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Safety clinical outcomes associated with the use of Idarucizumab for severe bleeding/emergency surgery: an observational population based study

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2. List of abbreviation

ATC	Anatomical therapeutic chemical classification system
DOAC	Direct oral anticoagulant
HAD	Healthcare administrative database
ICD-9CM	International classification of diseases, ninth revision, clinical modification
SDO	Hospital discharge record
VKA	Vitamin K antagonist

3. Abstract

Background and Rationale

Emergency surgery and life-threatening bleeding have been associated with increased morbidity and mortality among patients treated with anticoagulants. The recent increased use of direct oral anticoagulants (DOAC) has made the above more challenging. For many years, a specific antidote for these medication has not been available. Recently, the European Medicines Agency (EMA) approved a new monoclonal antibody called idarucizumab, a reversal agent for dabigatran.

Findings from the pivotal trial (RE-VERSE trial) showed that idarucizumab reversed the anticoagulant effect of dabigatran in 98% of treated individuals. However, some case reports and case series reported potential rebound effect in dabigatran levels after an initial dose of the drug.

So far, evidence on effectiveness and safety of idarucizumab in clinical practice is still limited. Therefore, new real-world studies are warranted to assess the relationship between idarucizumab use and safety clinical outcomes (i.e, mortality and re-hospitalization).

Objectives

This study aims at estimating:

- The risk of hospital mortality among idarucizumab treated individuals compared to non-treated individuals;
- The length of hospitalization among idarucizumab treated individuals compared to non-treated individuals;
- The risk of 30 days all-cause re-hospitalization among idarucizumab treated individuals compared to non-treated individuals.

Study Design

This will be a retrospective cohort study based on Healthcare administrative database (HAD).

Data source

This study will be based on the analysis of HAD from Tuscany (Italy). For each subject the following databases will be explored:

- Demographic registry;
- Hospital discharge records (SDO);
- Emergency department records;
- Outpatient care records;
- Prescription claims database;

- Database of diseases - specific exemption codes from co-payment to health care.

Methods

- Baseline demographic and clinical characteristics will be reported and compared across exposure cohorts by using frequencies and percentages for categorical variables (Pearson's chi-square test) and mean and standard deviation for continuous ones (Student's t-test and Mann-Whitney U test).
- The relationship between idarucizumab status and in-hospital mortality will be estimated by using univariate and multivariate logistic regression model. The results will be expressed as Odds Ratio (OR) with 95% confidence intervals (95%CI).
- The relationship between idarucizumab status and re-hospitalization, within 30 days, for any reasons will be estimated by using a Cox proportional hazard model with competing risk with death as the competing risk factor. Results will be expressed as unadjusted and adjusted Hazard Ratio (HR) with 95% confidence intervals (95%CI).
- The relationship between idarucizumab status and length of hospital stay will be estimated by using a general linear regression model with negative binomial distribution. The results will be expressed as Incidence Rate Ratio (IRR) with 95%CI.

4. Background and rationale

In the last decades, several anticoagulants have been approved for the prevention of stroke in patients with non-valvular atrial fibrillation and as preventive therapies for venous thromboembolism (Van Der Hulle 2014, Connolly 2009). These include dabigatran (Pradaxa ®), apixaban (Eliquis ®), rivaroxaban (Xarelto®) and edoxaban (Lixiana ®).

Although the new agents, classified as direct oral anticoagulants (DOAC), showed a favourable benefit-risk profile compared with older anticoagulants such as vitamin K antagonists (VKA), bleeding remains a relevant side effect. Bleeding represents a concern for both clinicians and patients because it is potentially associated with significant morbidity and mortality (**Singh 2020**). In case of bleeding caused by VKAs, the anticoagulant effect in emergency situation is reversed with a combination of vitamin K, fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa (**Schulman 2007**). Although haemodialysis is recommended for the elimination of dabigatran, and preclinical evidence suggests that concentrated coagulation factors may also reverse such type of bleeding (**Van Ryn 2010; Pragst 2012; Zhou 2011**), for many years a specific antidote for dabigatran or any other DOACs has not been available. In this context the absence of a reversal agent might have prevented the use of DOACs in many patients (**Van der Wall 2019**).

Recently, both the U.S Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved a specific reversal agent for dabigatran called idarucizumab (Praxbind ®). Idarucizumab is a humanised monoclonal antibody fragment (Fab) that rapidly and specifically binds to and leads to sustained neutralisation (up to 24h) and elimination of dabigatran with an affinity that is 350 times as high as that observed with thrombin (**Pollack 2015; Van Ryn 2010; Schiele 2013**).

Idarucizumab has been licensed in part on the basis of the results of an interim analysis of data on the first 90 patients enrolled in the Reversal Effect of Idarucizumab on Active Dabigatran (RE-VERSE AD) study (**Pollack 2015**). At the end of the aforementioned study, 503 patients treated with dabigatran were enrolled in the study cohort. The patients were grouped as following: group A, those with uncontrollable or life-threatening bleeding that was judged by clinician to require rapid anticoagulant reversal (301 patients); and group B, those who were about to undergo surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal haemostasis was required (202 patients). Patients were treated with 5 g of idarucizumab. The results of RE-VERSE AD showed that idarucizumab was associated with a reversed anticoagulation, rapidly and completely in more than 98% of treated individuals (**Pollack 2017**). In the same study, 23% of treated individuals presented an increase of dabigatran levels above 20 ng per millimetres during the next 24 hours, the majority of them within the first 12 hours (**Pollack**

2017). These elevations were associated with recurrent or continued bleeding, therefore some patients required a second dose of idarucizumab. The presence of this potential rebound in dabigatran levels after initial dose of idarucizumab was reported in several case reports and case series (**Rottenstreich 2016; Brennan 2019; Gendron 2017; Gendron 2018; Sheikh-Taha 2019**).

So far, few real word studies have been conducted to assess the effectiveness and safety of idarucizumab. These were conducted in specific setting such as ischemia-reperfusion setting (Berder 2020) or outside of European countries (**Singh 2020**). In addition, to the best of our knowledge, evidence on use of idarucizumab and related safety outcomes among treated and not treated individuals are limited and deserve further investigations. This calls for new studies able to provide more details on the relationship between idarucizumab use and safety clinical outcomes such as mortality and hospital readmission compared with untreated individuals.

5. Objectives

This study aims to determine the effect of idarucizumab on real world safety clinical outcomes in treated versus untreated individuals.

Specific objectives are as follows:

- To estimate the risk of hospital mortality among idarucizumab treated individuals compared to untreated individuals;
- To estimate the length of hospitalization among idarucizumab treated individuals compared to untreated individuals;
- To estimate the risk of 30 days all-cause re-hospitalization among idarucizumab compared to untreated non-treated individuals

6. Methods

6.1. Study design

This will be a retrospective cohort study based on the healthcare administrative database (HAD) of Tuscany (Italy).

6.2. Data Source

This study will be based on the analysis of Healthcare Administrative (HAD) data from Tuscany (Italy) that accounts for about 3,729,641 individuals (6% of Italian population).
The Tuscany HAD collects longitudinal pseudo-anonymized patient-level information on the utilization of healthcare services reimbursed by the National Healthcare Service and dispensed to all subjects who are residents and registered with a general practitioner in the relevant catchment areas. For each subject the following databases will be explored:

- Demographic registry: age, gender, start and end of registration in the Local Health Authority;
- Hospital discharge records: dates of admission and discharge, one main and five secondary diagnoses and 6 procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM);
- Emergency department records: dates of admission and discharge, one main and five secondary diagnoses and 6 procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM);
- Outpatient care records: healthcare services dispensed to free of charge or upon co-payment, such as specialist visits, laboratory or instrumental or bio-imaging diagnostic tests, and procedures in outpatient setting;
- Prescription records: information on drugs dispensing (e.g. active principle, ATC code, number of dispensed packages) as well as the date of dispensation. Drugs are registered in two databases: hospital pharmacies and community pharmacies;
- Database of diseases - specific exemption codes from co-payment to health care.

6.3. Study population

The study population will include adults (≥45 years old) under dabigatran treatment (ATC code: B01AE07) with emergency department access/hospitalization within the period January 1st, 2015 and December 31st, 2020 (see Tables 1 and 2 for details). The date of emergency department access/hospitalization will be considered as index date to define the patient's clinical characteristics and exposure assessment.

6.3.1. Inclusion criteria

- All individuals aged ≥ 45 years;
- Actively registered in the demographic registry at least one year prior to the index date;
- Emergency department access/hospitalization due to life-threatening bleeding or due to surgery or other invasive procedures that could not be delayed and for which normal haemostasis was required (see Paragraph 6.4 for details).

6.3.2. Exclusion criteria

- Use of dabigatran less than 90 days before the index date;
- Patients with less than 2 years of lookback prior the index date.

6.4. Cohort definition

In this study two cohorts of idarucizumab users will be identified. The first cohort (**Cohort A**) will include all individuals treated with idarucizumab due to life threatening bleeding (see Table 2 for details):

- Intracranial (subdural, subarachnoid, intracerebral);
- Gastrointestinal (lower, upper, unknown);
- Intramuscular;
- Retroperitoneal;
- Intrapericardial;
- Intraarticular;
- Intraocular;
- Trauma-related.

The second cohort (**Cohort B**) will include those who were treated with idarucizumab due to emergency surgery or procedure that cannot be delayed (see Table 2 for details):

- Abdominal condition or infection (hernia, peritoneal infection);
- Fracture or septic arthritis (involvement of the hip or femur);
- Cardiovascular condition (pacemaker implantation, aneurysm repair);
- Central nervous system condition (craniotomy);
- Pancreatic or hepatobiliary disease (cholecystitis, cholangitis);
- Respiratory condition (chest trauma);
- Kidney and urinary tract condition (acute renal failure);

- Septicaemia or sepsis;
- Skin condition (abscess, hematoma);
- Postoperative complications;
- Uterine condition.

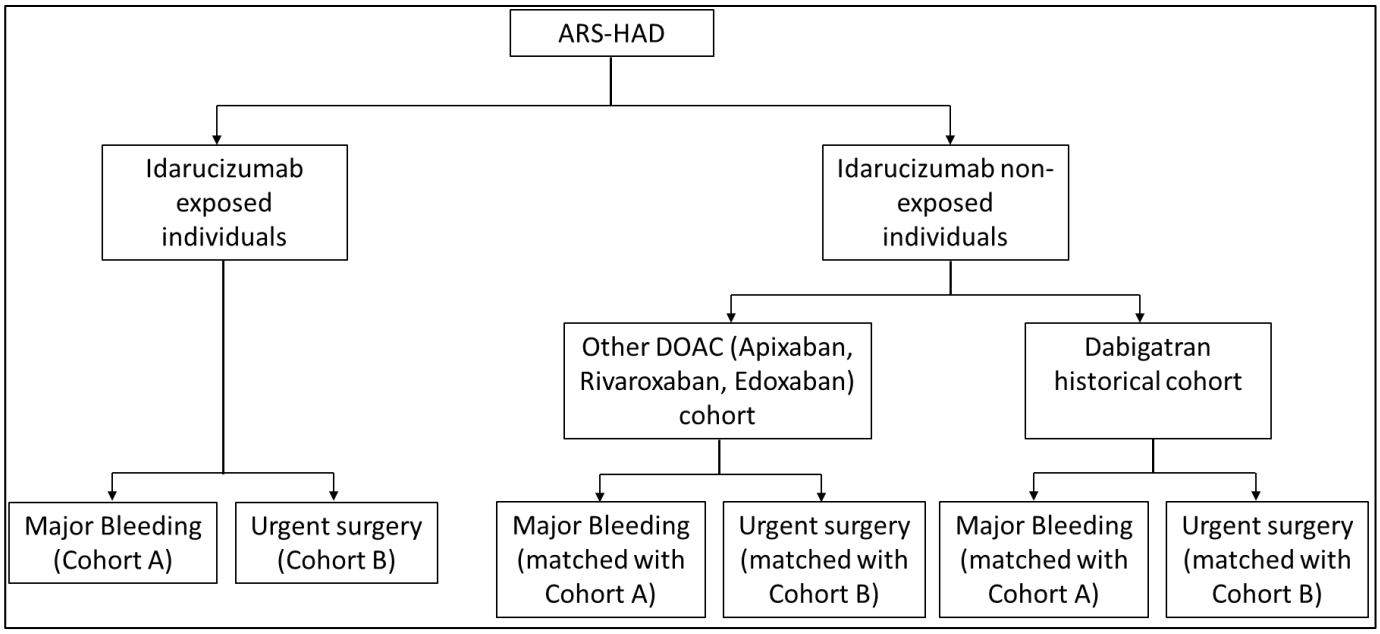
6.5. Exposure assessment and case definition

In Italy the use of idarucizumab is allowed only in hospital setting, during hospital admission or access to emergency department. This type of therapies is recorded by the hospital pharmacy records as daily transmission of a specific amount of drugs to a specific ward or emergency department. Therefore, a link between idarucizumab dispensing and users does not exist. For this reason, a probabilistic record-linkage will be used to link the idarucizumab dispensing at hospital ward or emergency department to dabigatran users accessing in the same departments within 1 day before or after drug dispensing date.

The exposed cohort will be matched with two cohorts including non-idarucizumab individuals (Figure 1). In particular, they will be selected as follows:

1. **Other DOAC cohort users.** This cohort will include all individuals treated with other DOACs (apixaban, edoxaban and rivaroxaban; see Table 1 for details) rather than dabigatran presenting an hospital admission, between January 1st, 2015 – December 31st, 2020, due to life threatening bleeding or emergency surgery/procedure that cannot be delayed (see Table 2 for details);
2. **Dabigatran historical cohort.** This cohort will include all dabigatran users referred to hospital due to life threatening bleeding or emergency surgery/procedure that cannot be delayed between January 1st, 2011 to December 31st, 2014, a period when idarucizumab was not available (see Tables 1 and 2 for details).

Figure 1. Cohort selection in the study period.



ARS-HAD: Healthcare Administrative Database of Tuscany.

6.6. Outcomes

- Risk of hospital mortality among idarucizumab treated individuals compared to untreated individuals. Mortality will be identified in SDO and demographic registry. In this analysis only the in-hospital events across the different cohorts will be considered.
- Length of hospitalization among idarucizumab treated individuals compared to untreated individuals. The length of hospitalization will be assessed as time between hospital access, with or without idarucizumab dispensing, and hospital discharge date;
- Thirty-day all-cause re-hospitalization risk in idarucizumab treated and untreated individuals. The event will be identified on the basis of having a hospitalization for any cause within 30 days from the discharge date of the initial hospitalization. The event will be identified in the SDO.

6.7. Follow-up

Patients will accumulate person time from data index until the first date between:

- End of follow-up (30 days after the hospital discharge date);
- Patient's exit from database;
- Outcome (as defined in Paragraph 6.6);
- End of study period, whichever occurred first.

6.8. Covariates

- Age (mean ± Standard deviation);
- Age class (45-54; 55-64; 65-74; 75-84; 85+)
- Sex;
- Number of hospitalizations prior the data index;
- Comorbidities at index date (see Table 3 for details). Comorbidities will be identified within 2 years prior the index date;
- Concomitant therapies at index date (see Table 4 for details). Drug exposure will be assessed within 6 months prior the index date;
- HAS-BLED index at index date will be calculated for each patient by summing points related to the comorbidities (see Table 5 for details) (**Ramagopalan 2018)**;
- Charlson Comorbidity index at index date will be calculated for each patient by summing points related to the comorbidities (see Table 6 for details). The score classes will be (0; 1-2; 3-4; 5+) (**Gonnella 2010; Ramagopalan 2018**).

6.9. Statistical analysis

6.9.1. Descriptive analysis

Baseline demographic and clinical characteristics will be reported and compared across exposure cohorts using standard statistical approaches. All categorical data will be shown as frequencies and percentages, and the statistics for continuous variable will be expressed as mean and standard deviation. Pearson's chi-square test will be used to compare categorical variables. Student's t-test will be used to compare continuous variables with normal distribution and the Mann-Whitney U test will be used to compare continuous variables with non-normal distribution.

For each study cohort, hospital mortality and 30 days all-cause re-hospitalization rates will be calculated by dividing the number of patients who experienced one of the study outcomes and the person-time at risk of developing the outcomes (since the data index). All rates will be reported with 95% confidence interval.

6.9.2. Cohort analysis

Cumulative hazard estimates will be plotted among the different exposure groups and log-rank tests will be used to compare outcome-free survival rate depending on the treatment status and study outcome. Then the relationship between idarucizumab exposure and in-hospital mortality, re-hospitalization for any cause and length of hospital stay will be estimated by using univariate and multivariate models. In particular:

- The relationship between idarucizumab status and in-hospital mortality will be estimated by using univariate and multivariate logistic regression model. The results will be expressed as Odds Ratio (OR) with 95% confidence intervals (95%CI);
- The relationship between idarucizumab status and re-hospitalization, within 30 days, for any reasons will be estimated by using a Cox proportional hazard model with competing risk with death as the competing risk factor. Results will be expressed as unadjusted and adjusted Hazard Ratio (HR) with 95% confidence intervals (95%CI);
- The relationship between idarucizumab status and length of hospital stay will be estimated by using a general linear regression model with negative binomial distribution. The results will be expressed as Incidence Rate Ratio (IRR) with 95%CI.

All the analyses will be performed for Cohort A and B (see 6.4 and 6.5 Paragraphs for details).

To address confounding resulting from imbalance in the baseline characteristics of the study population a multivariable logistic regression model to predict the propensity-score (PS) matched (1:1) analysis will be performed (**Austin 2008**). Each known predictor potentially associated to drug exposure and study outcomes will constitute the covariate vector which will be used to establish the propensity to drug use. In particular, the following variables will be considered: age, sex, comorbidities at index date, and HAS-BLED score. All variables will be imputed in the model in a non-parsimonious way according to methodological literature (**Patrick 2011**). Afterwards, exposure groups will be matched with non-exposed group by the corresponding PS±2 corresponding standard errors.

6.10. Data processing and data analysis

In this study both the data processing and data analysis will be performed by using the R studio software (version 4.0.2).

7. Ethical consideration

The study was approved by the governance board of ARS.

8. Dissemination and communication strategy

The study findings will be included in a report that will be shared with all the groups and experts. The main findings will be included in a manuscript that will be submitted to peer-review international journals. The partial and/or final results of the study will be included in abstracts that will be submitted to the relevant international conferences (e.g., ICPE, EUPHA, CTRIMS, AAN, EAN). Finally, a report will be included in the annual Tuscany drug report (Rapporto farmaci della Toscana).

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10. Appendix A

Table 1 – ATC codes associated with direct oral anticoagulants exposure.

Cohort exposure	Drug name	ATC code	Selection period
Cohort A and B	Idarucizumab	V03AB37	January 1st, 2015 – December 31st, 2020
Cohort A and B	Dabigatran	B01AE07	6 month prior index date
Other DOAC cohort	Rivaroxaban	B01AF01	January 1st, 2015 – December 31st, 2020
Other DOAC cohort	Edoxaban	B01AF03	January 1st, 2015 – December 31st, 2020
Other DOAC cohort	Apixaban	B01AF02	January 1st, 2015 – December 31st, 2020
Historical dabigatran cohort	Dabigatran	B01AE07	January 1st, 2011 to December 31st, 2014

Table 2 – Diagnosis associated with life threatening bleeding (Cohort A) and emergency surgery or procedure that cannot be delayed (cohort B).

	Diagnosis	ICD9-CM code
Cohort A	Gastrointestinal bleeding	456.0, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
	Intracranial bleeding	430.xx, 431.xx, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, 853.0x
	Bleeding from other sites	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11
Cohort B	Urgent surgeries	423.3, 441.0, 441.3, 441.5, 441.6, 512.0, 512.1, 530.4, 551*, 557.0, 567.21, 567.22, 567.3, 568.0, 596.1, 596.6, 728.86, 729.6, 729.7, 729.91, 729.92, 785.4, 806*, 807*, 860*, 870*, 871*, 878*, 885*, 886*, 887*, 895*, 896*, 897*, 900*, 901*, 902*

Table 3 – Algorithms for comorbidities identification in the study cohort at the index date.

Diasease	ICD-9 codes
Atrial fibrillation and flutter	427.3*
Heart failure	428*
Coronary heart disease	414*
Peripheral vascular disorder	443.9*
Myocardial infarction (MI)	410*, 411*, 412*, 413*
Hemorrhagic stroke	430*, 431*, 432*
Ischaemic stroke	434*
Transient ischemic attack (TIA)	435*
Systemic embolism (SE)	444*
Renal dysfunction	584*, 585*, 586
Liver dysfunction	571*
Gastrointestinal hemorrhage	578*
Arterial hypertension	401*
Diabetes mellitus	250*
Gastrointestinal (GI) cancer	150*-154*
Genitourinary cancer	182*-183*, 188*-189*

Table 4 – ATC code for concomitant therapies identification at the index date in the study cohort.

Drugs	ATC code
Antiplatelet drug	B01AC*
Antinflammatory medications (non-steroids)	M01A*
Gastric secretion inhibitor	A02B*
Statins	C10AA*
Antidepressants	N06A*
Heparins	B01AB*
Antineoplastic agents	L01*
Antipertensive agents	C02, C03, C07, C08, C09
Antidiabetics	A10*
Antineoplastic agents	L01*

Table 5 – HAS-BLED score algorithm.

Clinical characteristics	Study definition of the variable	Points awarded
H - Hypertension	ICD9-CM: 401-405	1
	ATC:	
A - Abnormal renal and liver function (1 point each)	Renal function - ICD9-CM: 582, 583, 585 and 586	1 or 2
	Liver function - ICD9-CM: 570-573 and 790.4	
S - Stroke	ICD9-CM: 433-438	1
B - Bleeding	ICD9-CM: 578, 430, 431, 432, 599.7, 786.3	1
L - Labile INRs	Not Applicable	
E - Elderly	Age of patients ≥ 65 years	1
D - Drugs or alcohol	ATC code: M01A	1 or 2

Table 6 – Charlson Comorbidity index score algorithm.

Clinical characteristics	Study definition of the variable (ICD9-CM)	Points awarded
Myocardial Infarction	410, 412	1
Dementia	290	1
Peptic ulcer disease	531-534	1
Congestive heart failure	428	1
Connective tissue/rheumatic disease	710, 714	1
Mild liver disease	571	1
Cerebrovascular disease	430-438	1
Diabetes mellitus	250.0-250.3	1
Chronic pulmonary disease	490-496, 500, 501	1
Peripheral vascular disease	4439, 7854	1
Hemiplegia	342	2
Leukemia	204-208	2
Any tumor	V580, V581, 140-239 excl. 196-199, 200-202, 204-208,	2
	ATC code: L01	
Diabetes with end-organ damage	250.4-250.6	2
Moderate or severe renal disease	583	2
Lymphoma	200-202	2
Moderate or severe liver disease	572	3
Acquired Immune Deficiency Syndrome	042-044	6
Metastatic solid tumor	196-199	6

For the CCI index and when a diagnosis is not be available, the prescriptions of specific drugs will be used as a proxy for the specific comorbidity; i.e., antihypertensive drugs (ATC: C02, C03, C07, C08, C09), statin (ATC: C10AA), organic nitrates (ATC: C01DA), antidiabetic drugs (ATC: A10A, A10B), anti-inflammatory and anti-rheumatic agents, non-steroids (ATC: M01A), macrolides (ATC: J01FA), proton pump inhibitors (ATC: A02BC).