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am Klinikum Augsburg

Dr. Ute Amann
Fachapothekerin für Klinische Pharmazie
Master of Public Health, postgrad.

Pharmakoepidemiologie: Arzneimittelanwendungsforschung

Studiengang Pharmazie, WS 2018/19
11.10.2018



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Zielsetzung des Seminars

- Einblicke in die Arzneimittelanwendungsforschung (drug utilization research = DUR) geben
- Notwendigkeit für DUR in der Pharmakoepidemiologie (PE) und Pharmakovigilanz aufzeigen
- Interesse für PE/DUR wecken
- Auf “exotische” Arbeitsplätze für Pharmazeuten hinweisen
- Beispiele aus der PE/DUR-Forschung zeigen bzw. diskutieren

Inhalte des Seminars / Contents

- **Relevance of Drug utilization research in Pharmacoepidemiology**
- Medication: assessment, drug treatment episodes, adherence and quality/safety
- Drug utilization studies - examples

Arzneimittelanwendungsforschung / Drug utilization research (DUR)

I. Definition

Drug utilization was defined by the World Health Organization (WHO) as the “marketing, distribution, prescription and use of drugs in a society, which special emphasis on the resulting medical, social, and economic consequences”

II. Concept and aims of drug utilization research (DUR)?

- Use of drugs in a society
- Drug safety, effectiveness, over-/underutilization, cost

Drug utilization research (DUR) is the key in pharmaceutical risk management

Drug safety = drug + 'context'

drug: specific characteristics of each drug such as data about pharmacokinetics, -dynamics and -genomics, and known adverse drug reactions

'context': patient-related aspects such as severity of the disease, co-morbidity, co-medication, susceptible phenotype, demographics and socioeconomic status, and usage environment (e.g., non-compliance, usage error, drug interaction)

- **Drug utilization research** investigates the 'context' of drug use in real-life patient care

Common aims of drug utilization studies

To estimate drug utilization in a society (population) by:

- User groups:
 - young vs. elderly persons (age)
 - men vs. women (sex)
 - 'special populations' = elderly, pregnant women or children
 - social classes (high vs. low income)
 - disease severity, patients' comorbidity
- Dose of treatment
 - prescribed daily dose vs. consumed daily dose
- Duration of treatment
- Indication: On- or Off-label (within a non-approved indication)
- Assessment of adherence to guidelines or medication adherence
- Frequency of relevant drug interactions
- Identification of over- or underutilization

Notwendigkeit für DUR in der Pharmako-epidemiologie (PE) und Pharmakovigilanz

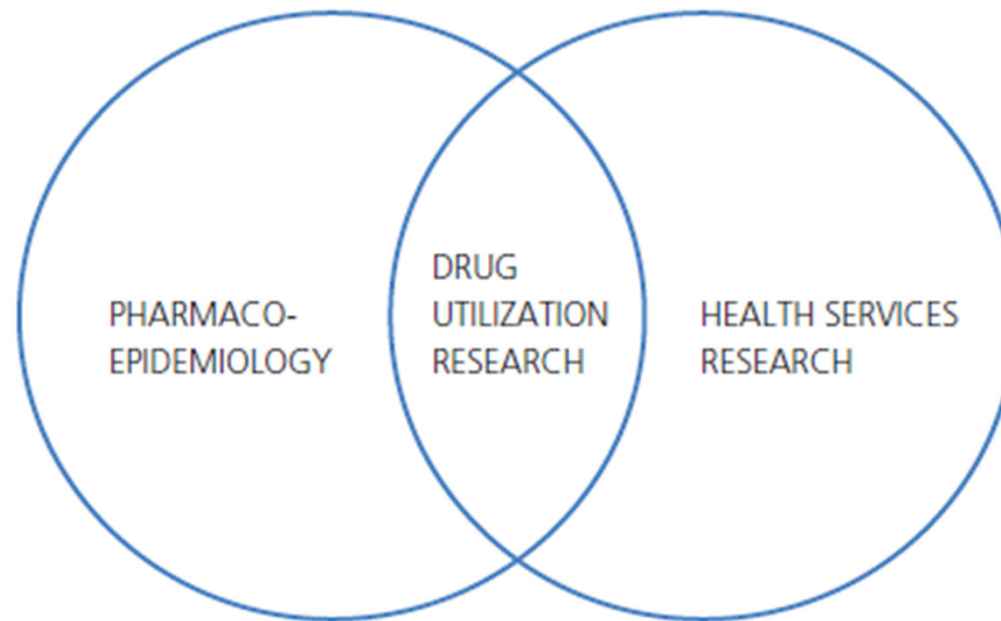
- Results of DUR can be used as denominator data for calculating frequency of adverse drug reactions (ADR) in real-life patient care

$$\text{Frequency of ADR} = \frac{\text{Number of patients with ADR}}{\text{Number of exposed persons}}$$

- Reported frequency of ADR are based on ,artificial‘ RCTs (small sample size, limited duration, homogeneous study population) often conducted before market approval
- DUR is sometimes required by the EMA/FDA for a newly-approved drug:
 - ✓ Post-authorization safety study (PASS)
 - ✓ Post-authorization efficacy studies (PAES)
 - ✓ Post-marketing safety surveillance and Risk Evaluation and Mitigation Strategies (REMS)

DUR, drug utilization research

Drug utilization research (DUR) and related fields



- Drug utilization research is part of **Pharmacoepidemiology (PE)**
- Drug utilization research links PE to **Health Services Research (Versorgungsforschung)**

Traditional description of DUR and PE

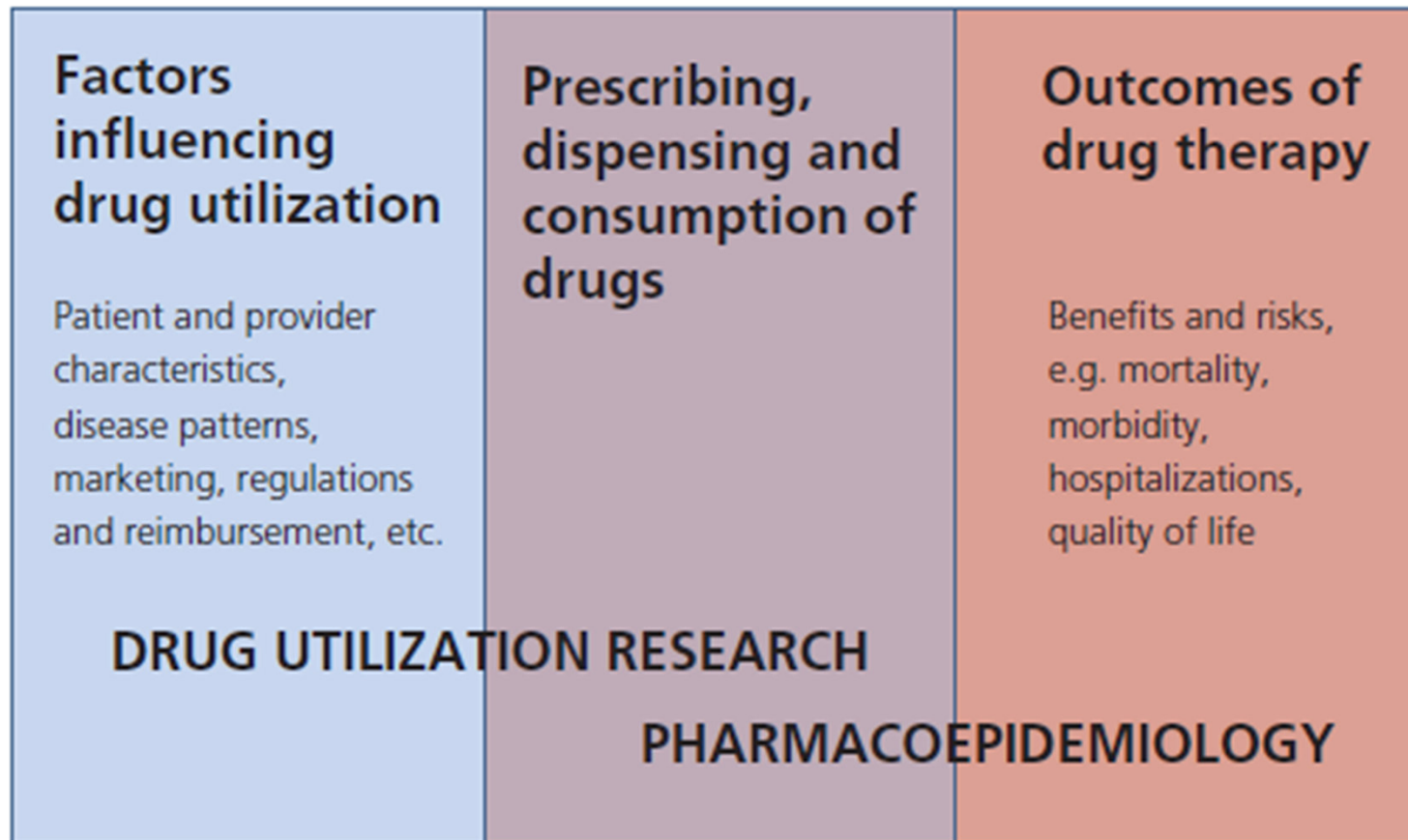
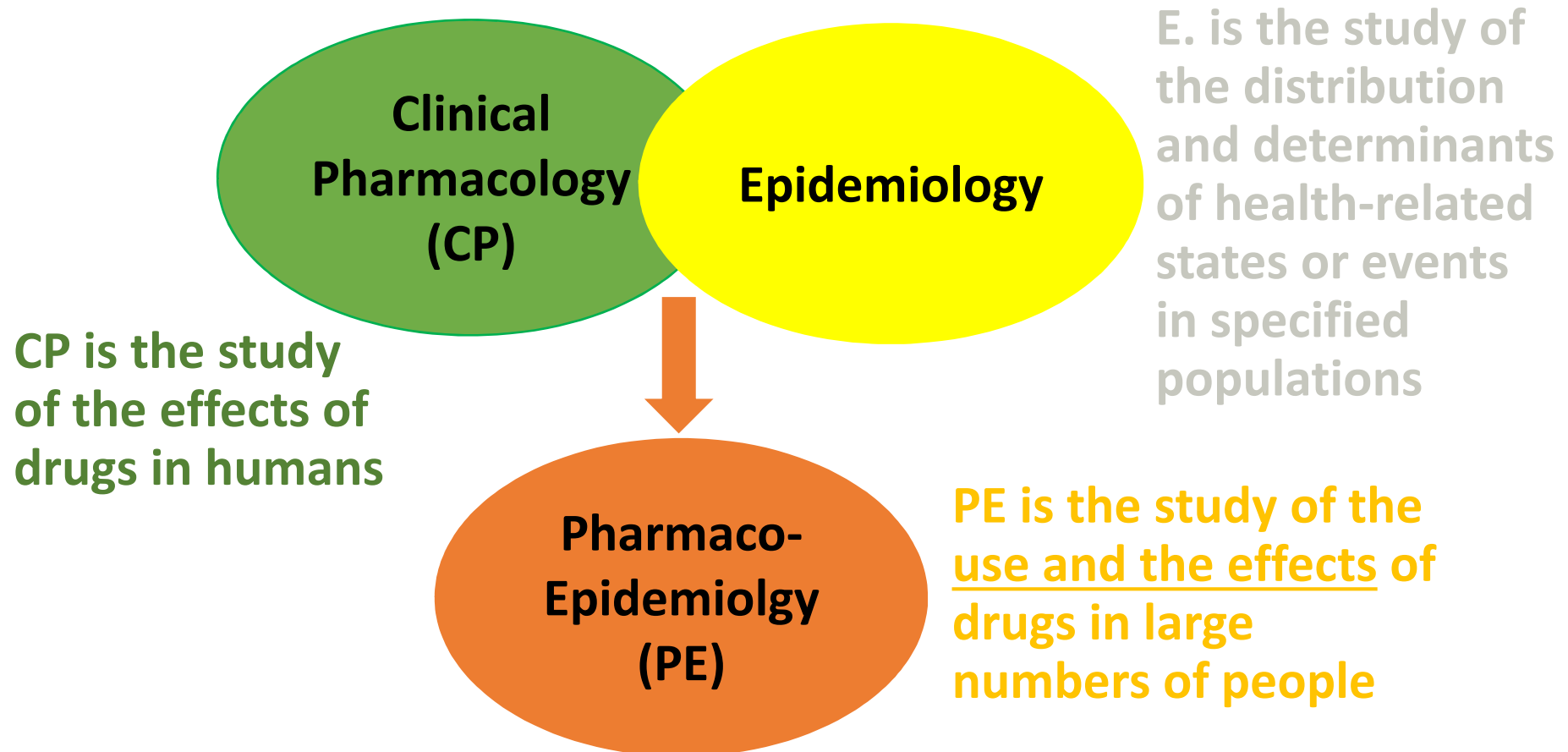


Figure 1.2 Traditional descriptions of drug utilization research and pharmacoepidemiology.

Definition Pharmacoepidemiology?



Contents

- Relevance of Drug utilization research in Pharmacoepidemiology
- **Medication: assessment, drug treatment episodes, adherence and quality/safety**
- Drug utilization studies - examples

How is drug use assessed?

Important data sources

- Databases on prescribed or dispensed drugs
 - Administrative claims/insurance data (e.g., GePaRD in Germany)
 - Population-based PE database (all Nordic countries)
- Health statistic database
 - Report of dispensed drugs by pharmacies
 - General Practice Research Database (UK), Health maintenance organizations (USA): used now as dedicated PE record linkage database
- Disease-based registries: medical charts, hospital discharge reports and self-reported drug intake by patients using a standardized questionnaire
- Field studies: patient interviews/questionnaire
- Electronic medication list

GePaRD, German Pharmacoepidemiological Research Database, BIPS, Bremen

Exercise: Medication Assessment

Common Method of medication assessment

- I. **Administrative claims database:** *reimbursed ambulatory medication*
- II. **Medical charts:** *drugs documented by physicians in general practice*
- III. **Field studies:** *medication use reported by patients*

Discuss (dis)advantage of each method

- Type of data source: Primary vs. secondary data
- Completeness: POM (Prescription Only Medicines), OTC (over the counter) drugs, restriction to specific disease or care (primary, ambulatory, hospital vs. ambulatory medication, privately vs. statutory insured persons)
- Medication use vs. prescription, daily dose, duration of use, single vs. multiple prescribing
- Costs of data collection

Prescription and OTC Medication use assessed with a standardized questionnaire or a software tool



IDOM-Software tool

...to gather data on medication based on the information provided by study participants and the packaging they bring with them to the KORA or NAKO study center

KORA, Cooperative Health Research in the Region of Augsburg, Germany; NAKO, The German National Cohort

13) Haben Sie innerhalb der letzten 7 Tage Medikamente verwendet? Denken Sie bitte auch an Insuline, die Pille, Hormonersatzpräparate oder länger wirkende Depotmittel für Frauen!

☐ Ja ☐ Nein → Wenn „Nein“, bitte weiter mit Frage 14



Wenn Ja, welche Medikamente waren das?

Machen Sie bitte Ihre Angaben in der folgenden Tabelle!

Gehen Sie dabei folgendermaßen vor:



Geben Sie den **genauen und vollständigen Namen** des Medikamentes an.

Wenn **vorhanden**: Tragen Sie die **PZN-Nummer** ein. Sie finden Sie meist unter dem **Strichcode** auf einer der 6 Seiten der Medikamentenschachtel. Die Buchstabenfolge „PZN“ steht immer vor der Nummer; die Nummer ist immer 7-stellig.

Tragen Sie bitte auch noch folgendes ein:

- die **Darreichungsform** (z. B. Dragees, Tabletten, Kapseln, Tropfen, Zäpfchen, Spritzen) des Medikamentes
- die **Packungsgröße** des Medikamentes, d. h. die Menge in der Packung mit Einheitsbezeichnung (z. B. 10 Tabletten)
- die **Dosierung**, d. h. die Menge, die Sie einnehmen mit Einheitsbezeichnung und das Zeitintervall (z. B. 1 Tabl. pro Tag)
- **Seit wann** Sie das Medikament einnehmen
- ob Sie das Medikament vom Arzt auf Rezept **verordnet** bekommen haben **oder nicht**
- ob Sie das Medikament **regelmäßig** (z. B. täglich, dreimal pro Woche, einmal pro Monat) **oder nach Bedarf** (z. B. bei Kopfschmerzen, bei Erkältungen oder bei Asthmaanfällen) gebrauchen.

Falls die Tabelle auf der nächsten Seite nicht ausreicht, um alle Ihre Medikamente einzutragen, können Sie die weiteren Medikamente auf einem zusätzlichen Blatt beilegen.

International Anatomical Therapeutic Chemical (ATC) classification system of medications

Drugs are classified in groups at five different levels:

- 1st level (main group) to 5th level (chemical substance, INN, “drug”)
- Example: diabetes drug **metformin** → **ATC code A10BA02**

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	metformin (5th level, chemical substance)

INN: International non-proprietary name

Defined daily dose (DDD)

... defined as the assumed average maintenance dose per day for a drug used for its main indication in adults

The screenshot shows the WHO Collaborating Centre for Drug Statistics Methodology website. The header includes navigation links: Home, ATC/DDD application form, Order ATC Index, WHO Centre, Contact us, Log in, and a Search box. The main content area displays the ATC/DDD Index for metformin. The left sidebar contains a menu with links to News, ATC/DDD Index (highlighted), Updates included in the ATC/DDD Index, ATC/DDD methodology, ATC, DDD, ATC/DDD alterations, cumulative lists, ATC/DDD Index and Guidelines, Use of ATC/DDD, Courses, Meetings/open session, Deadlines, and Links. The main content area shows the ATC code A10BA02 for metformin, with a DDD of 2 g O. The text "Last updated: 2016-12-20" is displayed below the table.

WHO Collaborating Centre for Drug Statistics Methodology

ATC/DDD Index

Updates included in the ATC/DDD Index

ATC/DDD methodology

ATC

DDD

ATC/DDD alterations, cumulative lists

ATC/DDD Index and Guidelines

Use of ATC/DDD

Courses

Meetings/open session

Deadlines

Links

Postal address:
WHO Collaborating
Centre for Drug Statistics
Methodology
Norwegian Institute of
Public Health
P.O.Box 4404 Nydalen
0403 Oslo
Norway

New search Show text from Guidelines

A ALIMENTARY TRACT AND METABOLISM

A10 DRUGS USED IN DIABETES

A10B BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS

A10BA Biguanides

ATC code	Name	DDD	U	Adm.R	Note
A10BA02	metformin	2	g	O	

List of abbreviations

Last updated: 2016-12-20

“Drug” metformin à DDD: 2 gram, administered orally

“Medication” for example Metformin-ratiopharm
500mg, 850mg, 1000mg tablets, average maintenance
dose: 500 or 850mg 2-3x daily, max. 3g/day

German ATC classification with DDD

Homepage

DIMDI

Classifications, Terminologies, Standards

Iris Institute

Downloadcenter

Alpha-ID

ATC/DDD

WG ATC/DDD

EDMA IVD Classification

ICD-10-GM

ICD-10-WHO

ICD-O-3

ICF

LOINC/RELMA

MeSH, UMLS

OID

OPS

UCUM

UMDNS

Collaboration

Your position: [Homepage](#) » [Classifications, Terminologies, Standards](#) » [ATC/DDD](#)

ATC-Classification with Defined Daily Doses

DIMDI publishes the annually updated official version of the German Anatomical Therapeutic Chemical (ATC)-Classification with defined daily doses (DDD) since January 1st, 2004.

You can download a PDF file of the official German ATC-Classification (in German) for free:

[ATC/DDD as PDF file for free at downloadcenter Classification](#)

You can download an Excel file of the official ATC-Classification with DDD from the WIdO website (on the right side below "Downloads") for free:

[ATC/DDD as Excel file for free at WIdO](#)

It is pointed out that in case of probable differences only the PDF file is binding which can be downloaded from the DIMDI website via the above mentioned link.

ATC-Classification.

In the ATC-Classification substances are divided into different groups according to the organ or organ system which they affect and their chemical, pharmacological and therapeutic properties. A defined daily dose is assigned to each active substance. Defined daily doses (DDD) are the assumed average daily maintenance dose for the main indication of each substance in adults.

Legal Background

DIMDI publishes the annually updated official version of the German ATC-Classification with defined daily doses according to § 73 Section 8 of the Fifth Book of the Social Security Statutes (SGB V) since January 1st, 2004.

Servicelinks

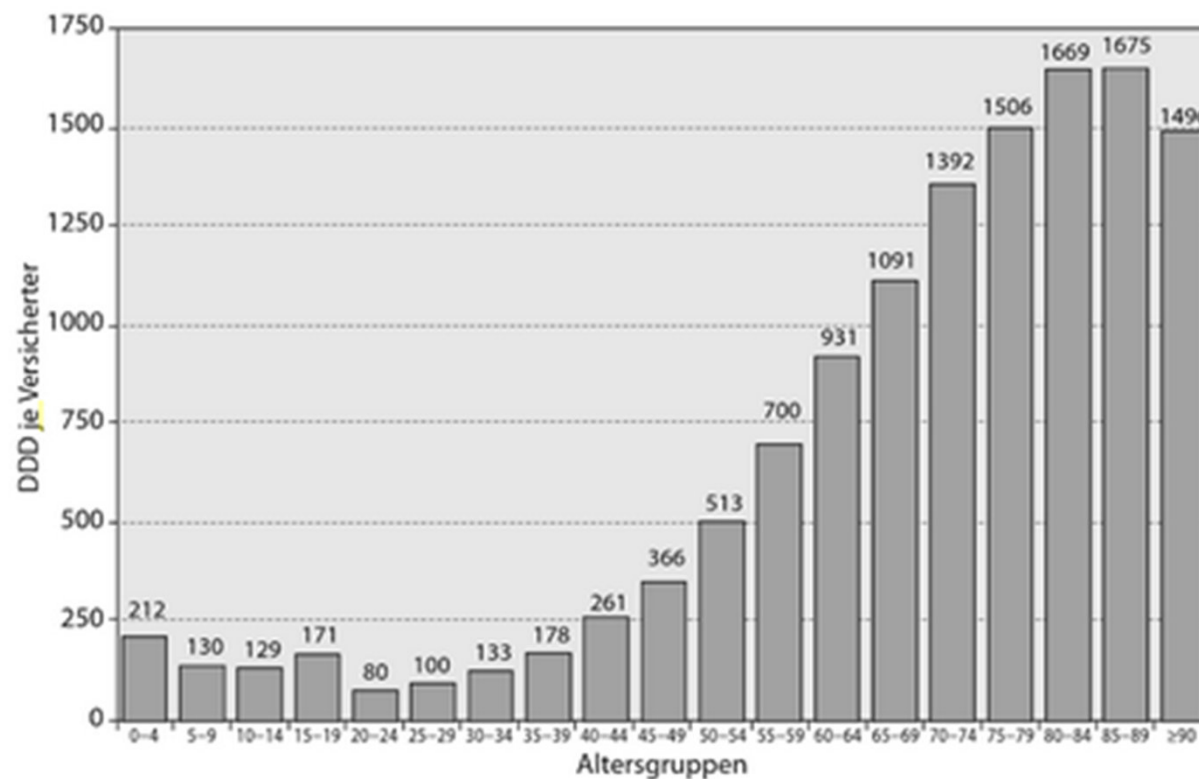
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- [ICD-10-GM online](#)
- [OPS German Procedure Classification online](#)
- [ICD-O-3 online](#)
- [ICF online](#)

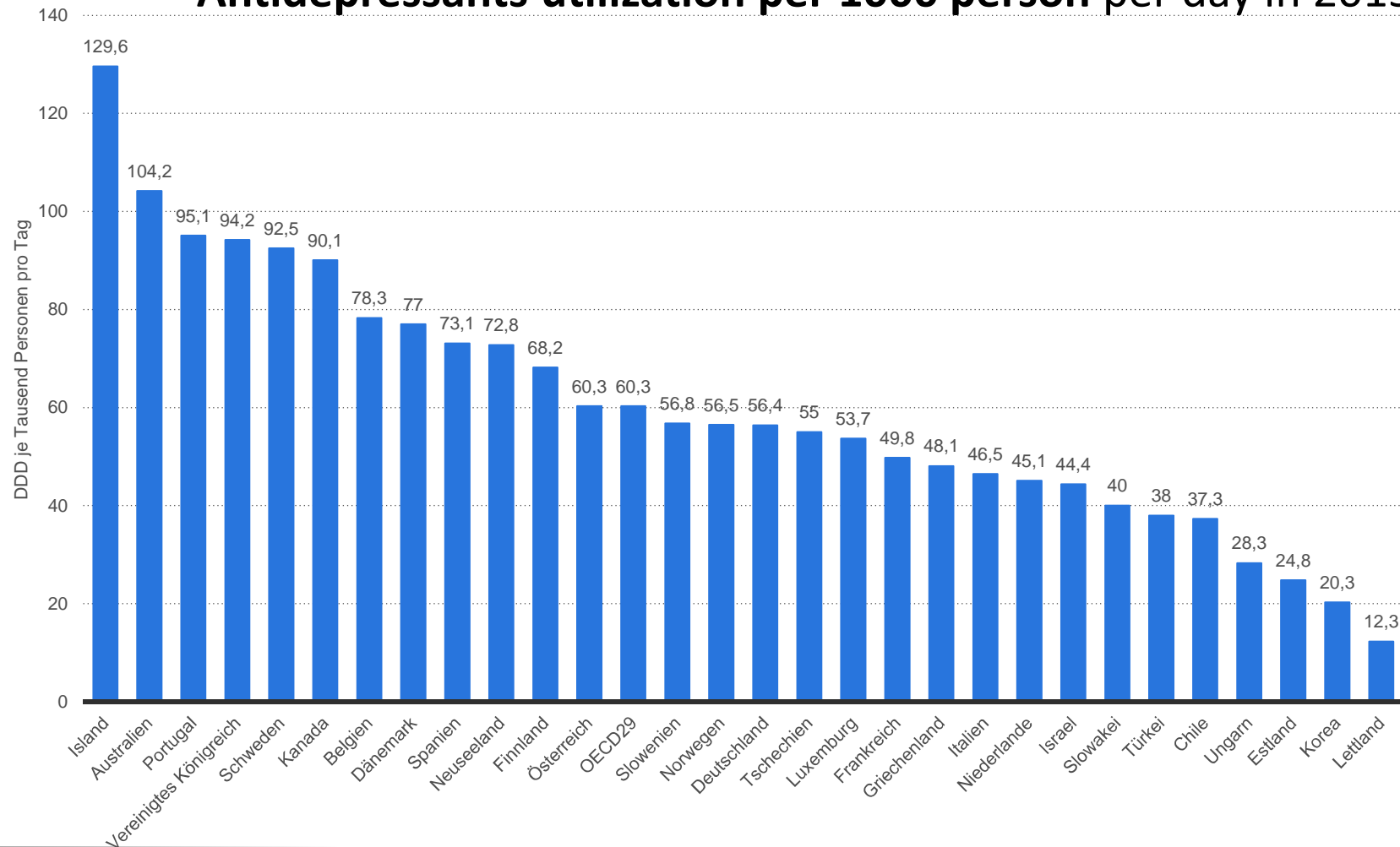
DDD are used to prescribe total drug use in large populations

Drug utilization per insured person in the German statutory health insurance in 2015 by age group



DDD are used to compare drug use in different countries

Antidepressants utilization per 1000 person per day in 2015



DDD are used to calculate duration of drug treatment episodes

If a prescribed daily dose (PDD) is not known, the duration of a package can be estimated by the amount of defined daily dose (DDD)

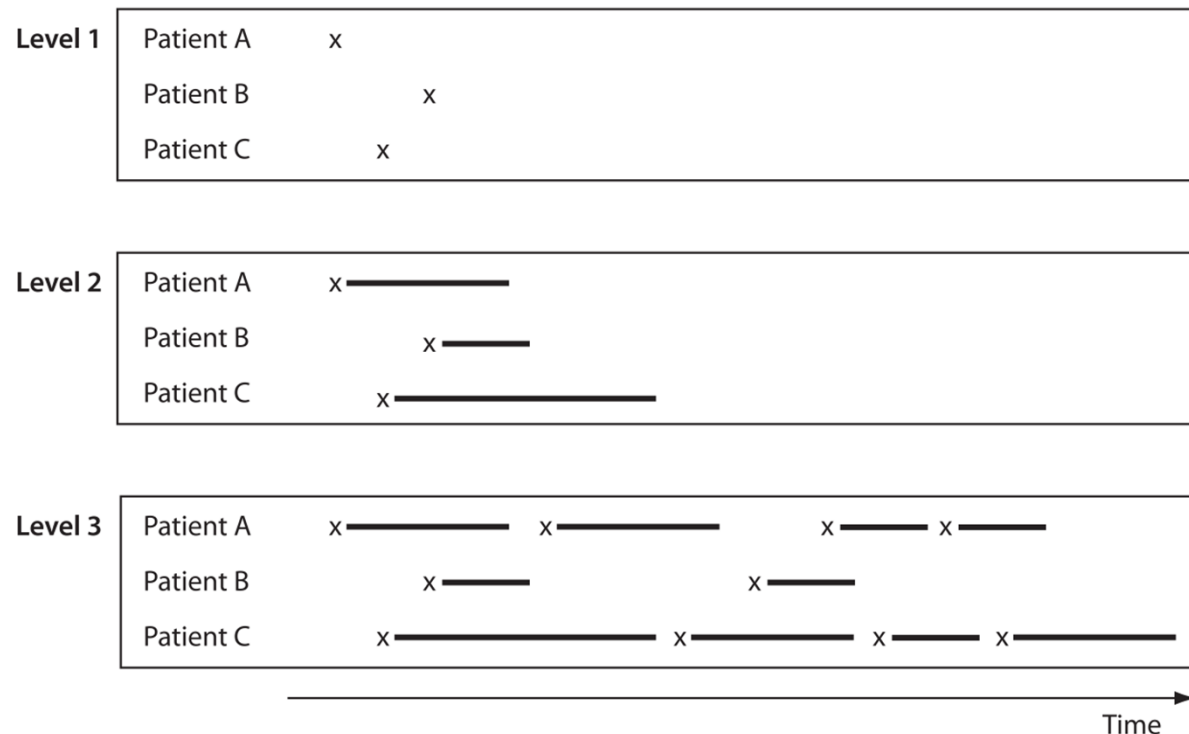
Examples:

- **Metformin à DDD: 2 gram**
- 1 package of `Metformin-ratiopharm 850mg`
120 tablets: $850\text{mg} \times 120 / 2000\text{mg} \hat{=}$ duration: 51 days
- 1 package of `Metformin-Mepha 500mg`
tablets: $500\text{mg} \times 50 / 2000\text{mg}$
duration: 12.5 days



Drug treatment episodes

Figure 1 The three levels of classifying drug exposure



- **Level 1:** Did/does the patient use drug x à yes/no
- **Level 2:** + Dose and amount of a drug prescribed (à estimation of the duration of a single prescription)
- **Level 3:** + multiple prescribing moments over time of the same drug

Medication adherence

- Appr. 50-80% of patients do not take medication as prescribed
- Medication-taking behavior is extremely complex and individual, requiring numerous multifactorial strategies (patient, physician, and health system) to improve adherence
- PE studies focusing on outcomes should consider:

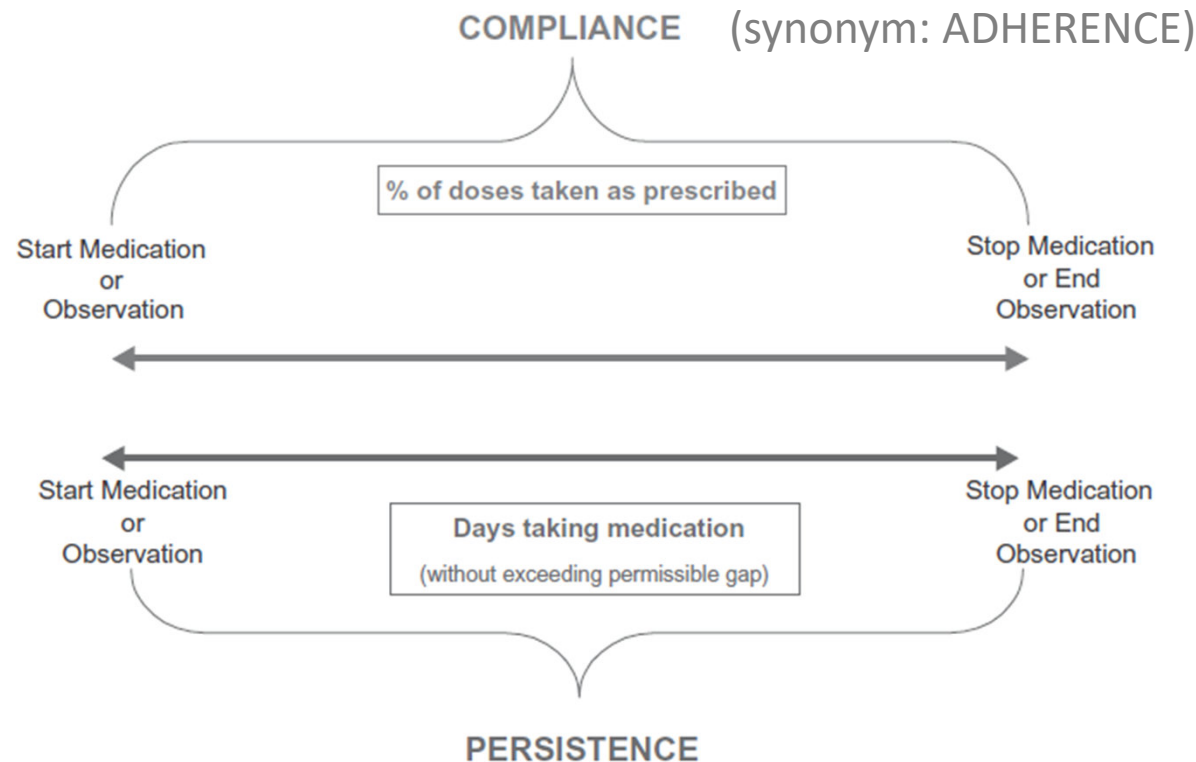
Treatment → **Adherence** → Outcomes

Definition of medication adherence and persistence of the ISPOR work group

- Medication **adherence** (synonym: compliance)
 - ... defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen."
 - How is the timing, dose, and frequency of a single drug in an individual patient?
- Medication **persistence**
 - ... defined as "the duration of time from initiation to discontinuation of therapy."
 - Is a patient continuing the drug for the prescribed duration?

ISPOR: International Society for Pharmacoeconomics and Outcomes Research (<https://www.ispor.org/>)

Medication adherence versus persistence



... to describe two aspects of **medication-taking behavior**

(e.g., patient's belief in the efficacy of medications, the severity of their illness, and their ability to control with medication)

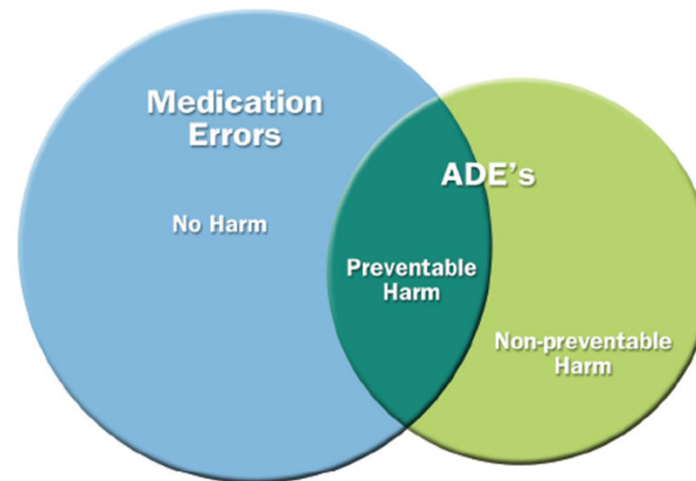
Drug safety and medication quality indicators as common 'outcomes' in PE/DUR studies

- Adverse drug event (ADE): drug-related **harm** associated with any dose
- Adverse drug reaction (ADR): drug-related **harm** that results from a "normally used" dose
- Medication error: with or without harm
 - drug interaction, double prescription, over/under dosing, wrong use of a medication, use in patients with contraindication
- Medication quality indicators
 - number of potentially inappropriate prescriptions in elderly persons
 - number of medication errors/100 patient days
 - medication appropriateness index¹

Medication Error or Adverse Drug Event (ADE)?

2 relevant Questions:

- Has a drug-related patient **harm** occurred?
- If yes, was the harm **preventable**?
 - Preventable ADE as a result of an medication error
 - Non-preventable ADE occurring with appropriate use



- “Preventable ADE” is harm caused by the use of a drug as a result of an error (e.g., patient given a normal dose of drug but the drug was contraindicated in this patient). These events warrant examination by the provider to determine why it happened.
- “Non-Preventable ADE” is drug-induced harm occurring with appropriate use of medication (e.g., anaphylaxis from penicillin in a patient and the patient had no previous history of an allergic reaction). While these are currently non-preventable, future studies may reveal ways in which they can be prevented.

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- Relevance of Drug utilization research in Pharmacoepidemiology
- Medication: assessment, drug treatment episodes, adherence and quality/safety
- **Drug utilization studies – examples**

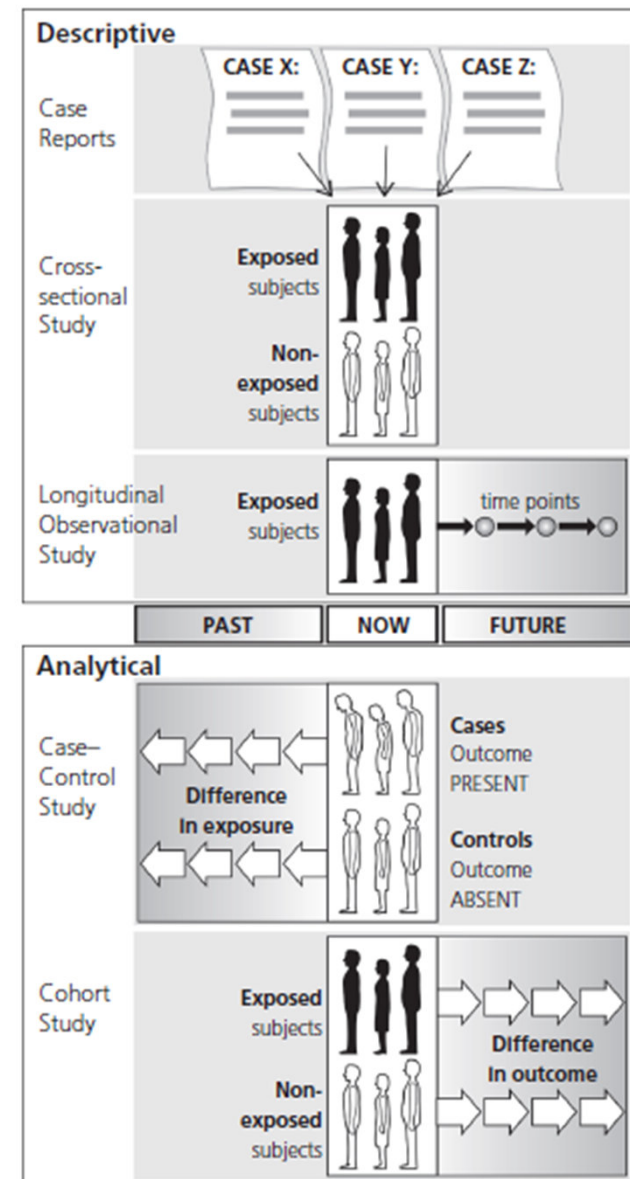
Study designs in PE/DUR

Descriptive studies

- Case reports
- Cross sectional study
- Longitudinal observational study (prospective or retrospective design, e.g. “closed” cohort of exposed subjects)

Analytical studies

- Case-Control study
- Cohort study



Examples of drug utilization studies in special populations: 1) pregnant women

Pharmacoepidemiol Drug Saf. 2006 May;15(5):327-37.

Antibiotics in pregnancy: analysis of potential risks and determinants in a large German statutory sickness fund population.

Amann U¹, Egen-Lappe V, Strunz-Lehner C, Hasford J.

+ Author information

Abstract

PURPOSE: Antibiotics are frequently prescribed drugs in pregnancy. The purpose of the study was to analyse the use, the potential risks and the determinants of systemic antibiotic prescriptions during pregnancy.

METHODS: A large, nation-wide acting German statutory sickness fund provided prescription data and personal data of 41,293 pregnant women. For this study, all prescriptions of systemic antibiotics (ATC: J01) dispensed to each woman during a 21-month period were analysed. We used the FDA risk classification system and enrolled a literature search to identify potentially harmful antibiotics. To investigate the impact of geographical and socio-economic determinants in antibiotic prescribing, a multivariate logistic regression model was performed.

RESULTS: Of the 41,293 women, 19.7% received at least one antibiotic drug during pregnancy. There was a shift to relatively safe and reduced antibiotic drug use during pregnancy. Prescribing of contraindicated antibacterials or potentially harmful drugs was seen in 521 women (1.3% of all women). In the logistic regression, being younger than 21 years (adjusted OR 2.14, 95%CI 1.80-2.53) or being welfare recipient (adjusted OR 1.57, CI 1.25-2.00) was strongly associated with higher antibiotic use. Significantly lower antibiotic use was seen in 5 of 16 German federal states (OR 0.74-0.83).

CONCLUSIONS: About 20% of pregnant women received antibiotics, and 1.3% received a harmful drug. To minimise the risks, detailed guidelines are needed for the antibiotic treatment during pregnancy.

Examples of drug utilization studies in special populations: 2) Elderly persons (> 64 years)

Dtsch Arztebl Int. 2012 Feb;109(5):69-75. doi: 10.3238/arztebl.2012.0069. Epub 2012 Feb 3.

Prescribing of potentially inappropriate medications for the elderly: an analysis based on the PRISCUS list.

Amann U¹, Schmedt N, Garbe E.

Author information

Abstract

BACKGROUND: The PRISCUS list of potentially inappropriate medications (PIM) for the elderly was published in 2010 and is the first systematically constructed list of this type in Germany. The aim of the present study is to estimate the baseline prevalence of the prescribing of PIM, as defined by the PRISCUS list.

METHODS: Pseudonymized claims data from three statutory health insurances in Germany, which together covered more than 8 million insurants, for the year 2007 were used to determine the age- and sex-standardized one-year period prevalence of PIM among the elderly, as well as the frequency of PIM prescribing per person. The study population included all insurants who were at least 65 years old and were continuously insured throughout the year 2007 or died during that year.

RESULTS: Of the 804 400 elderly persons in the study population, 201 472 (25.0%) received at least one PIM prescription in 2007. The PIM prevalence was higher in women than in men (32.0% vs. 23.3%) and increased with age. The most commonly prescribed PIM were amitriptyline (2.6%), acetyldigoxin (2.4%), tetrazepam (2.0%), and oxazepam (2.0%). 8.8% of all elderly persons received the same PIM drug four or more times in 2007.

CONCLUSION: These data show that PIM were frequently prescribed to elderly persons in Germany before the PRISCUS list was published. Medications on the PRISCUS list are not necessarily absolutely contraindicated, and this study contained no information about the individual risk/benefit analyses that may have been carried out before these drugs were prescribed; thus, no conclusion can be drawn about the prevalence of inappropriate prescribing. Further research is needed to validate the PRISCUS list, which was generated by expert consensus, as a basis for therapeutic guidelines in geriatric medicine.

Example of a drug utilization study in special populations: 3) pediatric patients


Received: 23 February 2017 | Revised: 1 June 2017 | Accepted: 18 July 2017

DOI: 10.1002/pds.4289

WILEY

ORIGINAL REPORT

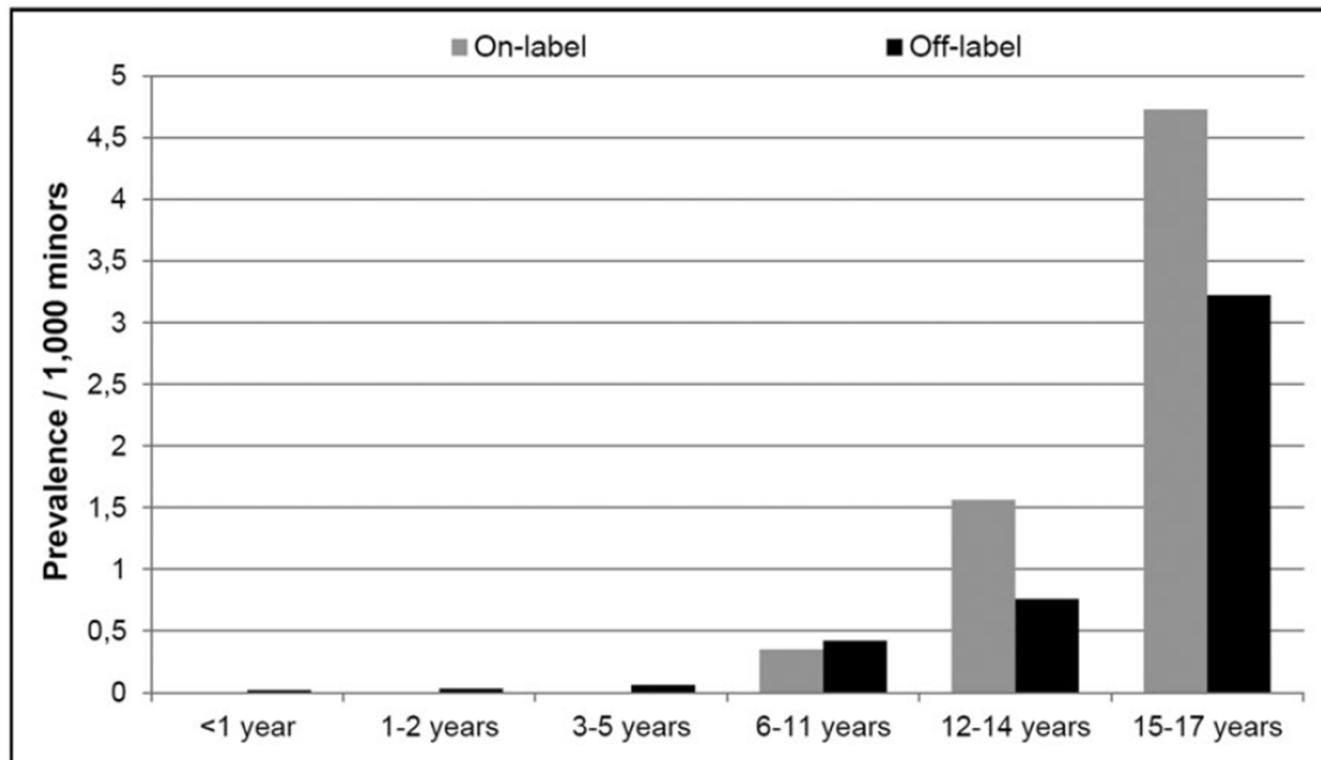
Extent and risks of antidepressant off-label use in children and adolescents in Germany between 2004 and 2011

Carsten Schröder¹  | Michael Dörks² | Bianca Kollhorst³ | Tilo Blenk¹ | Ralf W. Dittmann⁴ | Edeltraut Garbe¹ | Oliver Riedel¹

Aim of the study:

- to investigate the **prevalence** and the risks of off-label antidepressant prescribing over time in Germany in minors aged 0 to 17 years
- to analyse **prescribing patterns** regarding age, sex, drug class, and type of off-label use

Prevalence of on- and off-label antidepressant prescriptions in 2011 by age group



- Antidepressants (ATC code N06A) exposure analysed in a cross-sectional design for the year 2011

Antidepressant off-label use in pediatric patients over time

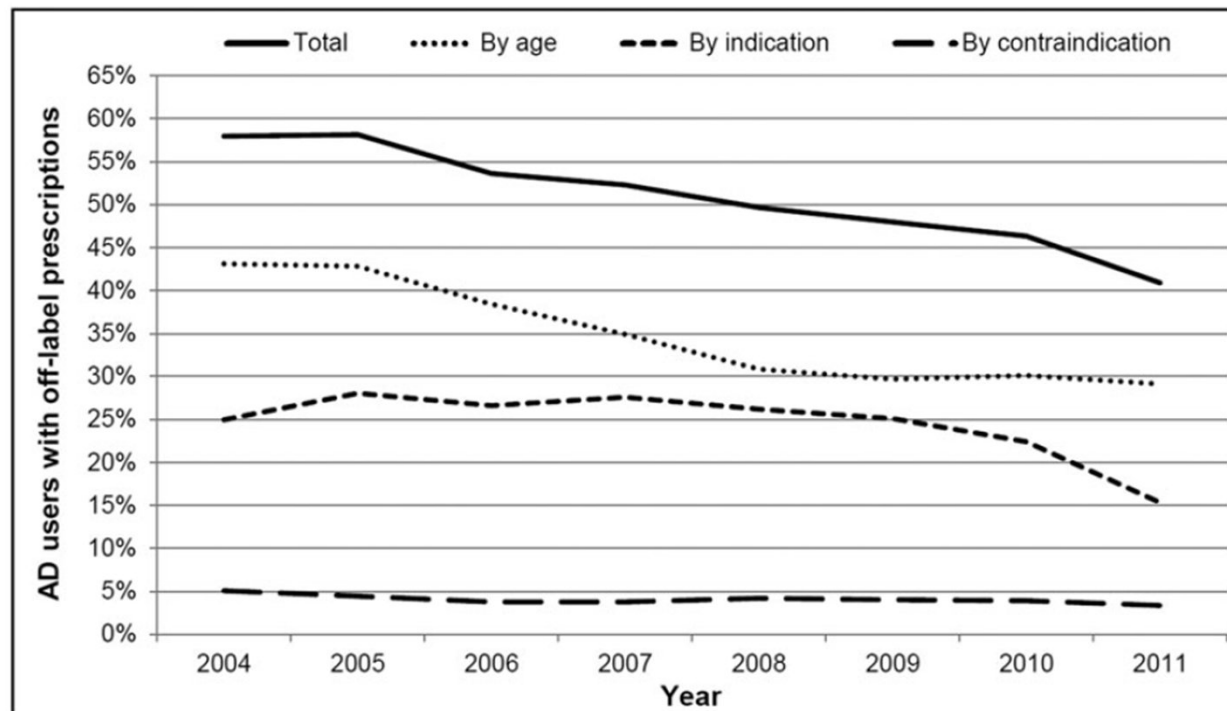


FIGURE 1 Share of antidepressant users with off-label prescriptions among all pediatric antidepressant (AD) users from 2004 (N = 3984) to 2011 (N = 4456). Note that one patient can contribute to more than one type of off-label use

Result:

- Total Off-label prescription share in Germany decreased from 58.0% in 2004 to 40.9% in 2011
- Most off-label prescriptions were off-label by age, followed by indication (most common hyperkinetic disorder) and by contraindication (medication or diagnosis)

Example of a drug utilization study with a new drug: oral anticoagulant Xarelto® (rivaroxaban)

Eur J Clin Pharmacol (2014) 70:975–981

DOI 10.1007/s00228-014-1697-7

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Use of rivaroxaban in Germany: a database drug utilization study of a drug started in hospital

Kathrin Jobski • Dirk Enders • Ute Amann •
Kiliana Suzart • Mari-Ann Wallander • Tania Schink •
Edeltraut Garbe

Aim of the study:

... to describe the **“use” of rivaroxaban** in Germany during a time period in which approval was limited to the prevention of venous thromboembolism (VTE) following hip or knee replacement.

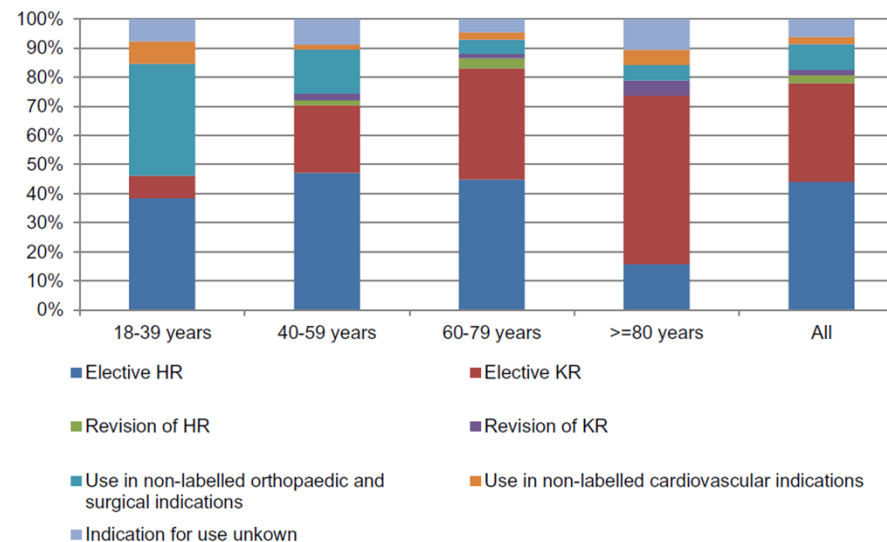
à “use” = distribution (prescribing and dispensing) by age, sex and potential indication; duration of use, and compliance with contraindications and precautions (e.g., potential interacting drugs)

On-label and non-label use of rivaroxaban

	Male N=212	Female N=228	Total N=440
On-label use	184 (86.8 %)	179 (78.5 %)	363 (82.5 %)
Elective HR	107 (50.5 %)	87 (38.2 %)	194 (44.1 %)
Elective KR	68 (32.1 %)	81 (35.5 %)	149 (33.9 %)
Revision of HR	7 (3.3 %)	5 (2.2 %)	12 (2.7 %)
Revision of KR	2 (0.9 %)	6 (2.6 %)	8 (1.8 %)
Use in non-labelled orthopaedic and surgical indications	13 (6.1 %)	26 (11.4 %)	39 (8.9 %)
Use in non-labelled cardiovascular indications	3 (1.4 %)	8 (3.5 %)	11 (2.5 %)
Indication for use unknown	12 (5.7 %)	15 (6.6 %)	27 (6.1 %)

Results:

- On-label use in 82.5% of episodes
- Off-label use (11.4%):
 - 2.5% in cardiac indications
 - 8.9% in non-labelled orthopaedic and surgical indications



HR, hip replacement; KH, knee replacement

Duration of rivaroxaban treatment

Results:

Treatment duration exceeded recommendations in

- 95% of the KR episodes

and in

- 56% of the HR episodes

HR, hip replacement; KH, knee replacement
SPC, Summary of Product Characteristics

Table 3 Duration of rivaroxaban treatment for labelled indications

Duration of treatment episode	No. of episodes
Elective KR, revision of KR	<i>N</i> =157
<11 days	3 (1.9 %)
11–<14 days	2 (1.3 %)
14 days	2 (1.3 %)
>14–21 days	35 (22.3 %)
>21–35 days	32 (20.4 %)
>35 days	83 (52.9 %)
Elective HR, revision of HR	<i>N</i> =206
<4 weeks	73 (35.4 %)
4–<5 weeks	15 (7.3 %)
5 weeks	2 (1.0 %)
>5–6 weeks	58 (28.2 %)
>6 weeks	58 (28.2 %)

Recommended treatment durations for rivaroxaban according to the SPC are 14 days in patients undergoing KR and 5 weeks in those undergoing HR. The German S3-Guideline generally recommends thromboprophylaxis for 11–14 days after KR and for 4–5 weeks after HR, respectively

Compliance with contraindications and precautions

Rivaroxaban is contraindicated in:

- Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Pregnant or breast-feeding women
- Persons aged <18years

Cautions is to be taken in:

- Patients with severe renal impairment (not recommended if creatinine clearance (CrCl) <15ml/min; caution if CrCl < 30ml/min)
- Patients receiving concomitant systemic treatment with potentially interacting drugs such as strong inhibitors of cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp)

Results:

- No rivaroxaban prescription seen in patients younger than 18 years
- None of the women in childbearing age (n=31) was found to be pregnant during rivaroxaban treatment

Prescribing of potentially interacting drugs

Results:

Prescribing of potentially interacting drugs in temporal relationship to rivaroxaban was rare except for non-steroidal anti-inflammatory drugs (NSAIDs)

Table 4 Patients receiving potentially interacting drugs prescribed in temporal relationship to rivaroxaban (rvx)

	Patients receiving potentially interacting drugs	
	During rvx treatment episodes* N=440	On the day of the first rvx prescription* N=440
CYP3A4 inhibitors	11 (2.5 %)	2 (0.5 %)
CYP3A4 inducers	3 (0.7 %)	2 (0.5 %)
P-gp inhibitors	6 (1.4 %)	3 (0.7 %)
Drugs affecting haemostasis	212 (48.2 %)	164 (37.3 %)
NSAIDs	203 (46.1 %)	159 (36.1 %)
Platelet aggregation inhibitors	7 (1.6 %)	1 (0.2 %)
Heparins and fondaparinux	15 (3.4 %)	5 (1.1 %)
Vitamin K antagonists	0 (0.0 %)	0 (0.0 %)

*Totals may not add up if patients received drugs from different categories

Exercise: Journal Club “Reading scientific papers”

Methods of the rivaroxaban DUS

- Study type?
- Data source?
- Study period?
- How was the duration of rivaroxaban treatment estimated?
- How was one treatment episode defined?

DUS, drug utilization study

Exercise / Answer

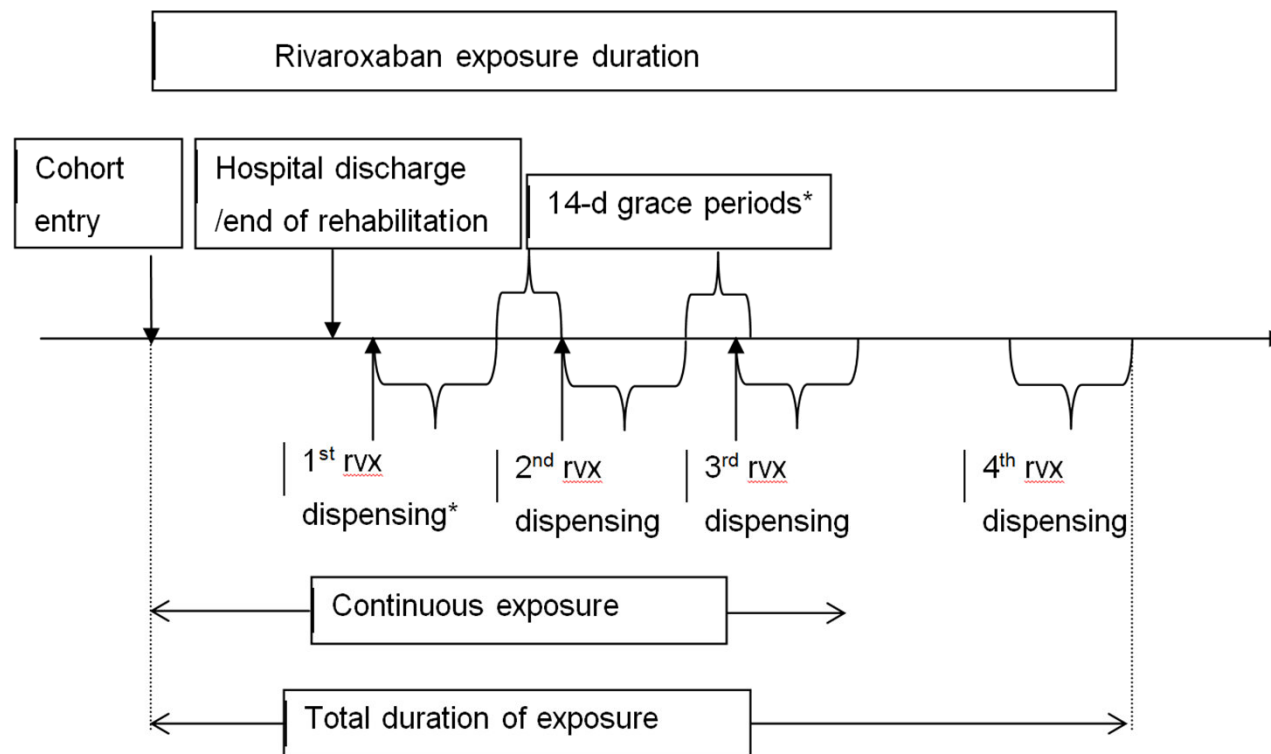
Methods of the rivaroxaban DUS

- Study type? retrospective cohort study ('claims database study')
- Data source? One statutory health insurance included in the GePaRD (German Pharmacoepidemiological Research Database)
- Study period? October 2008 (launch of Rivaroxaban in Germany) to December 2009
- How was the duration of rivaroxaban treatment estimated? Estimated by the amount of the dispensed tablets (Dose: 1 tablet a 10mg per day, ATC code B01AF01)
- How was one treatment episode defined? Subsequent prescriptions (continuous exposure), allowing for a gap of maximum 14 days

DUS, drug utilization study

Retrospective cohort study based on claims data

Definition of rivaroxaban exposure: 1 episode (continuous exposure) and total duration of exposure



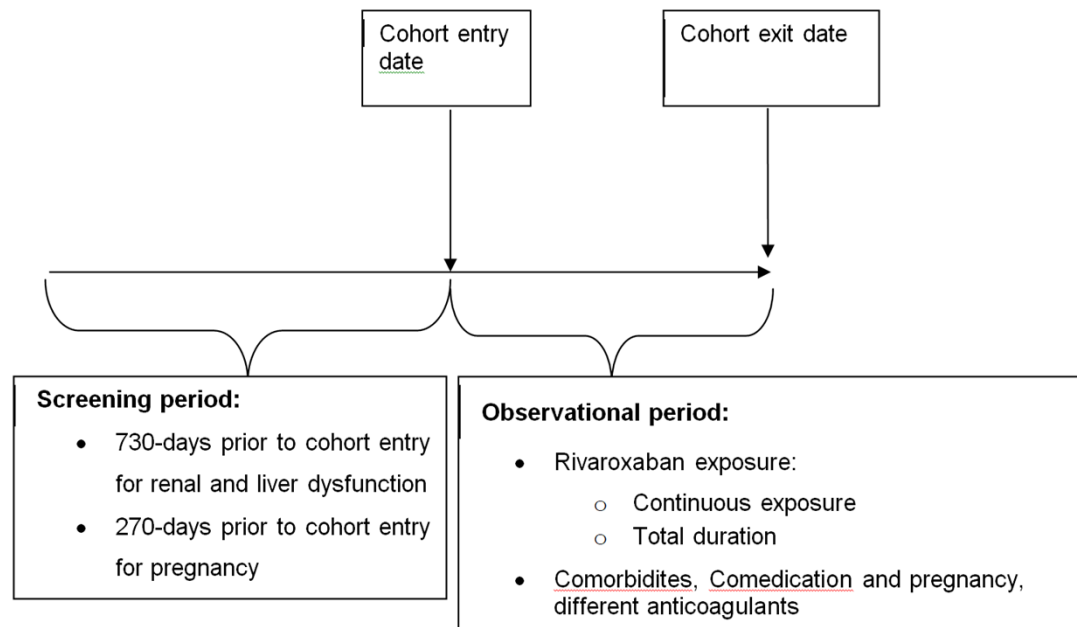
* 14-d grace period only for subsequent dispensing, not for single dispensing

Result:

- 425 rivaroxaban user
- 440 treatment episodes

Retrospective cohort study based on claims data

Definition of observational (rivaroxaban exposure) and screening period



Examples of Drug utilization studies for health services research in Cardiovascular disease

With the aim to investigate ...

- the adherence to guidelines, e.g. use of evidence-based medication after acute myocardial infarction
- the impact of medication use on health outcomes (short- and long-term survival) in real-life patient care

Based on a epidemiological disease-based registry:

- MONICA/KORA Myocardial Infarction Registry Augsburg
- established for cardiovascular research since 1984

MONICA/KORA Myocardial Infarction Registry

MONICA

Monitoring of trends and determinants in cardiovascular disease (1984 to 1995):

project coordinated by WHO

KORA

Kooperative Gesundheitsforschung in der Region Augsburg – Cooperative Health Research in the Region of Augsburg (since 1996)

Registry of MI and cardiac death

Surveys (S1-4) & Follow-up surveys (F4, FF4)



Population based MI registry

Study region Augsburg

About 653.000 inhabitants

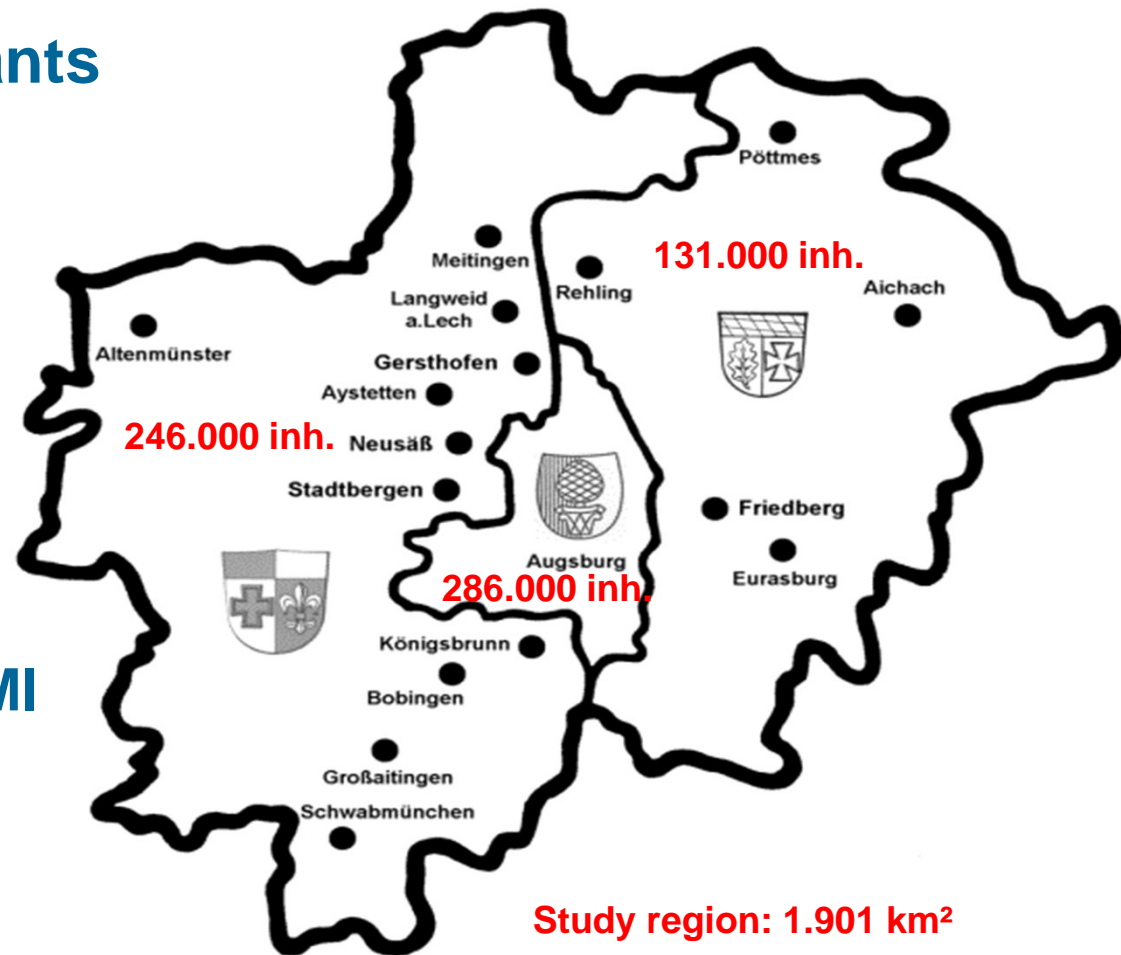
•aged 25-74 years:

- 216.000 men
- 214.000 women

•aged 75-84 years:

- 21.000 men
- 29.000 women

à About 1.700 cases of MI
or cardiac death per year
(5.000 suspected cases
were screened per year)



MONICA/KORA MI Registry



➔ Located at the Augsburg hospital, where approx. 80% of all MIs in the study region are treated

The team

- 1 physician: Dr. med. Margit Heier
(since 01.04.2017 temporary head of the registry)
- 3 study nurses
- 0.5 secretary/responsible for death certificates
- 0.5 medical documentation specialist



Evidence-based medications (EBMs) for patients with acute MI: standard of care since 2004*

A combination of the following drugs:

§ **Antiplatelet agent** (e.g. aspirin and/or clopidogrel)

à to inhibit platelet aggregation

§ **Beta-blocker**

à to decrease heart rate, blood pressure and oxygen demand in the heart

§ **Statin**

à to decrease LDL-cholesterol level in the blood

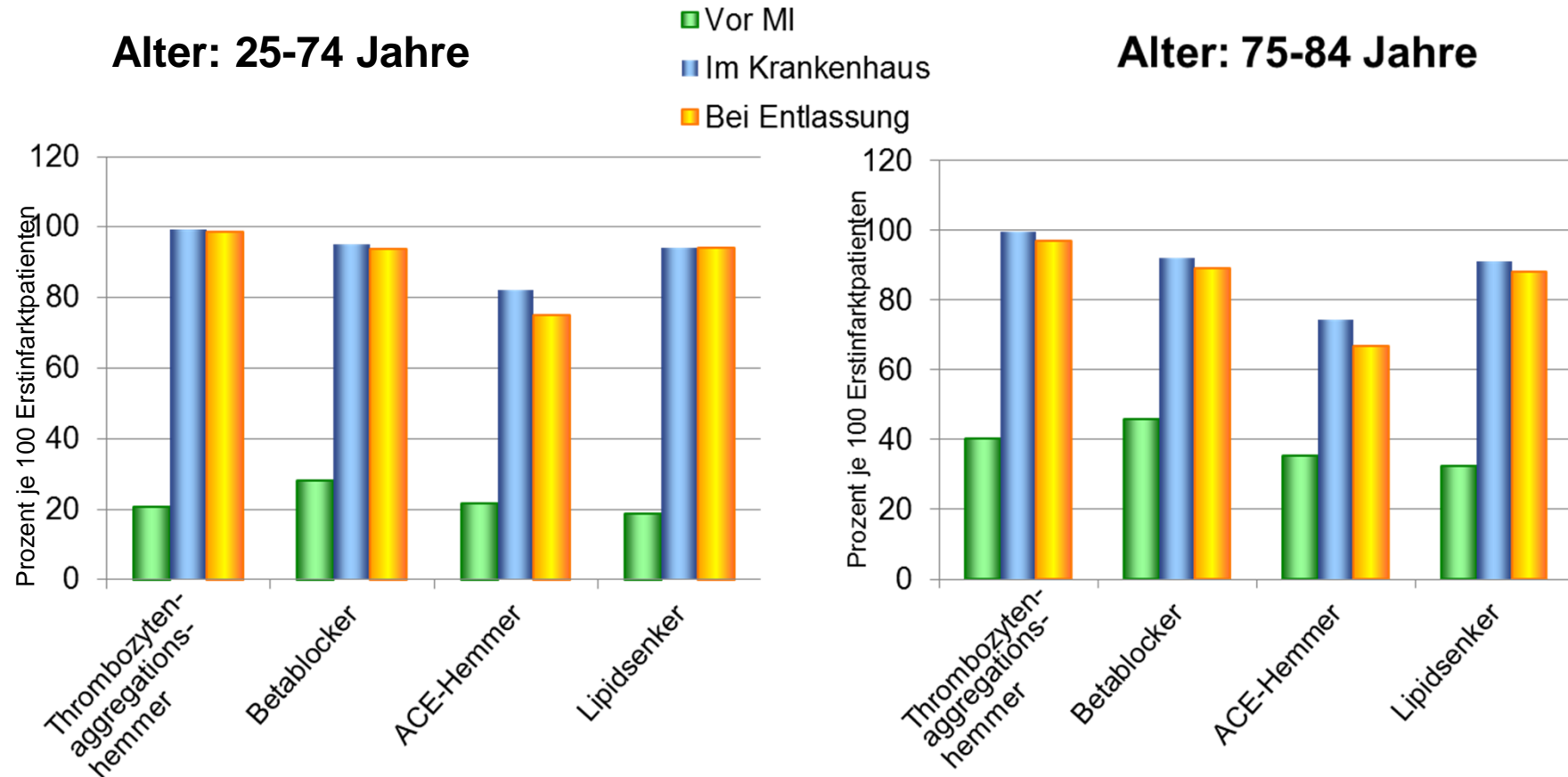
§ **ACEI/ARB** (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker)

à to decrease blood pressure

Medikamentöse Therapie bei Erstinfarkt (%)

MONICA/KORA Herzinfarktregister Augsburg

2012-2015



Utilization of EBM's and the impact on long-term survival in real-life patient care

Clin Res Cardiol. 2014 Aug;103(8):655-64. doi: 10.1007/s00392-014-0688-0. Epub 2014 Mar 7.

Long-term survival in patients with different combinations of evidence-based medications after incident acute myocardial infarction: results from the MONICA/KORA Myocardial Infarction Registry.

Amann U¹, Kirchberger I, Heier M, Golücke H, von Scheidt W, Kuch B, Peters A, Meisinger C.

Author information

Abstract

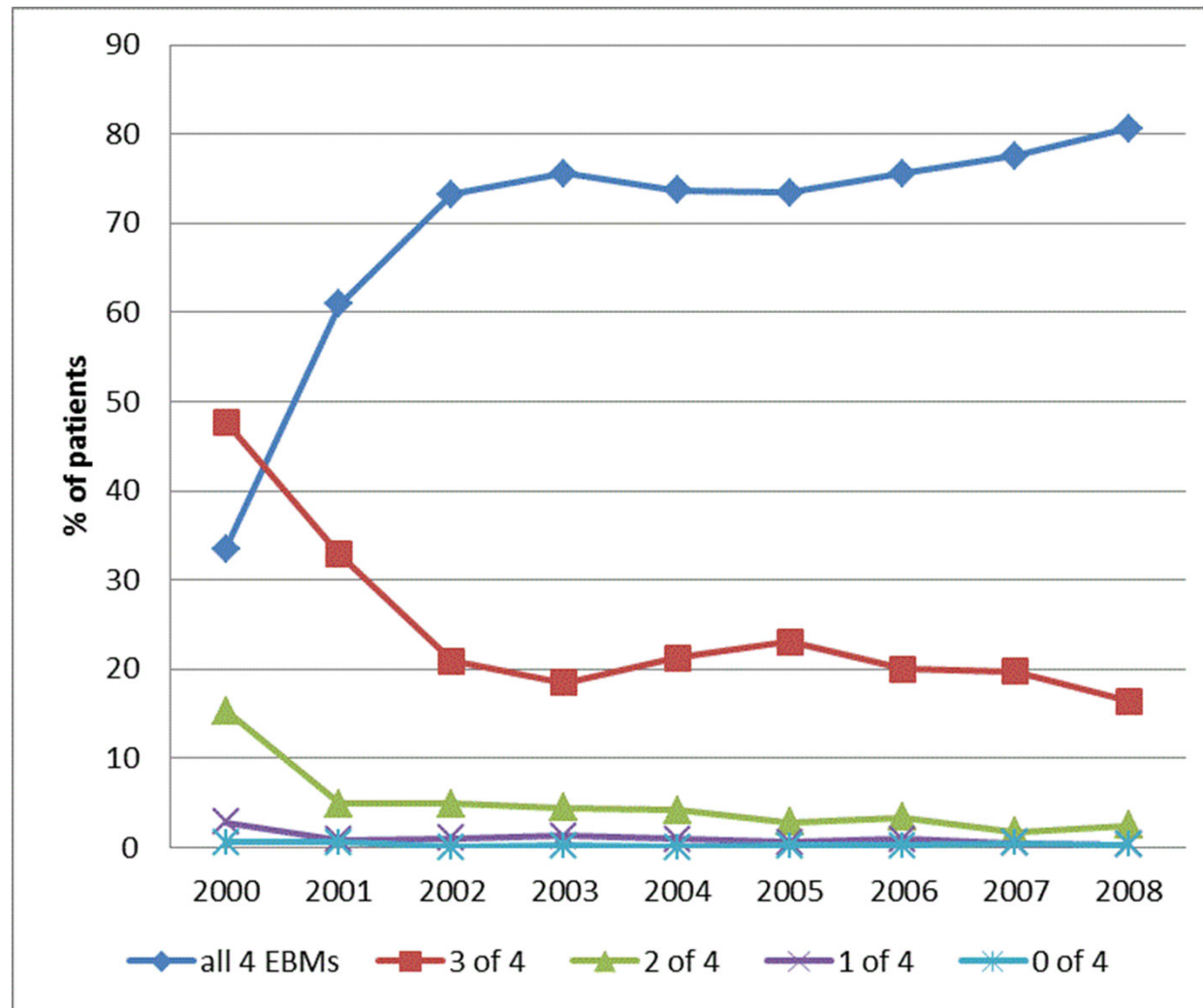
BACKGROUND: Use of the four evidence-based medications [EBMs: antiplatelet agent, beta-blocker, statin and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB)] after acute myocardial infarction (AMI) has a clear impact on 1-year survival. Aim of this study was to evaluate the association between different EBM combinations at discharge and long-term survival after AMI.

METHODS: From a German population-based AMI registry, 2,886 men and 958 women were included, aged 28-74 years, hospitalized with an incident AMI between 2000 and 2008. All data were collected by standardized interviews and chart review. All-cause mortality was assessed for all registered persons in 2010. Median follow-up time was 6.0 years (interquartile range 4.1 years). Survival analyses and multivariate Cox regression analysis were conducted.

RESULTS: Of the 3,844 patients, 70.3 % were prescribed all four EBM's; 23.8 % received three, 4.6 % two, and 1.3 % were discharged with one or no EBM. Long-term survival was 71.7 % [95 % confidence interval (CI) 55.4-82.9 %], 64.7 % (95 % CI 59.2-69.6 %) and 60.2 % (95 % CI 51.9-67.5 %) in patients with four, three and <3 EBM's, respectively. Patients prescribed three or less EBM's without ACEI/ARB showed similar long-term survival to those receiving four EBM's. In Cox regression analysis after adjustment for confounding variables, the hazard ratio for long-term mortality in patients with four EBM's versus three or less EBM's was 0.63 (95 % CI 0.53-0.74).

CONCLUSIONS: Prescribing of a combination of all four EBM's appeared to improve clinical outcomes in AMI patients by significantly reducing long-term mortality. Hospital discharge is a critical time for optimal long-term management.

Use of the Evidence-Based-Medications (EBMs) at hospital discharge between 2000-2008



**N=3.844 aged
28-74 year**

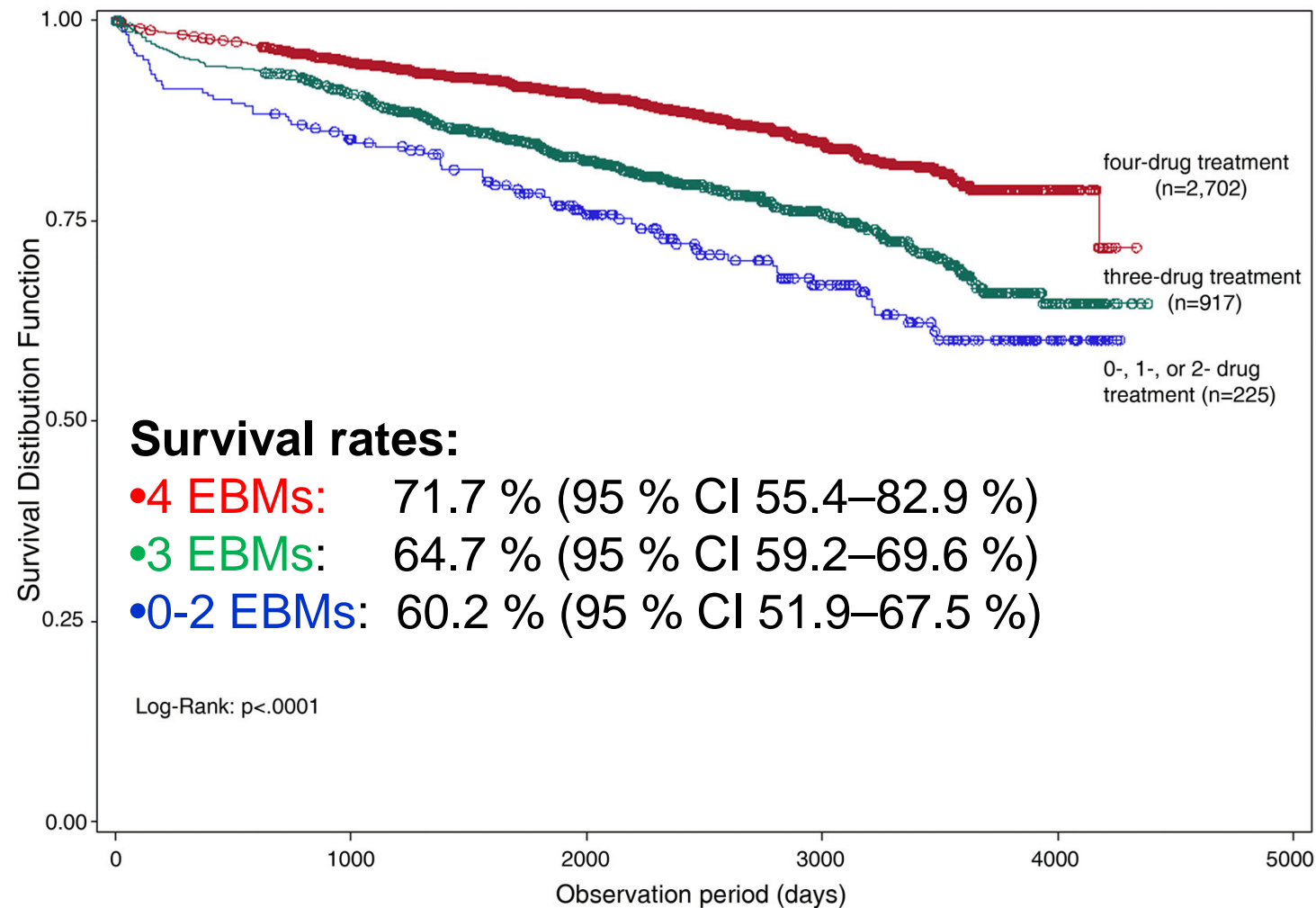
2000-2008:

70.3 % with 4 EBM
23.8 % with 3 EBM*
4.6% with 2 EBM
1.3% with 0-1 EBM

***3 EBM:**

no ACEI/ARB (13%)
no Statin (7%)
no Beta-blocker (2%)
no Antiplatelet (1.6%)

Kaplan-Meier survival plots by EBM treatment for all-cause mortality



Median follow-up period of 6 years after an acute MI

Cox proportional hazard regression model 4 EBMVs versus 0-3 EBMVs

Total (n=3,844)	HR [95% CI]	p-value
Unadjusted	0.52 [0.44-0.61]	<.0001
Model 4*	0.63 [0.53-0.74]	<.0001

* **Adjusted for:**

age (cont.) and sex, employment, smoking, type of MI, reperfusion therapy (e.g. PCI), any in-hospital complication, history of stroke, diabetes, hyperlipidemia, and hypertension

Relative risk reduction of ? 37%

PCI: Percutaneous coronary intervention

Conclusion: EBM use & long-term survival after acute myocardial infarction

- There is a high proportion of patients receiving all four guideline-recommended EBMs at hospital discharge.
- This observational study showed an association between EBM treatment and long-term survival.
- Patients with the four-EBM treatment showed a 37% reduction of long-term all-cause mortality risk compared to patients prescribed three or less EBMs.

Drug utilization studies in long-term survivors after acute myocardial infarction



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Medication use in long-term survivors from the MONICA/KORA Myocardial Infarction Registry☆

Ute Amann^{a,b,e,*}, Inge Kirchberger^{a,b}, Margit Heier^{a,b}, Christian Thilo^c, Bernhard Kuch^{c,d}, Christa Meisinger^e

^a MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Augsburg, Germany

^b Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

^c Department of Internal Medicine I - Cardiology, Central Hospital of Augsburg, Augsburg, Germany

^d Department of Internal Medicine/Cardiology, Hospital of Nördlingen, Nördlingen, Germany

^e Chair of Epidemiology, Ludwig-Maximilians-Universität München, UNIKA-T, Augsburg, Germany

Aim of the study:

- to provide a **comprehensive description of total medication** use 3 or more years after an acute myocardial infarction
- to **identify factors** associated with secondary prevention medication use in long-term survivors

Data source of medication use: postal follow-up survey in 2011

Abstract

BACKGROUND: Prior studies reported high guideline adherence for secondary prevention medications (SPM) at hospital discharge in patients with acute myocardial infarction (AMI). Less is known about medication use in long-term AMI survivors.

METHODS: Of the 2077 registered persons with an AMI between 2000 and 2008 who responded to a postal follow-up survey in 2011, 1311 men and 356 women, aged between 34.4 and 84.9 years, reported medication intake 7 days prior to the survey. These study participants also had their current health condition and comorbidities assessed. Information regarding index AMI was selected from the population-based MONICA/KORA MI registry. Multivariable logistic regression models were conducted to identify factors associated with SPM use (all 4 drug classes).

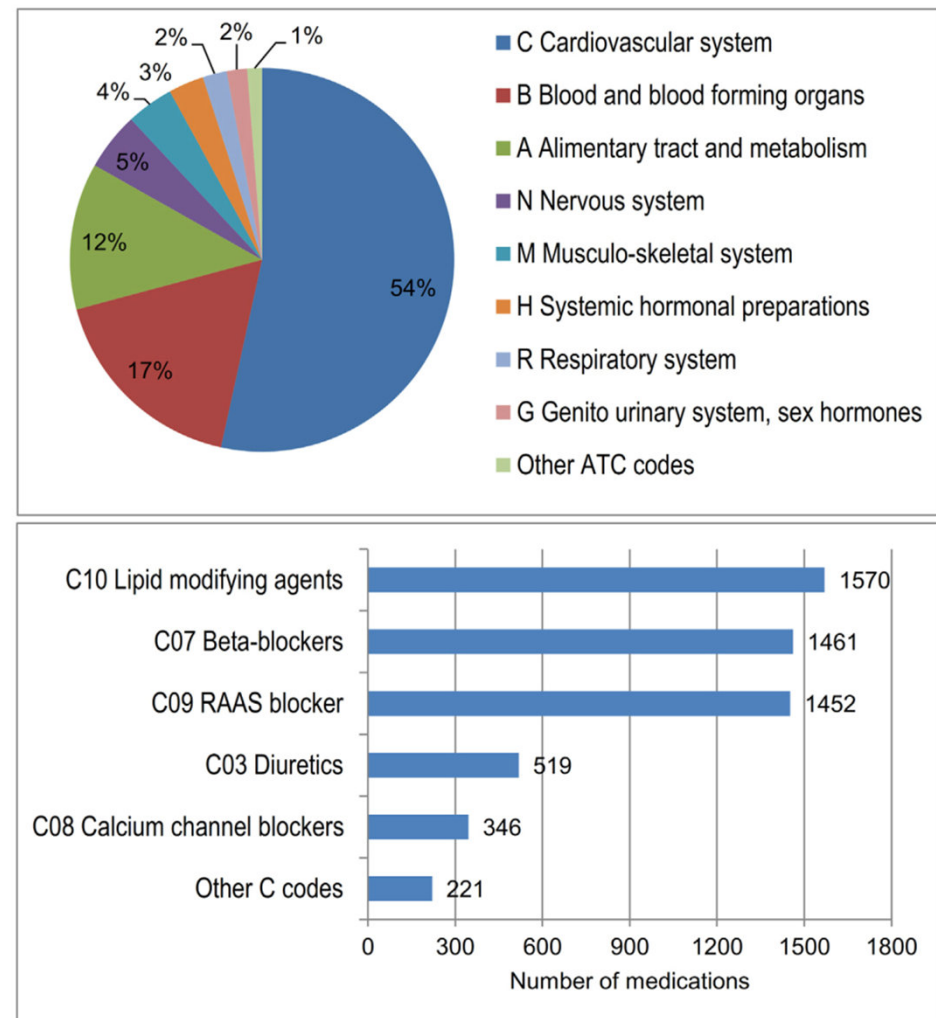
Based on data from the population-based MONICA/KORA Myocardial infarction registry, Augsburg, Germany:

- Patients are interviewed during hospital stay and medication use are collected by review of medical chart and discharge report stay using a standardized questionnaire
- Follow-up survey mailed to the registered persons still alive in 2011 including a question on medication intake within 7 days prior to the survey.

Medication use after median time of 6.1 years after acute MI

Results:

- N=1,667 drug user
- Total of 10,422 medications
- Polypharmacy (> 4 medications /person): 73.8%
- Use of secondary prevention medication (SPM) was high:
 - Ø Antiplatelet agents: 90.9%
 - Ø Beta-blockers: 86.7%
 - Ø Statins: 85.4%
 - Ø Renin-angiotensin-aldosterone system blockers: 79.3%



Results: Several factors were associated with use of secondary prevention medication (SPM)

Table 4

Factors associated with 4 SPM use at follow-up in AMI survivors ($n = 1468^a$).

	OR [95% CI]	p Value
Sex (men vs. women)	1.30 [0.97–1.74]	0.076
Characteristics assessed at follow-up		
Age (cont.)	0.99 [0.98–1.00]	0.073
Lung disorders (yes vs. no)	0.17 [0.10–0.30]	<0.0001
Neurological disorders (yes vs. no)	0.34 [0.18–0.67]	0.002
Cancer (yes vs. no)	0.45 [0.25–0.79]	0.005
Depression (yes vs. no)	0.53 [0.37–0.75]	0.001
Joint disorders (yes vs. no)	0.75 [0.57–0.97]	0.029
Diabetes (yes vs. no)	0.75 [0.57–0.99]	0.042
Number of medications (cont.)	1.48 [1.38–1.58]	<0.0001
Characteristics assessed at index AMI		
4 SPM prescription at discharge (yes vs. no)	2.68 [2.05–3.52]	<0.0001
Hypertension (yes vs. no)	1.48 [1.12–1.95]	0.006
Any revascularization therapy (yes vs. no)	2.46 [1.66–3.65]	<0.0001

SPM secondary prevention medication (4 SPM was defined as combined use of antiplatelet agent, beta-blocker, statin and renin-angiotensin-aldosterone system blocker), AMI acute myocardial infarction, OR odds ratio, CI confidence interval.

^a Note: 199 observations were deleted due to missing values for the explanatory variables.

Results:

SPM use several years after acute MI was associated with treatment at hospital discharge at index MI and patients' comorbidities

Summary: Aims of drug utilization studies (DUS)

- Different 'aims' of DUS:
 - To analyze differences in utilization of drugs, e.g. between countries or regions
 - To analyze patient-related aspects and usage environment
 - To analyze factors influencing the prescribing patterns of physicians
 - To assess and promote aspects of rational, guideline-based prescribing
- Compared to 'classical' PE studies with the aim...
 - To assess the effectiveness and safety of drug therapy

Pharmacoepidemiology (PE) is a dynamic research field with increasing level of complexity

- 1960s: thalidomide disaster, birth of PE to improve medication safety
- 1990s: growth of databases based on administrative claims data or medical records, development of methods (challenges of bias and confounding), linkage to clinical data or disease-based registries
- Ongoing monitoring of new medicines with increasing levels of complexity
- Future: linking drug utilization to genetic data

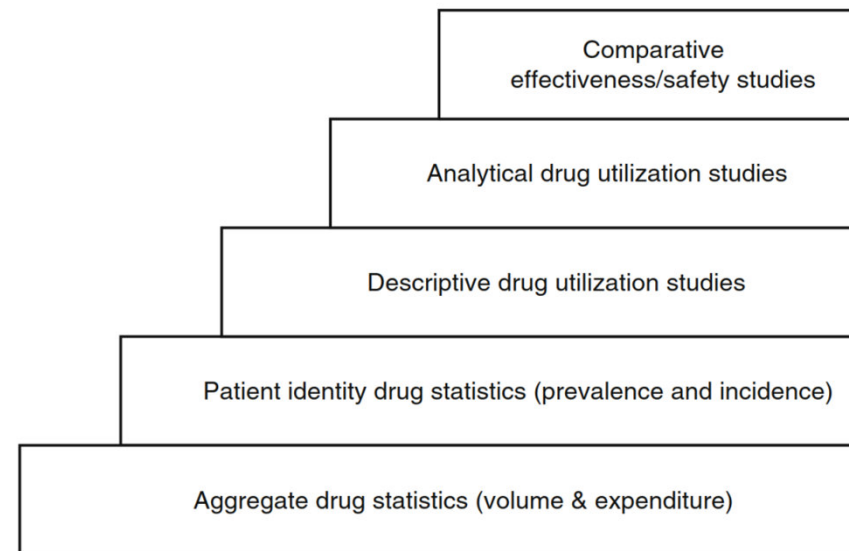


Fig. 2 Different types of monitoring of new medicines with increasing levels of complexity

à increasing impact of PE on clinical medicine and rational use of drugs

Vielen Dank für Ihre Aufmerksamkeit!



Kontaktdaten

Dr. Ute Amann, MPH
Lehrstuhl für Epidemiologie
der LMU München am UNIKA-T Augsburg
Neusässer Str. 47
86156 Augsburg

Email:

u.amann@unika-t.de

ute.amann@helmholtz-muenchen.de

