XXVII Seminario Nazionale

LA VALUTAZIONE DELL'USO E DELLA SICUREZZA DEI FARMACI: ESPERIENZE IN ITALIA

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ISTITUTO SUPERIORE DI SANITÀ
CNRVF - Farmacoepidemiologia

Inappropriatezza prescrittiva in pazienti adulti di due regioni italiane: dati preliminari del progetto EDU.RE.DRUG

EDU.RE.DRUG project, funded by Italian Medicines Agency (AIFA)

Manuela Casula, *PhD*

UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE E BIOMOLECOLARI

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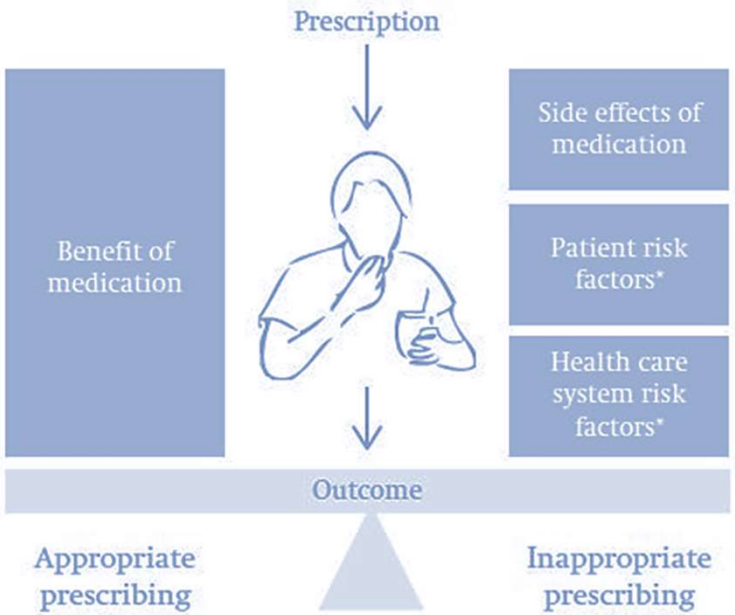
BACKGROUND

The appropriate prescription of medication should "**maximize efficacy and safety, minimize cost, and respect patient's preferences**".

Patients receive medications appropriate to their **clinical needs**, in **doses** that meet their own individual requirements, for an adequate **period of time**, and at the **lowest cost** to them and their community.

WHO, 1985



Inappropriate prescribing is **highly prevalent in older people** and has become a **global healthcare concern** because of its association with negative health outcomes including adverse drug events (ADEs), hospitalization, mortality and healthcare resource utilization and wastage.

EDU.RE.DRUG project: AIMS

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The **primary objectives** of the study are

- the retrospective **evaluation of rates of indicators** of appropriate prescribing (standardized drug-, disease- and patient-related process indicators), using Regional administrative demographic and pharmaceutical prescription databases
- the assessment of the **effectiveness of informative and/or educational interventions** addressed to general practitioners and their patients, aimed at improving prescribing quality and promoting proper drug use.

  Intervention effectiveness will be assessed measuring the variation in rates of inappropriate prescription indicators (ΔPIP).

METHODS - Flow Chart

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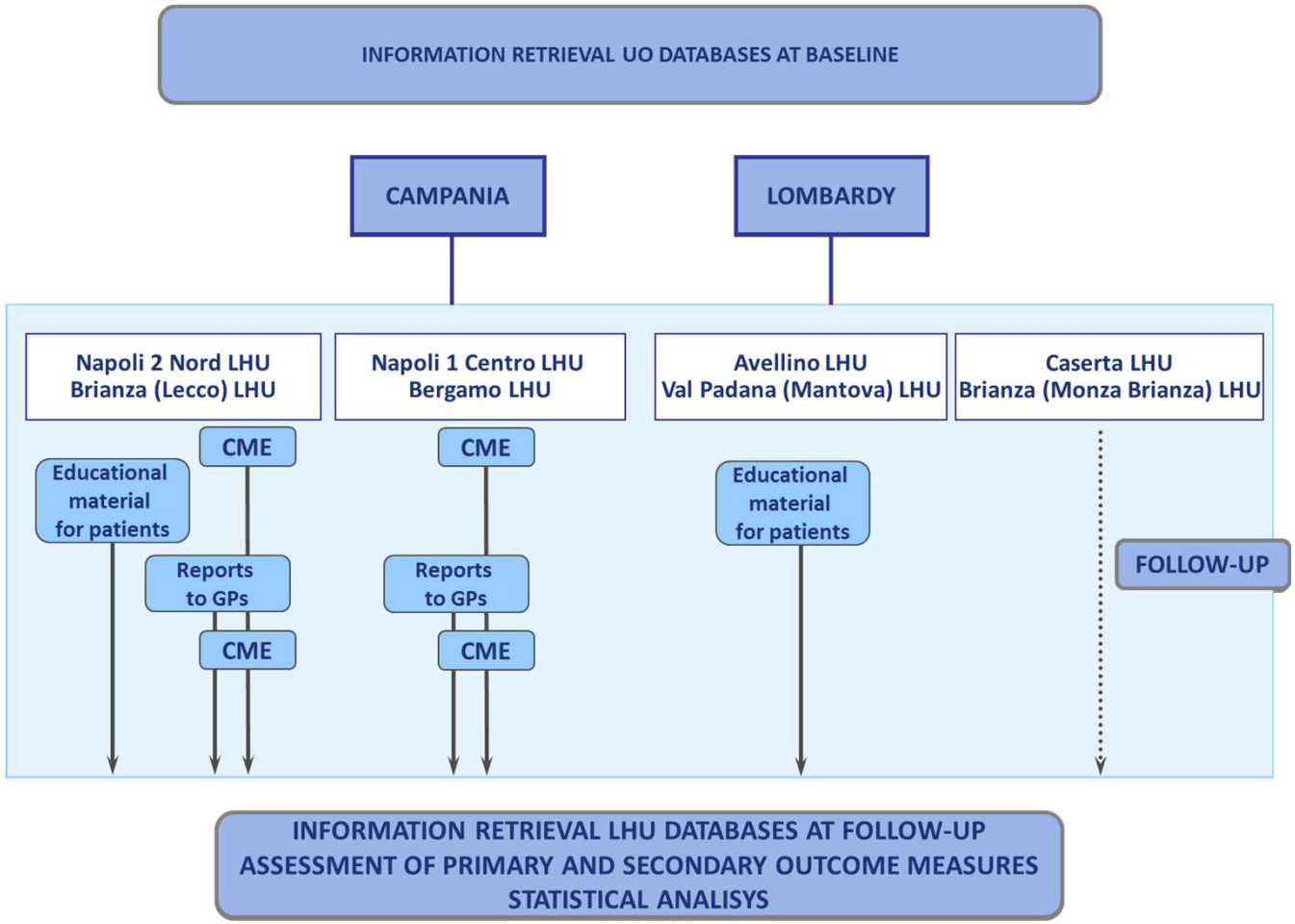
Study design

Multi-centre, open-label, parallel-arm, controlled, **pragmatic trial** directed to general practitioners and their patients.

Study population

The study population is composed by **all GPs** and all their **adult patients** of **Lombardy and Campania**.
The analysis focuses on **elderly** (over 65 years).



Indicators of appropriateness

You can't manage what you can't measure

Explicit (criterion-based)

- developed from literature reviews, expert opinions, consensus techniques
- lists of drugs, drug-classes, dosages (drug/disease specific)
- applied with little/no clinical judgement
- regular updates needed
- country-specific adaption necessary
- e.g. tools: Beers, McLeod, START&STOPP, PRISCUS

Implicit (judgement-based)

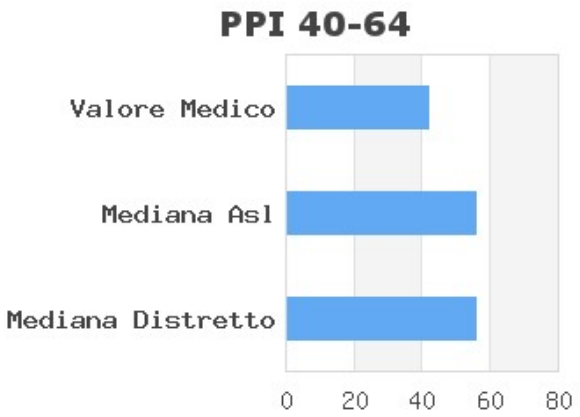
- rely on expert professional judgement
- focus on the patient, address entire medication regimen (patient specific) and clinical individual context
- time consuming
- e.g. tools: MAI, PAI, Lipton Criteria

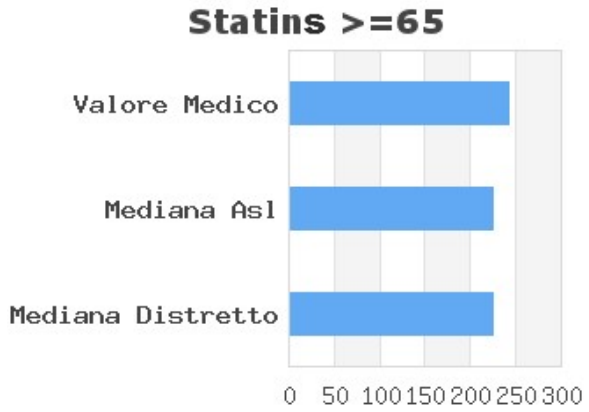
GPs' performance indicators

- **General characteristics of prescription behavior**

- **Polytherapy**

- **Under/overprescribing** of selected drugs or drug classes, estimated as percentage of patients on treatment and as amount of DDD per 1000 ab die:
  - PPIs
  - ACE-inhibitors
  - Angiotensin receptor blockers
  - Statins
  - Antibiotics
  - SSRIs
  - SNRIs
  - Anti-asthmatic drugs





Potential DDIs

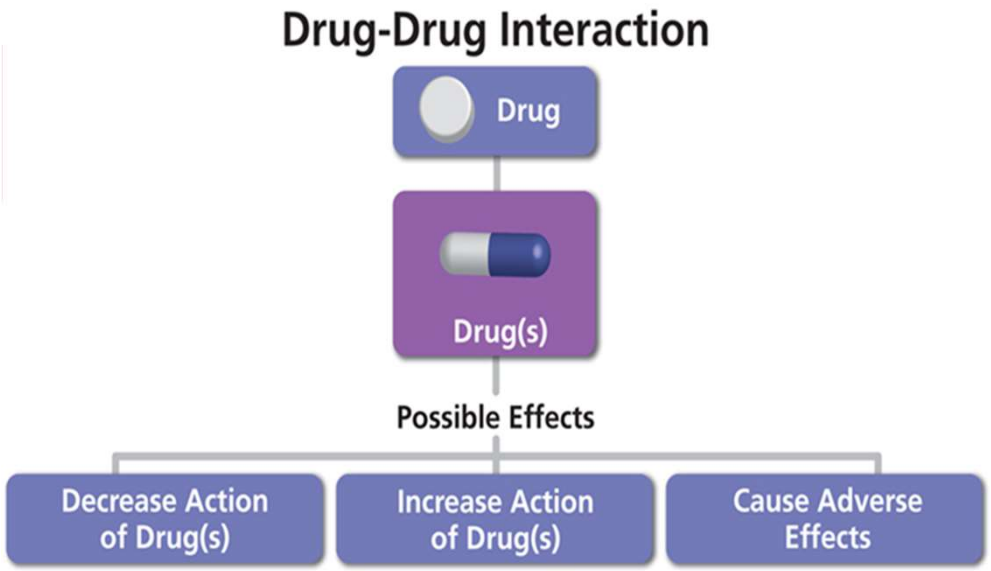
• **Drug–Drug Interactions** (**DDIs**), defined as ‘‘two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered’’, are preventable medication errors associated with serious adverse events and death

• the prevalence of potential DDIs among ambulatory patients can be investigated by examining administrative databases (**MediRisk**)

• All drug interactions are classified according to two parameters:

-clinical relevance that takes into account potential clinical outcomes, and the type, quality, and relevance of supporting clinical data (**A, B, C, D**)

-pharmacological documentation (**0, 1, 2, 3, 4**)



Therapeutic Duplication

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• **Therapeutic duplication** (TD) is defined as prescribing and dispensing of two or more drugs from the same therapeutic category such that the combined daily dose puts the patient at increased risk of adverse drug reactions without additional therapeutic benefits.
TD has no clinical benefit and only results in waste of medications, adverse drug reactions, reduced patient safety and excess healthcare costs.

• To evaluate this indicator we check for therapeutic duplication between drugs by cross referencing the **ATC codes** (Anatomical Therapeutic Chemical codes) as defined by the WHO.

	ATC Level	ATC Code	ATC Text
1	Anatomical Main Group	*A*	*Alimentary tract and metabolism*
2	Therapeutic Subgroup	*A10*	*Drugs used in diabetes*
3	Pharmacological Subgroup	*A10B*	*Oral blood glucose lowering drugs*
4	Chemical Subgroup	*A10B A*	*Biguanides*
5	Chemical Substance	*A10B A02*	*Metformin (DRecNo: 827)*

List of PIM (Italian harmonization)

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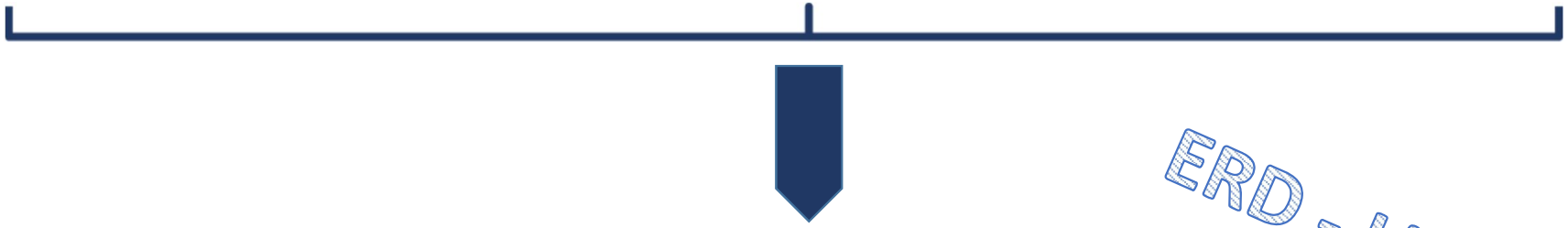
Beers Criteria
updated in 2015
by *American Geriatric Society*

STOPP
(Screening Tool of Older People's Prescriptions)
updated in 2014

EU(7)-PIM List
European list of potentially inappropriate medications for older people (2015)



ERD - List

LIST OF POTENTIAL INAPPROPRIATE DRUGS FOR OLDER PEOPLE IN ITALY:

Among 288 original drugs, 192 are in commerce in Italy and 123 are reimbursed by Italian National Health Service

Anticholinergic or Sedative Burden Scores

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Drugs with ACB Score of 1

Generic Name	Brand Name
Alimemazine	Theralen™
Alverine	Spasmonal™
Alprazolam	Xanax™
Aripiprazole	Abilify™
Asenapine	Saphris™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Cetirizine	Zyrtec™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clidinium	Librax™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Desloratadine	Clarinex™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Iloperidone	Fanapt™
Isosorbide	Isordil™, Ismo™
Levocetirizine	Xyzal™
Loperamide	Immodium™, others
Loratadine	Claritin™
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	Procardia™, Adalat™
Paliperidone	Invega™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Venlafaxine	Effexor™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
Meperidine	Demerol™
Methotrimeprazine	Levoprome™
Molindone	Moban™
Nefopam	Nefogesic™
Oxcarbazepine	Trilepta™
Pimozide	Orap™

Categorical Scoring:

- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:

- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. [3]
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. [4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. [4]

Aging Brain Care

www.agingbraincare.org

Drugs with ACB Score of 3

Generic Name	Brand Name
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Doxylamine	Unisom™, others
Fesoterodine	Toviaz™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Propiverine	Detrunorm™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Solifenacin	Vesicare™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™
Trospium	Sanctura™

Anticholinergic Burden Score

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Drugs with ACB Score of 1

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Aripiprazole	Abilify™
Asenapine	Saphris™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Cetirizine	Zyrtec™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clidinium	Librax™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Desloratadine	Clarinex™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Iloperidone	Fanapt™
Isosorbide	Isordil™, Ismo™
Levocetirizine	Xyzal™
Loperamide	Immodium™, others
Loratadine	Claritin™
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	Procardia™, Adalat™
Paliperidone	Invega™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Venlafaxine	Effexor™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
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Methotrimeprazine	Levoprome™
Molindone	Moban™
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Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Doxylamine	Unisom™, others
Fesoterodine	Toviaz™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Propiverine	Detrunorm™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Solifenacin	Vesicare™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™
Trospium	Sanctura™

Sedative Load Model

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• The **Sedative Load (SL) Model** was developed by reviewing the summary of product characteristics for all drugs available in Finland from 1998 to 2001 (Linjakumpu et al. 2003). The model was developed to represent a comprehensive classification of all drugs on market and to include also drugs for somatic disorders.

• All drugs are classified into 1 of 4 groups based on their sedative potential:

-Group 1 (primary sedatives, 40 drugs) included only psychotropics were assigned a sedative rating of **2**.

-Group 2 (drugs with sedation as a prominent side effect or preparations with a sedating component, 80 drugs) included many drugs for somatic disorders. They were assigned a sedative rating of **1**.

-Group 3 (drugs with sedation as a potential adverse effect, 220 drugs) included the major medicinal categories, and only drugs for somatic disorders.

-Group 4 (drugs with no known sedation). Drugs in groups 3 and 4 were not assigned a sedative rating.

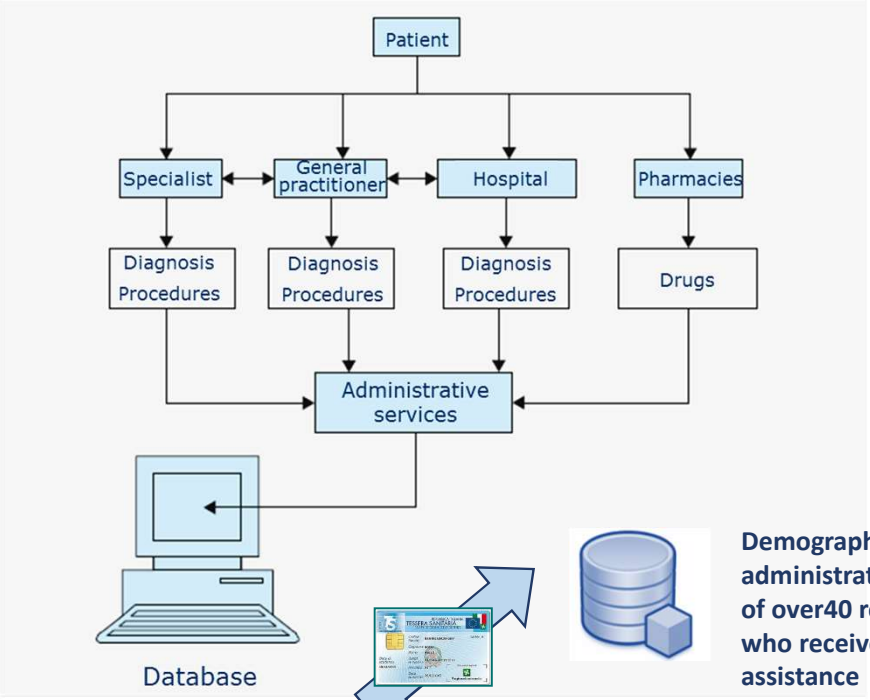
• Only regularly used drugs are considered when calculating sedative load.

• Sedative load was calculated by summing the sedative rating for each drug in a person's medication regimen, according to the following formula:

$$\text{Sedative Loading (SL)} = \sum_{k=1}^{n} SR_k$$

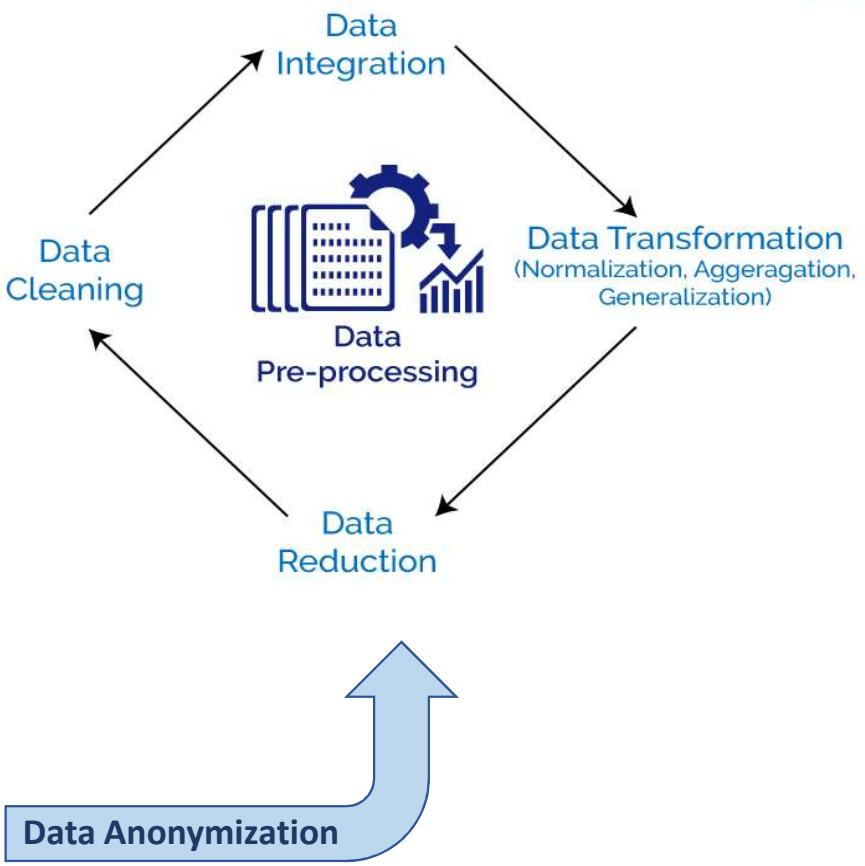
where: n = number of drugs and SR_k = sedative rating for drug k

METHODS – Data sources management



Demographic and administrative data of over40 residents who receive NHS assistance

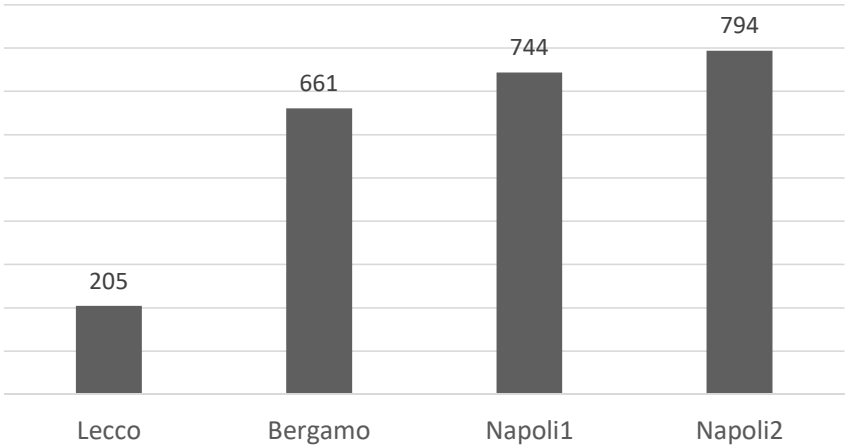
Outpatient prescriptions for drugs dispensed and reimbursed by the NHS

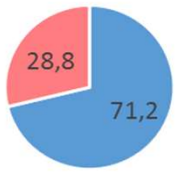
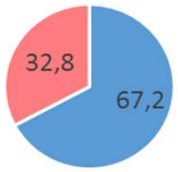
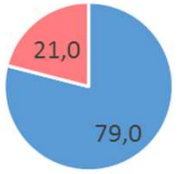
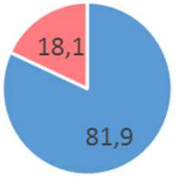


RESULTS

LHU	LHU Population	Prescriptions in 2016
Bergamo	1.108.298	**7.072.098**
Lecco	339.254	**2.125.844**
Tot Lombardy	1.447.552	9.197.942
Napoli 1 Centro	1.032.705	**11.772.353**
Napoli 2 Nord	1.052.947	**10.861.379**
Tot Campania	2.085.652	22.633.732

General Practitioners working in 2016



Gender, %				
GP Age, mean (SD)	58,3 (7,0)	57,7 (6,9)	61,7 (4,5)	60,0 (5,0)
GP Population, mean (SD)	1465 (214)	1407 (274)	714 (277)	657 (266)

RESULTS

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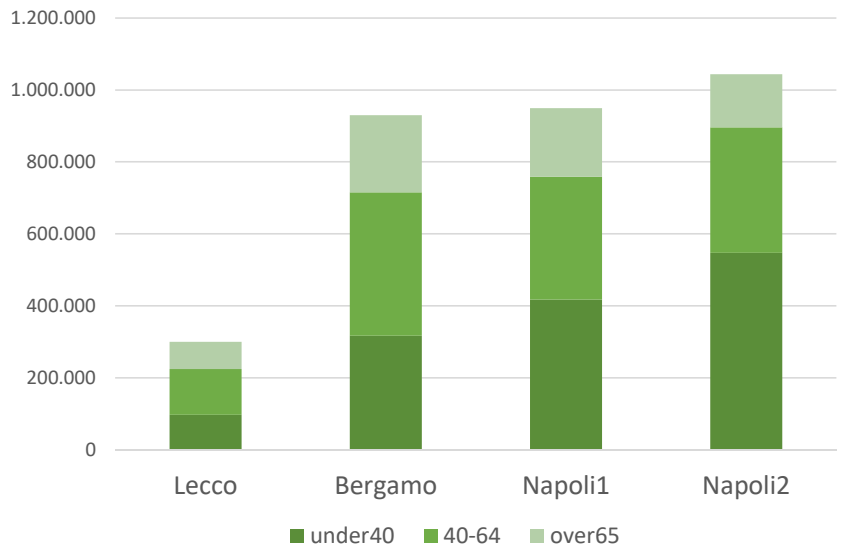
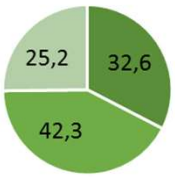
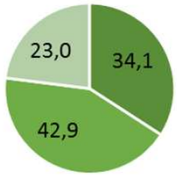
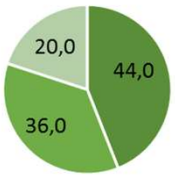
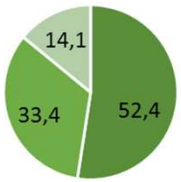
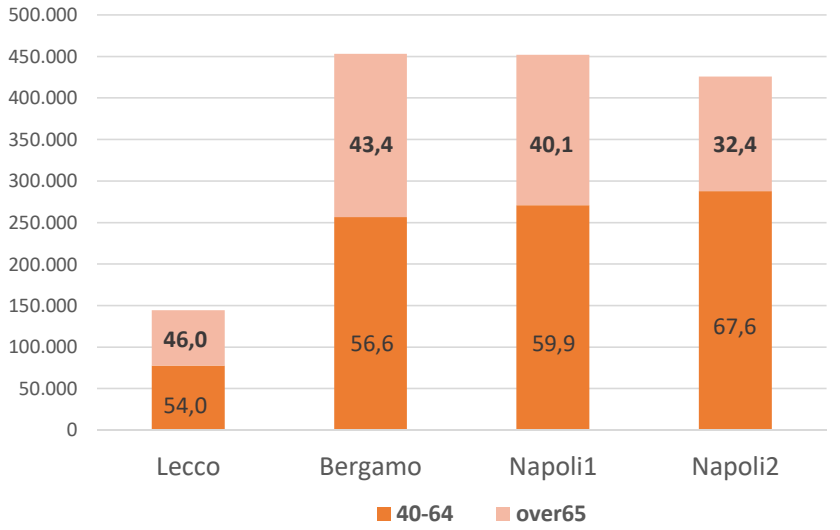
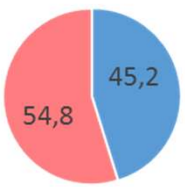
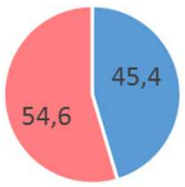
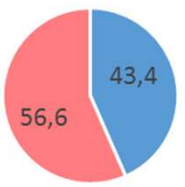
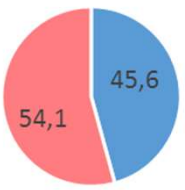
Age distribution of LHUs population



	Lecco	Bergamo	Napoli1	Napoli2
Percentage				

Over40 patients with at least 1 prescription in 2016



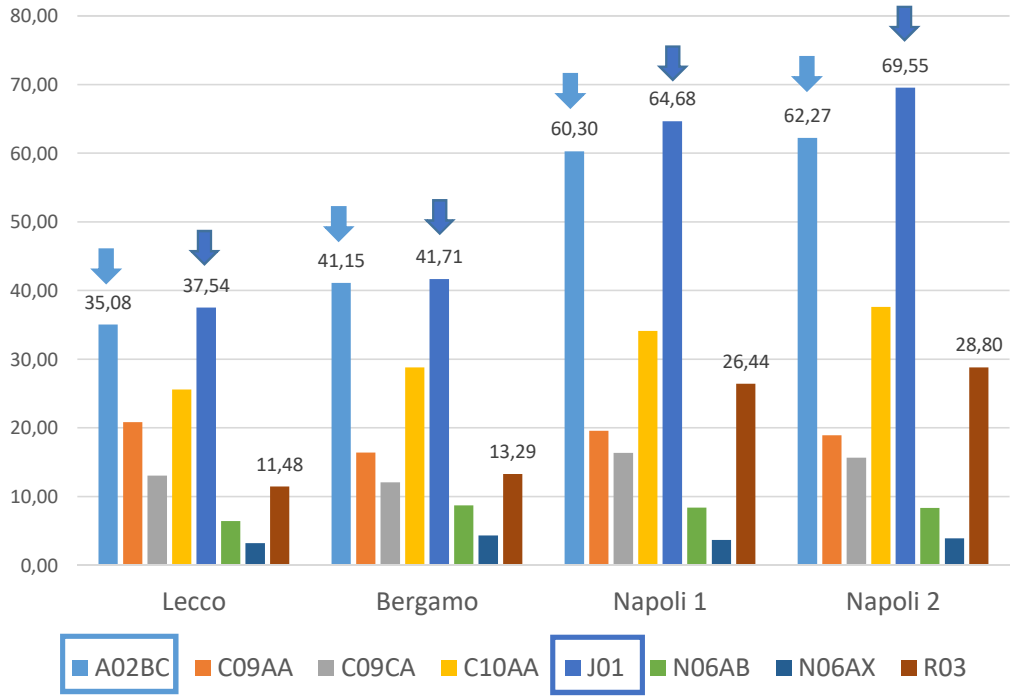
	Lecco	Bergamo	Napoli1	Napoli2
Gender, %				
Age, mean (SD)	63,0 (13,5)	62,2 (13,5)	61,4 (13,3)	58,9 (12,7)

RESULTS

Polytherapy

Number of drugs		1-4	5-9	≥10
Lecco	40-64 years	53,6	7,2	0,6
	Over 65 years	47,5	34,2	6,3
Bergamo	40-64 years	55,4	8,0	0,8
	Over 65 years	46,3	37,0	8,9
Napoli 1	40-64 years	49,9	19,2	4,1
	Over 65 years	28,0	43,2	22,6
Napoli 2	40-64 years	53,0	22,5	4,7
	Over 65 years	25,2	40,1	23,5

% of elderly on treatment



RESULTS

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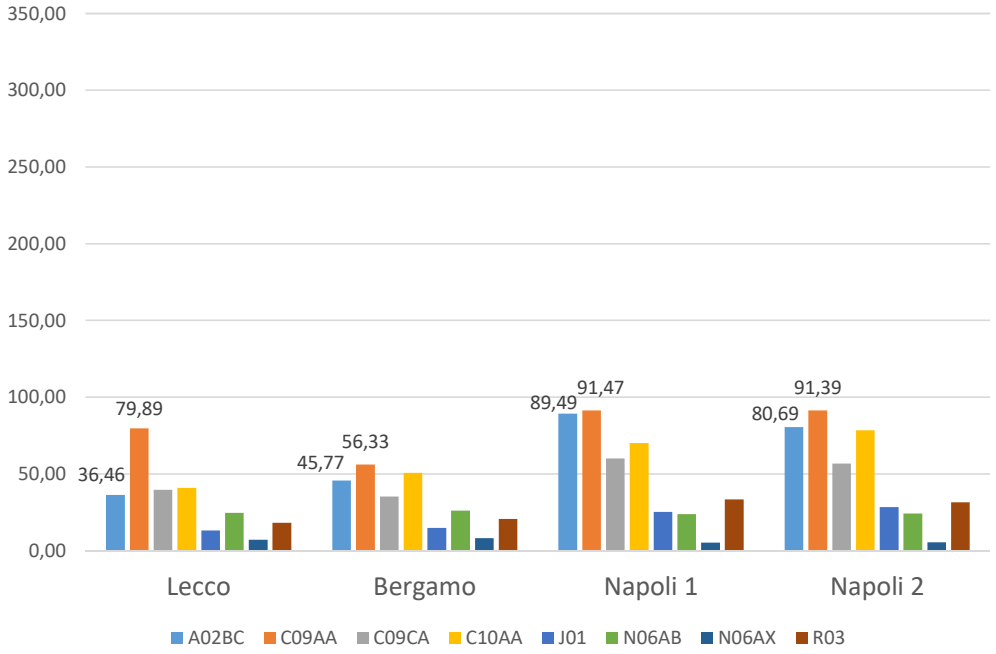
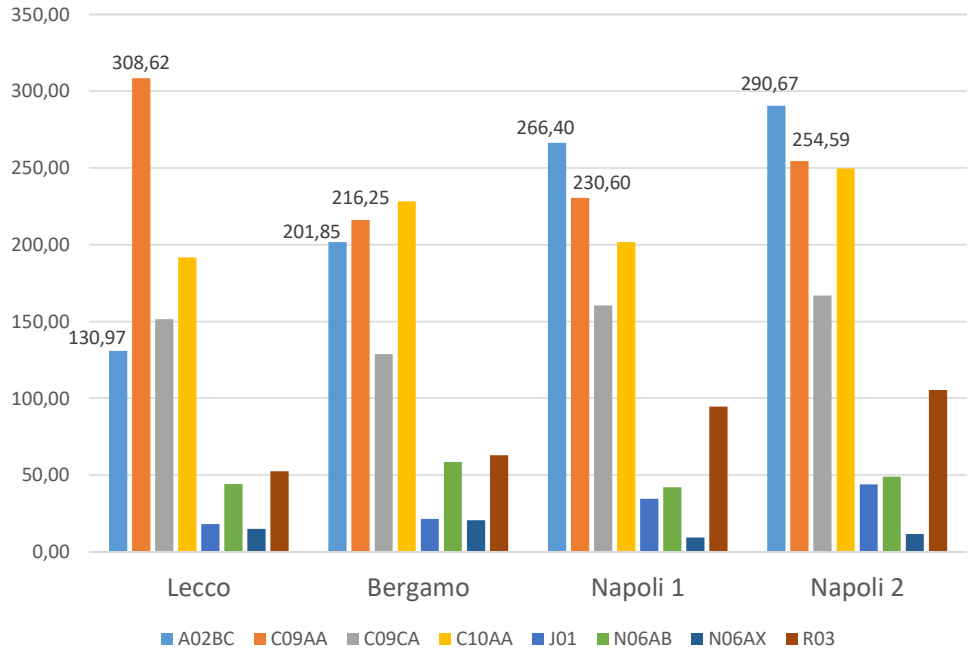
DDD/1000 ab * die
40-64 years



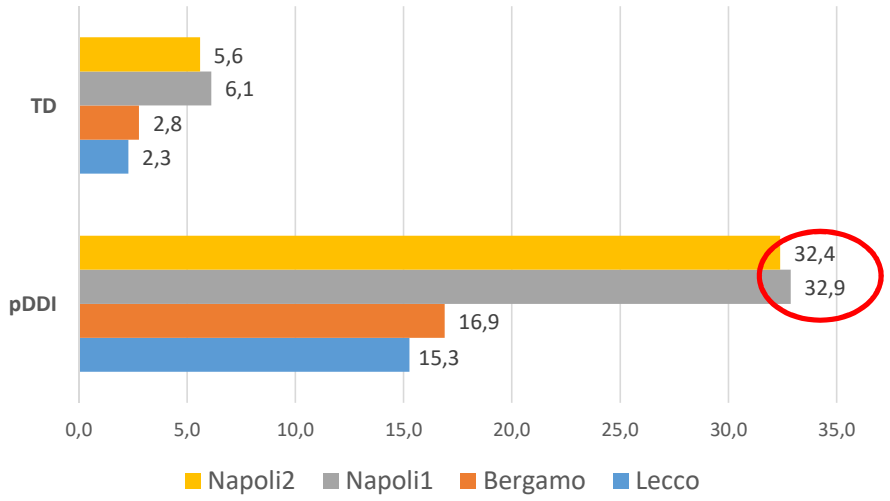
DDD/1000 ab * die
Over 65 years



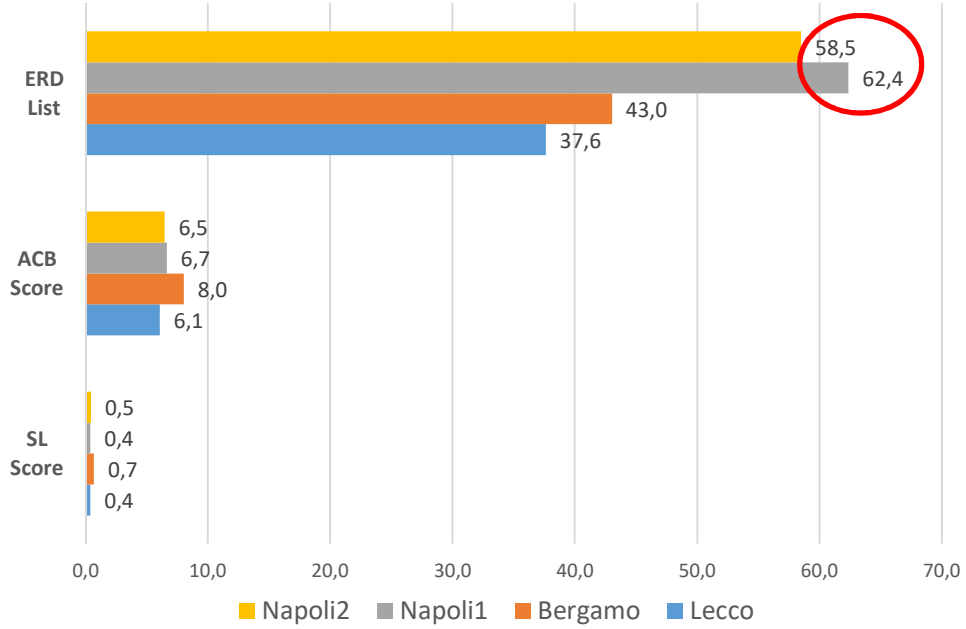
RESULTS

Inappropriateness of prescribing

Over40



Elderly



CONCLUSIONS

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- The prescription of potentially inappropriate drugs in adult patients is widespread, with some remarkable geographical differences

- It is necessary to implement local strategies to improve the rational use of drugs, including information/education for healthcare professionals and for the public from independent sources and the identification of therapeutic areas most affected by inappropriate prescribing, in order to establish priorities for action, focus efforts and optimize the scarce resources available

- enhancing safe prescribing practices
- reducing costs associated with inappropriate/unnecessary prescribing
- optimizing healthcare resource utilization and wastage

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Azienda Sanitaria Locale Napoli 1 Centro

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA
DiSMeQ
Dipartimento di Statistica e Metodi Quantitativi

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Thanks for your attention!