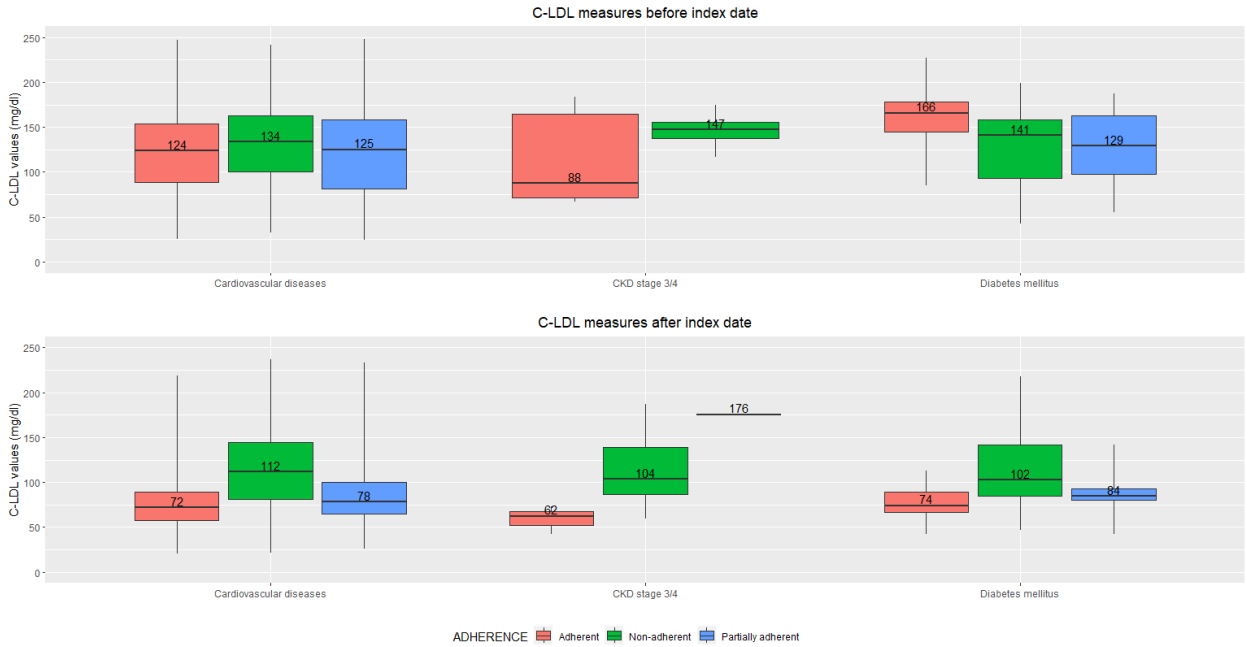


Figure 56. Box plots showing median C-LDL values (horizontal black lines) measured before and after index date for adherent, partially adherent and non-adherent patients in the three study samples. Note that the single black line indicates a single partially adherent patient with CKD and with C-LDL measures after the index date for a C10 drug (as shown in Table 31).
Abbreviations: CKD, chronic kidney disease

To conclude the investigation on the use of lipid-lowering drugs in the AUSL VdA, a focus was made on older patients (age ≥65 years) to assess their persistence to hypolipidemic treatment. A total of 9958 older patients was included in the analysis: median age was 74.0 years and 53.6% of patients were females. The most common lipid-lowering drug used by older patients was atorvastatin (47.3%), followed by simvastatin (29.6%) and rosuvastatin (16.9%); 2115 older patients (21.2%) were treated with more than one lipid-lowering drug during the entire study period. The most frequent change of therapy involved switching from simvastatin to atorvastatin (298 out of 2115 patients, 14.1%), followed by switching from atorvastatin to rosuvastatin/ezetimibe (284 patients, 13.4%) and by switching or adding of ezetimibe to atorvastatin (203 patients, 9.6%). Figure 57 shows the alluvial diagram constructed to observe the therapy intensifications that occurred each quarter of the study period.

Persistence was measured only for older patients treated with a single active ingredient during the entire study period (January 1, 2016 to December 31, 2022): 7843 patients on statin and/or ezetimibe monotherapy. The highest persistence is observed for fluvastatin, rosuvastatin and simvastatin/ezetimibe, although for all lipid-lowering drugs analyzed, less than half of the patients were persistent to treatment at 2 years. Median time to discontinuation to hypolipidemic treatment is shown in Figure 58 and Table 32.

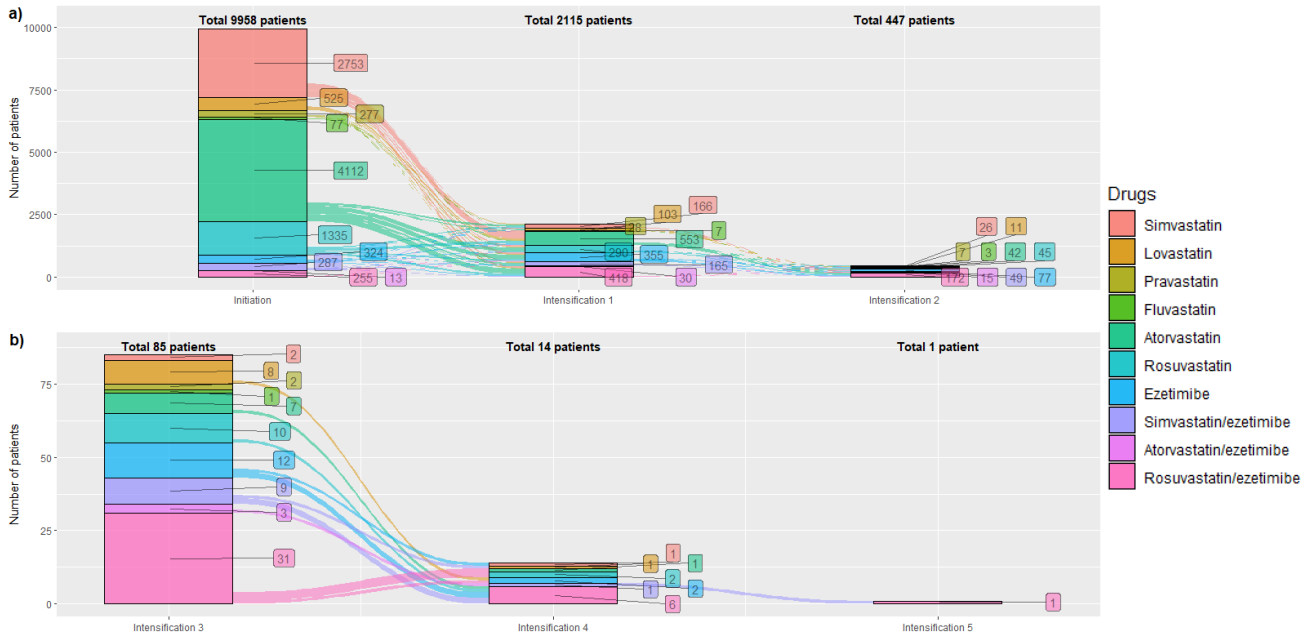


Figure 57. Alluvial diagram of intensifications of therapy with lipid-lowering drugs. Intensifications were measured every 4 months during the study period (January 1, 2016 – December 31, 2022). The colored boxes show the number of patients treated with each of the drugs analyzed

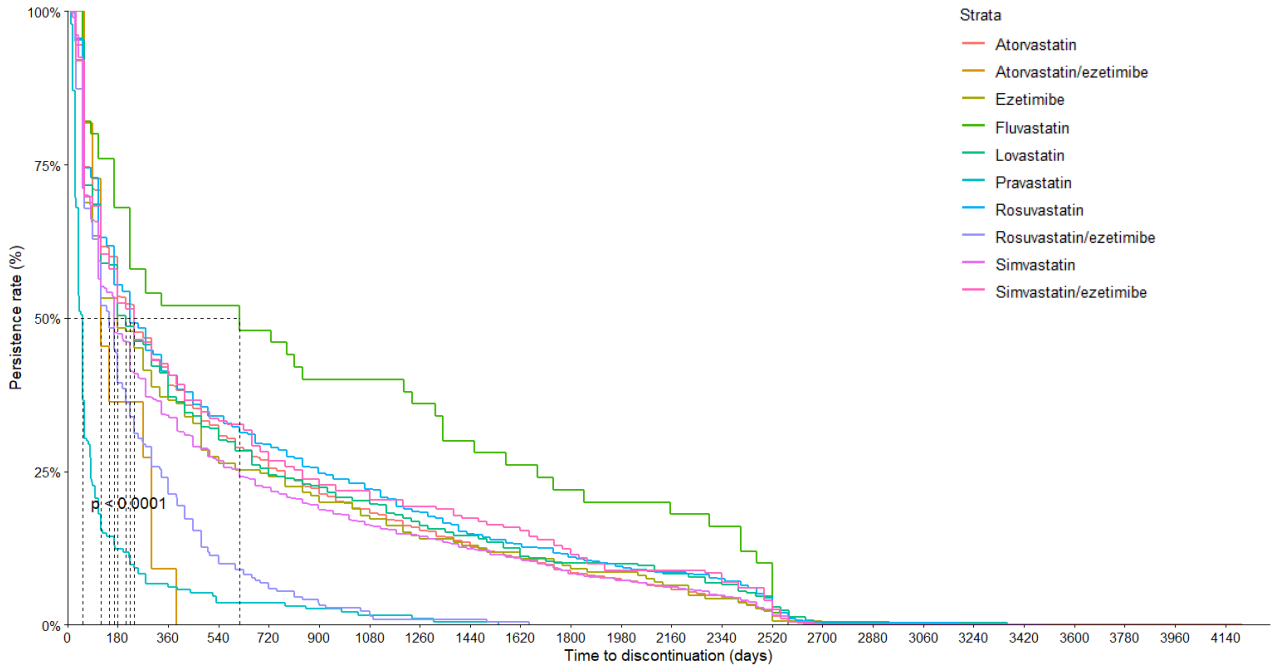


Figure 58. Persistence to hypolipidemic treatment in patients over 65 on statin and/or ezetimibe monotherapy throughout the study period (January 1, 2016 – December 31, 2022)

Table 32. Results on persistence to hypolipidemic treatment for patients over 65 on statin and/or ezetimibe monotherapy

Lipid-lowering drug	Patients, n (%) n=7843	Time to discontinuation, median (days)	Patients persistent at 2 years, n (%)
Atorvastatin	3361 (42.8)	240	856 (25,5)
Simvastatin	2212 (28.2)	168	481 (21,7)
Rosuvastatin	1021 (13.0)	224	295 (28,9)
Lovastatin	385 (4.9)	210	94 (24,4)
Rosuvastatin/ezetimibe	221 (2.8)	150	13 (5,9)
Simvastatin/ezetimibe	202 (2.6)	240	54 (26,7)
Pravastatin	194 (2.5)	56	7 (3,6)
Ezetimibe	186 (2.4)	180	45 (24,2)
Fluvastatin	50 (0.6)	616	23 (46,0)
Atorvastatin/ezetimibe	11 (0,1)	120	0 (0,0)

The results described above were the subject of four reports that were shared and commented on with hospital pharmacists of the AUSL VdA. Results deemed to be of greatest interest have also been the subject of posters presented at international congresses and scientific publications (cited below):

- Armando LG, *et al*. Use of lipid-lowering drugs in patients living in the Valle d'Aosta Region (Italy). Poster presented at the 28th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Naples, Italy, 21-22 November 2024.
- Armando LG, *et al*. Medication adherence and time to initiation of lipid-lowering drug dispensing by pharmacies in the Valle d'Aosta Region (Italy) in patients with

conditions associated with atherosclerotic cardiovascular diseases. Submitted to the International Journal of Pharmacy Practice.

Moreover, it is the intention of both the Study Group on Drug Utilisation Research of the DSTF and the AUSL VdA to deepen and refine these analyses for publication in international scientific journals in 2025.

4.3.3. Other DURs subjects of scientific publications

Other DUR studies were conducted during the Ph.D. that will not be discussed in detail in the present dissertation. Data source were drug dispensing data from the AUSL VdA, the ASL TO4 and other Piedmontese healthcare facilities. All the results obtained from these data were included in reports for hospital pharmacists with whom we collaborated. The most relevant studies were presented at national and international conferences and were the subject of scientific publications. The corresponding citations are as follows:

- Armando LG, *et al*. Persistence to Medications for Benign Prostatic Hyperplasia/Benign Prostatic Obstruction-Associated Lower Urinary Tract Symptoms in the ASL TO4 Regione Piemonte (Italy). *Healthcare* **2022**; 10:2567. doi: 10.3390/healthcare10122567.
- Miglio G, *et al*. Management of Benign Prostatic Obstruction-Associated Lower Urinary Symptoms in the ASL TO4 Regione Piemonte (Italy): Prescription Behaviour and Twelve-Months Medication Persistence. Abstract no. SIF2281 from the 41st SIF National Congress, Rome, Italy, 16-19 November 2022). *Pharmadvances* **2023**; 5. doi: 10.36118/pharmadvances.2023.50.
- Miglio G, *et al*. Assessment of medication adherence and persistence among patients on antithyroid drug therapy in the ASL TO4 Regione Piemonte (Italy): a retrospective longitudinal cohort study. Abstract no. SIF22593 from the 41st SIF National Congress, Rome, Italy, 16-19 November 2022). *Pharmadvances* **2023**; 5. doi: 10.36118/pharmadvances.2023.50.
- Armando LG, *et al*. Assessing medication adherence and persistence to statins in adults of the ASLTO4 (Piedmont, Italy). Abstracts no. ESPACOMP-22-P35 from the 26th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Berlin, Germany, 17–19 November 2022. *Int J Clin Pharm* **2023**. doi: 10.1007/s11096-023-01537-5.
- Armando LG, *et al*. Impact of the COVID-19 Pandemic on the Use of Antidepressants by Young Adults in the ASL TO4 Regione Piemonte (Italy). *Pharmacy* **2024**; 12:21. doi: 10.3390/pharmacy12010021.
- Fassina D, *et al*. Analisi di farmacoutilizzazione e valutazione dell'aderenza terapeutica nei pazienti affetti da Emofilia A grave: il confronto tra emicizumab e fattore VIII presso un'ASL del Piemonte. Abstract presented at the XLV SIFO National

Congress, Naples, Italy, 17-20 October 2024.

- Sillano S, *et al*. Valutazione dell'aderenza terapeutica in pazienti trattati con alirocumab presso un'ASL piemontese. Abstract presented at the XLV SIFO National Congress, Naples, Italy, 17-20 October 2024.
- Sillano S, *et al*. Aderenza a terapia con alirocumab nel periodo 2017-2023: i dati real life di un'Azienda Sanitaria Locale piemontese. *Boll SIFO* **2024**; 70(5):375-383. doi: 10.1704/4376.43729.

5. DISCUSSION OF KEY FINDINGS

This research work helped deepen methodologies for conducting DUR with EHRs, in particular with drug dispensing data, to provide LHAs with tools to monitor prescription patterns of GPs, prescriptive appropriateness and the use of medications by specific categories of patients. These results allowed for the identification of potential areas of improvement for more appropriate management of pharmacological therapies, as well as strengthened relationships between the DSTF and healthcare facilities in northern Italy. Existing collaborations will certainly continue in the coming months and will be renewed, as well as the possibility of establishing new research agreements to conduct DUR with other healthcare facilities. In fact, several LHAs and healthcare facilities, but not only, are requesting collaborations with the Study Group on Drug Utilization Research of the DSTF (a group created during my Ph.D. and of which I am a member) to conduct analyses on drug use and prescriptive appropriateness. This growing interest reinforces the value of the research conducted and opens new perspectives for future studies aimed at exploring innovative methodologies for therapy monitoring and health policy support.

In particular, DUR conducted in recent years have yielded results that could help hospital pharmacists and physicians promote safer use of medications. A key finding includes poor adherence to pharmacological treatments for chronic diseases such as diabetes and atherosclerosis, with possible consequences on health outcomes (hospitalizations, worsening health status) and healthcare costs. Patient education policies and adherence monitoring may reduce these issues. Another critical issue that emerged was the presence of PIPs, such as the use of sulfonylureas or the use of non-first-line medications to treat naïve patients; this finding suggests the usefulness of decision-support tools for clinicians that can identify PIPs and other MRPs in real time.

Related to this aspect (PIPs), an innovative element of this research was the updating of the knowledge-base of the NavFarma® CDSS, with the aim of optimizing the process of medication review and providing healthcare professionals with a simple but comprehensive tool that can support them in daily clinical practice. Updating the information already present on NavFarma®, which are the result of pre-doctoral collaborations between Infologic s.r.l. and the DSTF, and integrating it with new evidence obtained from the revision of scientific

literature has made it possible both to improve the accuracy of the information provided by the system and to expand the recommendations useful for effective medication review.

Specifically, the inclusion on the NavFarma® knowledge-base of updated recommendations to deprescribe specific drug classes, the addition of decision-making algorithms derived from the revision of clinical guidelines to treat common diseases (e.g., type 2 diabetes mellitus and major depressive disorder) and the reporting of PIPs and possible ADRs (e.g., potentially nephrotoxic drugs or drugs that may prolong the QT interval) according to the latest internationally validated studies allow optimizing clinical decision-making and improving the quality of patient care. In addition, close cooperation with the Infologic staff and discussion with NavFarma® users during and beyond the pilot study led to an extensive update of the platform's functionality and appearance. Among the most useful features introduced there are the customizable summary report templates developed to enable users to extract the desired information either to use as medical reports or to deliver to patients; this feature, in particular, has facilitated the use of the platform and made it usable in real time in clinical practice.

In this landscape, the clinical pharmacist plays a key role in the process of optimization of drug prescriptions and medication review. In fact, in my experience, it is the clinical pharmacist who uses the information provided by CDSSs to identify possible pharmacological interactions, inappropriate prescriptions or deprescription opportunities. Therefore, his or her expertise, supported by technology, enables the implementation of interprofessional collaboration with prescribing physicians that make possible the improvement of prescriptive appropriateness, the reduction of the risk of adverse events and the optimization of drug therapies, especially in complex or polypharmacy patients. Therefore, including the clinical pharmacist into hospital and territorial healthcare teams is crucial to ensure safe and rational drug use, as a previously conducted literature review has already shown. [20]

Another innovative aspect and starting point for this research project concerns the integration into the NavFarma® knowledge-base of information on the environmental impact of drugs. In fact, it has been known for years that some active ingredients can have negative effects on the ecosystem, polluting water and interfering with wildlife. Updating the NavFarma® knowledge-base with information on the environmental sustainability of drugs could guide clinicians toward more eco-friendly treatment choices, reducing the release of harmful substances into the environment and promoting more sustainable healthcare.

Modelled on the initiative promoted in Sweden (Pharmaceuticals and Environment database) [109], the possibility of posting online and making the green table implemented on NavFarma® public so that it can be consulted by healthcare professionals interested in environmental sustainability should be considered. This had already been done a few years ago with the table on possible interactions between drugs and herbs, vitamins or minerals, which after being developed in the DSTF and integrated into the NavFarma® knowledge-base had been made public by Infologic s.r.l. for free reference by community and hospital pharmacists (DAHLIA website). [106]

Also in the context of environmental sustainability of drugs, pharmacists (both hospital and community) assume an important role as they could inform physicians and patients about the environmental impact of drugs and guide them toward less environmentally harmful choices. To strengthen this competence, it is essential to implement training programs for pharmacists; in particular, it would be appropriate to include in the curriculum of pharmacists specific courses devoted to the environmental impact of drugs, the evaluation of ecotoxicity of active ingredients and the rational use of medicines. From my point of view, the availability of tools that summarize this knowledge combined with appropriate training could make the pharmacist a point of reference in promoting eco-sustainable drug practices.

Several initiatives to promote greener and more sustainable pharmacies have been implemented in Europe and are summarized in the document by the PGEU. [75] For example, in Belgium, pharmacist together with other stakeholders in the health sector regularly organize awareness campaigns to inform the public about the proper disposal of expired medications. In addition, an information booklet has been created and disseminated among citizens with instructions on how to properly dispose of expired or unused medications. In France, pharmacies mandatorily collect unused medications returned by patients, which are delivered to wholesalers who dispose of them properly. This campaign is publicized in pharmacies, big cities and beyond, and pharmacists have a stamp to place on prescriptions to remind patients to return unused medicines to the pharmacy. In Finland, the medicines agency has announced that it will release an environmental classification of medications in the coming years, while in Sweden a pharmacy has started an eco-label on over the counter (OTC) medications to help customers make responsible choices. Other European states, such as Czech Republic, Denmark and Italy, have agreements with companies responsible for collecting and disposing of expired medications from pharmacies (Assinde for Italy). [75]

6. FUTURE PERSPECTIVES

To conclude, not only the collaborations between the DSTF and healthcare facilities to conduct DUR will be strengthened, but also the collaboration with the Infologic s.r.l. will continue in the near future to ensure that the NavFarma® knowledge-base is always updated with new evidence and to further improve the NavFarma® CDSS to ensure greater use by healthcare professionals. In 2025, new webinars have planned by the Infologic company with DSTF researchers participation to illustrate the potential of NavFarma® to both consolidated and new users, with the aim of sharing experiences among the community of NavFarma® users and creating a network of clinical pharmacists, researchers and physicians experts in the field of medication review.

Our vision is that this group of experts on the use of drugs, in collaboration with healthcare facilities and with the Infologic company, can provide a sustainable model for the implementation of the medication review process in healthcare. Having an up-to-date CDSS is crucial to ensure technological support for the medication review process and to ease the workload of clinical pharmacists, promoting the quality of care in general, but innovation in digital tools supporting healthcare requires resources both in terms of personnel and economics. Therefore, participation in national and international calls for proposals and sharing experiences with key players in medication review will be essential to ensure adequate quality of service provided.

During the doctoral years, the DSTF together with the Infologic company applied to the international call “Transforming health and care systems” (THCS) [260] for the years 2023 and 2024 and the project “*Nord Ovest Digitale e Sostenibile*” (NODES) – Spoke 5: *Industria della salute e silver economy* [261] for the year 2023. These projects, unfortunately, did not receive funding but were deemed by the evaluators to be of an appropriate level both in terms of research design and social implications. The first project was written with the collaboration of international partners such as the University of Basel, the University of Saint Galles and the University of Edinburgh and concerned the identification of patients at risk of MRPs and the subsequent review of pharmacological therapies. The NODES project, on the other hand, concerned the creation and dissemination of a digital knowledge-base for healthcare professionals to support medication review.

The interest of both Infologic s.r.l. and the DSTF is to continue to participate in calls of this kind in order to have the strength to continue the work begun over the past few years.

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SUPPLEMENTARY MATERIALS

Table S1. Main activities carried out during the three years of Ph.D.

1st year
Scoping review to analyse strengths and limitations of CDSS
Research agreements with LHA and collection of drug dispensing data
Introduction to RStudio to conduct DUR
Update of the NavFarma® existing knowledge-base
Bibliographic research on the environmental impact of medications
2nd year
6-month period of research at Infologic s.r.l. to update and implement NavFarma®
Creation of new tables to feed the NavFarma® knowledge-base
DUR to assess medication adherence and persistence and identify prescription patterns
Participation in the calls for proposals "Transforming health and care systems (THCS)" and "*Nord Ovest Digitale e Sostenibile (NODES) – Industria della Salute e Silver Economy*"
3rd year
Pilot study to test the updated NavFarma® knowledge-base
Update of the NavFarma® features and webinars with NavFarma® users to illustrate the new version
DUR to investigate the use of lipid-lowering drugs in patients in the Valle d'Aosta Region
Bibliographic research on the ethical aspects related to the use of CDSS in clinical practice

Abbreviations: CDSS, clinical decision support system; LHA, Local Health Authority; DUR, drug utilization research

Table S2. List of peer-reviewed scientific publications classified according to topic

Papers published in scientific journals (8)	**Topics**
1) Armando LG, *et al*. *Healthcare* 2022;10:2567. doi:10.3390/healthcare10122567	DUR
2) Mucherino S, *et al*. *Healthcare* 2023;11:846. doi:10.3390/healthcare11060846	Medication adherence/DUR
3) Armando LG, *et al*. *BMJ Health and Care Informatics* 2023;30:e100683. doi:10.1136/bmjhci-2022-100683	CDSS
4) Armando LG, *et al*. *Healthcare* 2023;11:1655. doi:10.3390/healthcare11111655	Medication adherence/DUR
5) Armando LG, *et al*. *GIFaC* 2023; 37(4):174-178	Medication review
6) Armando LG, *et al*. *Pharmacy* 2024;12:21. doi:10.3390/pharmacy12010021	DUR
7) Grigolo S, *et al*. *Healthcare* 2024;12:231. doi:10.3390/healthcare12020231	Medication review
8) Sillano S, *et al*. *Boll SIFO* 2024;70(5):375-383. doi:10.1704/4376.43729	Medication adherence/DUR
Abstracts published in scientific journals (7)	
1-2) Miglio G, *et al*. Abstracts of the 41st Congress of SIF. *The Official Journal of SIF* 2023. doi:10.36118/pharmadvances.2023.50 (2 abstracts)	DUR
3-5) Armando LG, *et al*. Abstracts of the 26th ESPACOMP Annual Meeting. *Int J Clin Pharm* 2023. doi:10.1007/s11096-023-01537-5 (3 abstracts)	Medication adherence/DUR
6-7) Armando LG, *et al*. Abstracts of the 27th ESPACOMP Annual Meeting. *Int J Clin Pharm* 2024; doi:10.1007/s11096-023-01688-5 (2 abstracts)	Medication review/DUR
Posters presented at national/international congresses (4)	
1) Fassina D, *et al*. Poster presented at the XLV SIFO National Congress, Naples, Italy, 17-20 October 2024	Medication adherence/DUR
2) Sillano S, *et al*. Poster presented at the XLV SIFO National Congress, Naples, Italy, 17-20 October 2024	Medication adherence/DUR
3-4) Armando LG, *et al*. Posters presented at the 28th ESPACOMP Annual Meeting, Naples, Italy, 21-22 November 2024 (2 posters)	DUR
Papers submitted to scientific journals (1)	
1) Armando LG, *et al*. Medication adherence and time to initiation of lipid-lowering drug dispensing by pharmacies in the Valle d'Aosta Region (Italy) in patients with conditions associated with atherosclerotic cardiovascular diseases. Submitted to the *Internal Journal of Pharmacy Practice* (under review)	Medication adherence/DUR

Abbreviations: DUR, drug utilization research; CDSS, clinical decision support system;