Addressing inpatient admissions and readmissions due to adverse drug reactions in the oldest old

INTERNATIONAL SEMINAR
REPOSI 2015
Milan, Italy 24-25 September
TARGETING THE BURDEN
OF POLYPHARMACY IN THE ELDERLY

Bellvitge Hospital Universitari

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Importance

❖ **Adverse Drug Reactions** (ADRs) in the older population form a large healthcare problem, resulting in significant **morbi-mortality**, **healthcare consumption** and **high costs**.

❖ Because of aging societies and an increasing life expectancy, ADRs might be expected to become an even more **serious public health problem**.

❖ Thus, prospective studies on their prevalence and clinical characteristics carried out specifically in **elderly hospitalized patients** would be useful in developing preventive strategies.

Importance

❖ While the prevalence and impact of adverse drug reactions (ADRs) has been well studied in the general adult population, much **less is known about ADRs in the elderly**.

❖ **Older persons** experience an increased disease burden and a corresponding increase in drug use, with a corresponding **increased risk of ADRs**.

❖ Additionally, there is a variety of **age-related physiological changes** affecting the pharmacokinetics and pharmacodynamics of medications, which may further increase the risk of ADRs in older persons.

*Some meta-analyses of observational studies have reported proportions of **ADR-related admissions** in older people ranging from **10% to 17%,** although these figures arose from heterogeneous studies, most of them with a small sample size.*

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Systematic review

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Clinical Interventions in Aging 2014:9 2079–2086

Open Access Full Text Article

REVIEW

A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting

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Abstract: Adverse drug reactions (ADRs) are an important health issue. While prevalence and risk factors associated with ADRs in the general adult population have been well documented, much less is known about ADRs in the elderly population. The aim of this study was to review the published literature to estimate the prevalence of ADRs in the elderly in the acute care setting and identify factors associated with an increased risk of an ADR in the elderly. A systematic review of studies published between 2003 and 2013 was conducted in the Cochrane Database of Systematic Reviews, EMBASE, Google Scholar and MEDLINE. Key search terms included: "adverse drug reactions", "adverse effects", "elderly patients and hospital admission", "drug therapy", "drug adverse effects", "drug related", "aged", "older patients", "geriatric", "hospitalization", and "emergency admissions". For inclusion in the review, studies had to focus on ADRs in the elderly and had to include an explicit definition of what was considered an ADR and/or an explicit assessment of causality, and a clear description of the method used for ADR identification, and had to describe factors associated with an increased risk of an ADR. Fourteen hospital-based observational studies exploring ADRs in the elderly in the acute care setting were eligible for inclusion in this review. The mean prevalence of ADRs in the elderly in the studies

Systematic review

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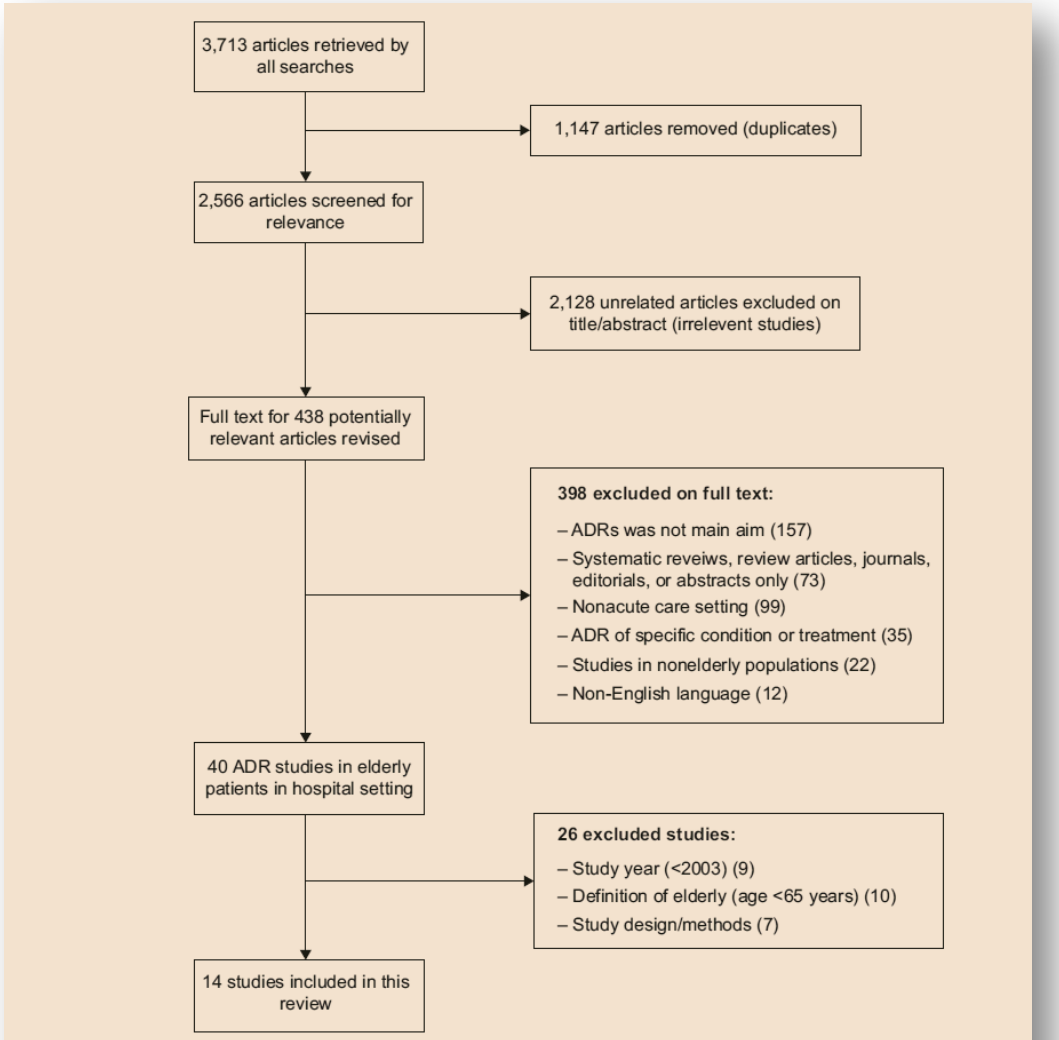

Figure 1 Search strategy and identification of included studies.
Abbreviation: ADR, adverse drug reaction.

Systematic review

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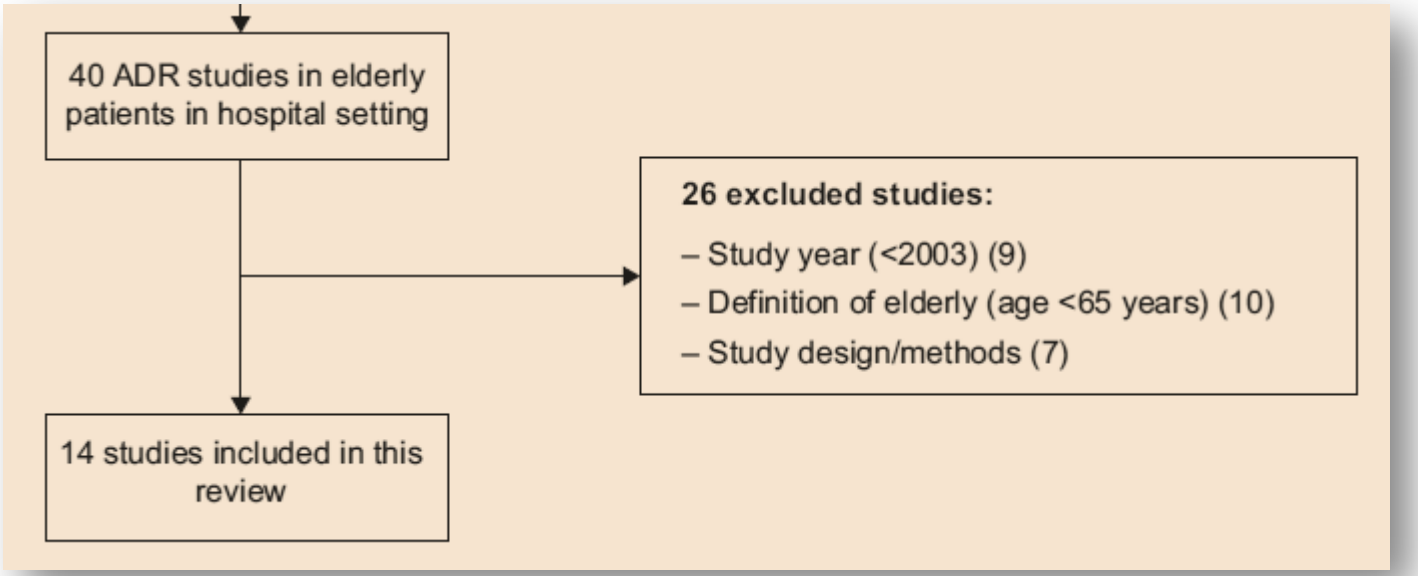

Our data

Aims of our study:

1. To assess the **prevalence** of ADR-related hospital admissions of patients aged ≥ 65 years in our 3rd-level teaching hospital.

2. To compare the in-hospital **mortality** rates between patients admitted for ADRs and patients admitted for other causes

3. To **characterize the ADRs**, the **drugs involved**, and suspected **drug-drug interactions** (DDIs)

Study design, setting and participants

Study Design: **Cross-sectional study** from 2008 to 2014

Setting: **Bellvitge University Hospital**, a **750-bed** tertiary-care teaching hospital for **adults** which provides acute care to a **1.3-million population** (excluding oncology, pediatrics, obstetrics and burns). The hospital registers **33,000 admissions** and receives approximately **120,000 emergency visits per year**. Historically, 10%-12% of the patients registered in the Emergency Department (ED) are admitted, contributing to approximately **46%** of the total hospital admissions. Roughly 90% of the remaining scheduled admissions are surgery patients, totaling approximately 18,000 patients per year.

Participants: ADR-related admissions of patients aged **≥65 years** prospectively identified through the **Pharmacovigilance Program** (*a systematic daily review of admission diagnosis of all patients urgently hospitalized by the Clinical Pharmacology Department*).

Pharmacovigilance program

Since 2008, the **Clinical Pharmacology Department** has been carrying out a **Pharmacovigilance Program** which it is based on **prospective identification** of cases of ADRs leading to hospitalization through a systematic daily review of admission diagnosis of patients urgently admitted.

The definition of ADR used is that currently in force in the regulatory framework of the European Union (any response to a drug which is noxious and unintended). ADRs and suspected drugs are coded by using the **Medical Dictionary for Regulatory Activities** (**MedDRA**) version 17.0 and the **Anatomical Therapeutic Chemical Classification** (ATC), respectively.

Data collection and variables

Primary endpoint was urgent admission caused by an ADR in population aged ≥ 65 years

Variables evaluated in each patient were collected from the centralized information system of the hospital, and included demographic data (age and sex), ADRs, suspected drugs, presence of a suspected DDI, number of different drugs used at the time of arrival at the hospital.

Outcomes were categorized as "*recovered*", "*recovered with sequelae*", "*not yet recovered*", "*death due to the ADR*", and "*death from other causes*".

Polypharmacy was categorized as **≥5 different drugs** used before admission.

1. Prevalence of ADR hospital admission and mortality rates according to age subgroups

❖ ADRs were suspected to be the main reason for urgent admission in **1,976 out of 60,263 patients** aged ≥65 years

❖ **Prevalence** of ADR-related hospitalization was **3.3%** [95% CI 3.1-3.4%].

❖ The **crude in-hospital mortality rate was 10.2%** in patients with ADR-related admission and 9% in patients admitted for other causes (p=0.077).

❖ Most patients (**86%**) were exposed to **polypharmacy** and **drug-drug interaction** was suspected in **49%** of cases.

1. Prevalence of ADR hospital admission and mortality rates according to age subgroups

Age subgroup	ADR-related admissions				Non-ADR-related admissions				Total admissions
	Total	Prevalence of ADR-related admission	In-hospital death	Mortality rate	Total	In-hospital death	Mortality rate		No.
	No.	% (95% CI)	No.	% (95% CI)	No.	No.	% (95% CI)	*P*	
65-74 years	662	3.0 (2.8-3.2)[a]	55	8.3 (6.4-10.6)[b]	21 412	1 374	6.4 (6.1-6.8)[c,d]	.06	22 074
75-84 years	905	3.5 (3.3-3.7)	95	10.5 (8.6-12.6)	24 912	2 324	9.3 (9.0-9.7)[d]	.26	25 817
≥ 85 years	409	3.3 (3.0-3.6)	52	12.7 (9.7-16.2)	11 963	1 568	13.1 (12.5-13.7)	.88	12 372
Total	**1 976**	**3.3 (3.1-3.4)**	**202**	**10.2 (8.9-11.6)**	**58 287**	**5 266**	**9.0 (8.8-9.3)**	**.08**	**60 263**

1. Prevalence of ADR hospital admission and mortality rates according to age subgroups

We evaluated more than 60,000 emergency hospital admissions, showing a point prevalence of 3.3%, which was lower than that obtained through meta-analyses with smaller sample sizes.

*Our overall prevalence of 3.3% was equal to that reported in a large Italian study in older adults conducted by **Onder et al**. The study enrolled more than 28,000 patients and observed a similar prevalence of ADR-related hospital admission of 3.4%.*

Onder G, Pedone C, Landi F, et al. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc. 2002;50(12):1962-1968.

1. Prevalence of ADR hospital admission and mortality rates according to age subgroups

Prevalence: Systematic reviews showed that larger investigations displayed lower prevalence of ADR-related hospital admissions, while smaller studies observed higher figures.

*Some studies reported that there was a **4-fold increase of prevalence in the elderly** compared to the adult population; however, it has been suggested that these important differences in the ADR prevalence in age subgroups could be explained, at least in part, because larger studies (with a sample size greater than 2,000) are lacking in elderly population.*

Mortality: Our results highlight the clinical relevance of drug-induced disorders in the elderly, since they can be as **serious and life-threatening** as any other acute pathology that merits urgent hospital admission.

2. Suspected drugs by therapeutic subgroup and comparison between age subgroups

We observed that the therapeutic subgroups accounting for two thirds of the overall suspected pharmacological exposures in all age subgroups were:

1) antithrombotics,
2) diuretics,
3) RAS inhibitors,
4) NSAIDs.

2. Suspected drugs by therapeutic subgroup and comparison between age subgroups

Therapeutic subgroups	Age subgroup			Total
	65-74 years	**75-84 years**	**≥ 85 years**	
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**
Antithrombotics	309 (26.8)	459 (28.4)	176 (24.4)	**944 (27.1)**
Non-steroidal antiinflammatory and antirheumatic drugs	117 (10.1)	150 (9.3)	74 (10.3)	**341 (9.8)**
High-ceiling diuretics	**67 (5.8)***	**142 (8.8)**	**86 (11.9)**	**295 (8.5)**
Angiotensin-converting enzyme inhibitors	**46 (4.0)***	**106 (6.6)**	**67 (9.3)**	**219 (6.3)**
Antidepressants	66 (5.7)	92 (5.7)	34 (4.7)	**192 (5.5)**
Potassium-sparing diuretics	41 (3.6)	63 (3.9)	22 (3.1)	**126 (3.6)**
Cardiac glycosides	**19 (1.6)***	**61 (3.8)**	**34 (4.7)**	**114 (3.3)**
Beta-blocking agents	33 (2.9)	61 (3.8)	20 (2.8)	**114 (3.3)**
Angiotensin II antagonists	27 (2.3)	45 (2.8)	19 (2.6)	**91 (2.6)**
Immunosupressants	**70 (6.1)***	**21 (1.3)[b]**	**0 (0)**	**91 (2.6)**
Corticosteroids	**43 (3.7)***	**21 (1.3)**	**4 (0.6)**	**68 (2.0)**
Others	315 (27.3)	393 (24.3)	184 (25.6)	**892 (25.6)**
Total	**1 153 (100)**	**1 614 (100)**	**720 (100)**	**3 487 (100)**

* $P < 0.05$; comparing age subgroups

3. Most frequent adverse drug reactions and drug-reaction associations and comparison between age subgroups

Unfortunately, most studies publishing descriptive information about specific ADRs included a very low number of cases (about 100 cases or less).

The large number of cases included in the present study allowed us to make an accurate description of the most common ADRs and suspected drugs.

3. Most frequent adverse drug reactions and drug-reaction associations and comparison between age subgroups

In our study, a large proportion of elderly patients admitted due to ADRs was exposed to **polypharmacy** (86%), and a **DDI** was suspected in 49% of cases.

Polypharmacy has been shown to be the most consistent and strongest predictor of ADRs in older adults.

Furthermore, there is a strong association between the number of drugs used and the probability of serious **Drug-Drug Interactions** (DDIs).

Our results are comparable to those observed in other studies, in which 73% of patients were taking ≥4 drugs (Franceschi M et al. Drug Saf. 2008;31:545-556) or 93% of patients were taking ≥5 drugs (Marcum ZA et al. J Am Geriatr Soc. 2012;60:34-41). However, the proportion of DDIs found in other studies is lower that observed in ours (20%-32%).

3. Most frequent adverse drug reactions and drug-reaction associations and comparison between age subgroups

ADRs and drug-reaction associations	Age subgroup			Total
	65-74 years (n = 662) No. (%)	75-84 years (n = 905) No. (%)	≥ 85 years (n = 409) No. (%)	(n = 1 976) No. (%)
Acute renal failure	**125 (18.9)***	**205 (22.7)***	**123 (30.1)**	453 (22.9)
RAS inhibitors and diuretics	**47 (7.1)***	**118 (13.0)**	**75 (18.3)**	240 (12.1)
RAS inhibitors, diuretics and NSAIDs	22 (3.3)	28 (3.1)	16 (3.9)	66 (3.3)
Diuretics	14 (2.1)	12 (1.3)	8 (2.0)	34 (1.7)
RAS inhibitors	6 (0.9)	19 (2.1)	9 (2.2)	34 (1.7)
Upper gastrointestinal bleeding	123 (18.6)	134 (14.8)	71 (17.4)	328 (16.6)
Antiplatelet drugs	32 (4.8)	32 (3.5)	22 (5.4)	86 (4.4)
Vitamin K antagonists	23 (3.5)	29 (3.2)	10 (2.4)	62 (3.1)
NSAIDs	17 (2.6)	18 (2.0)	10 (2.4)	45 (2.3)
NSAIDs and antiplatelet drugs	11 (1.7)	8 (0.9)	8 (2.0)	27 (1.4)
NSAIDs and vitamin K antagonists	4 (0.6)	13 (1.4)	2 (0.5)	19 (1.0)
Lower gastrointestinal bleeding	61 (9.2)	106 (11.7)	54 (13.2)	221 (11.2)
Vitamin K antagonists	15 (2.3)	18 (2.0)	15 (3.7)	48 (2.4)
Antiplatelet drugs	10 (1.5)	23 (2.5)	11 (2.7)	44 (2.2)
NSAIDs	12 (1.8)	9 (1.0)	10 (2.4)	31 (1.6)
Intracranial bleeding	**62 (9.4)[e]**	**101 (11.2)***	**21 (5.1)**	184 (9.3)
Vitamin K antagonists	**45 (6.8)**	**70 (7.7)[g]**	**15 (3.7)**	130 (6.6)
Vitamin K antagonists and SSRIs	7 (1.1)	17 (1.9)	2 (0.5)	26 (1.3)
Digitalis intoxication	**14 (2.1)***	**42 (4.6)**	**28 (6.8)**	74 (3.7)
Digoxin	**6 (0.9)***	**19 (2.1)***	**19 (4.6)**	44 (2.2)
Digoxin and other drugs	8 (1.2)	23 (2.5)	9 (2.2)	40 (2.0)
Atrioventricular block	22 (3.3)	35 (3.9)	8 (2.0)	65 (3.3)
Beta-blocking agents	10 (1.5)	16 (1.8)	2 (0.5)	28 (1.4)
Muscular hematoma	11 (1.7)	26 (2.9)	11 (2.7)	48 (2.4)
Vitamin K antagonists	4 (0.6)	11 (1.2)	3 (0.7)	18 (0.9)
Hyponatremia	12 (1.8)	16 (1.8)	16 (3.9)	44 (2.2)
Diuretics and SSRIs	7 (1.1)	5 (0.6)	5 (1.2)	17 (0.9)

3. Most frequent adverse drug reactions and drug-reaction associations and comparison between age subgroups

Most frequent **drug-reaction associations** were:

→ **acute renal failure** related to renin-angiotensin system (RAS) inhibitors,

→ **gastrointestinal bleeding** by antithrombotics and/or non-steroidal anti-inflammatories,

→ **intracranial bleeding** induced by vitamin K antagonists.

3. Most frequent adverse drug reactions and drug-reaction associations and comparison between age subgroups

A large study by Budnitz et al. found a high proportion of ADRs related to antidiabetic drugs (23% of ADRs were antidiabetic-induced hypoglycemia).

The much lower frequency of this ADR in our study (<1%) could likely be explained by the fact that in our hospital most cases of hypoglycemia related to antidiabetic drugs are managed in the ED-Observation Unit, and they are usually discharged within the first 24 hours without requiring hospital admission in a medical ward.

Budnitz DS, Loovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365(21):2002-2012.

Limitations

Some **limitations** could have led us to underestimate the prevalence of ADR-related hospitalizations:

1. Our method is based on the **admission diagnosis**; thus, we could have failed to identify some ADR-cases which were hospitalized due to unspecific and presumptive diagnoses on admission, and afterwards discharged with a diagnosis of ADR.

2. We could not provide the total **precise number of different drugs taken** by patients since only six drugs per case were entered onto the database.

3. The present study was conducted in a **single, third-level teaching hospital**; any extrapolation of our results to other settings would require caution.

Current intervention

1979 **Catalan Health System**

1986 **Spanish Health System ("NHS")**

1990 **Llei Ordenació Sanitària de Catalunya**

Health Care Department → Health Policy, Planning
Catalan Health Service → Finances, Funding
Hospitals, Primary Care → Health Care Suppliers

Primary Care Centers	Hospitals
300	68

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Electronic Medical Record (SAP)

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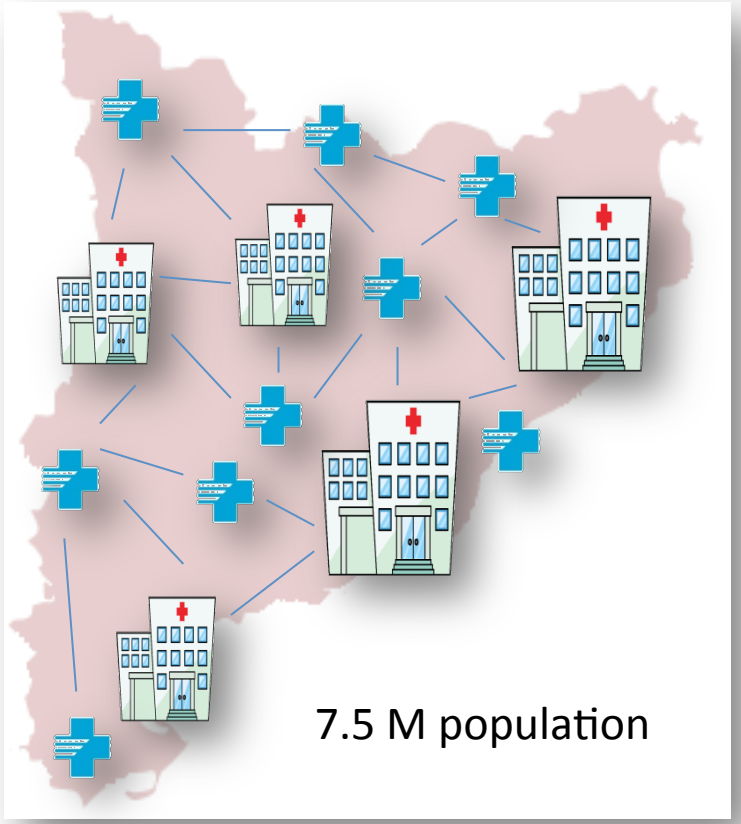

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Electronic Prescription

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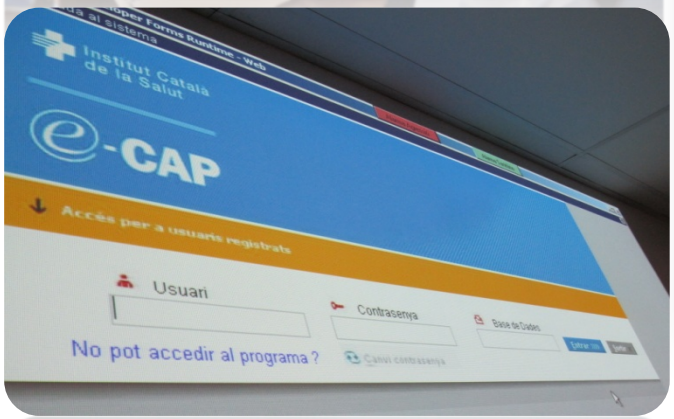

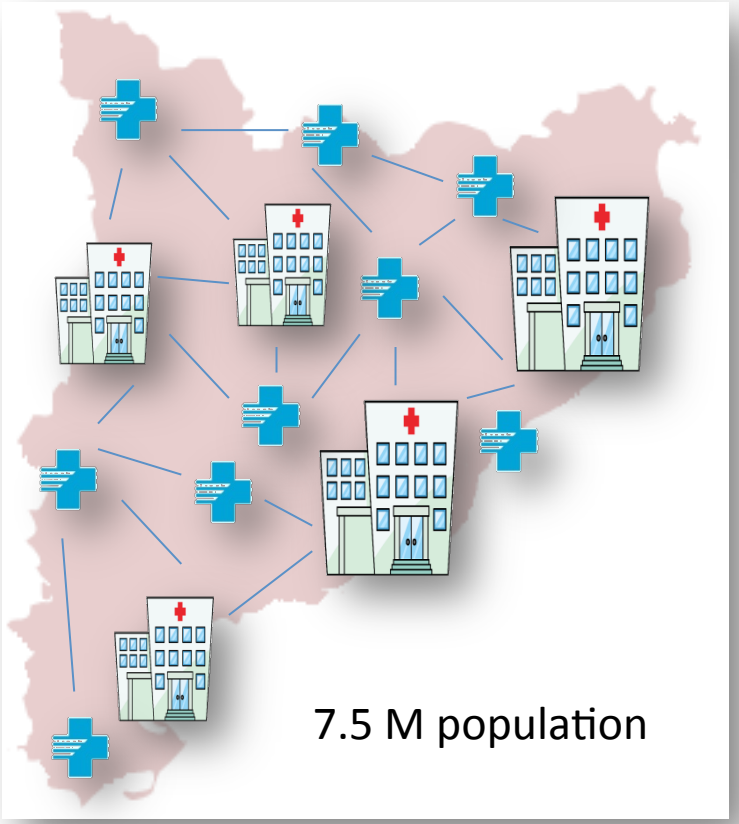

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Benefits of e-prescribing

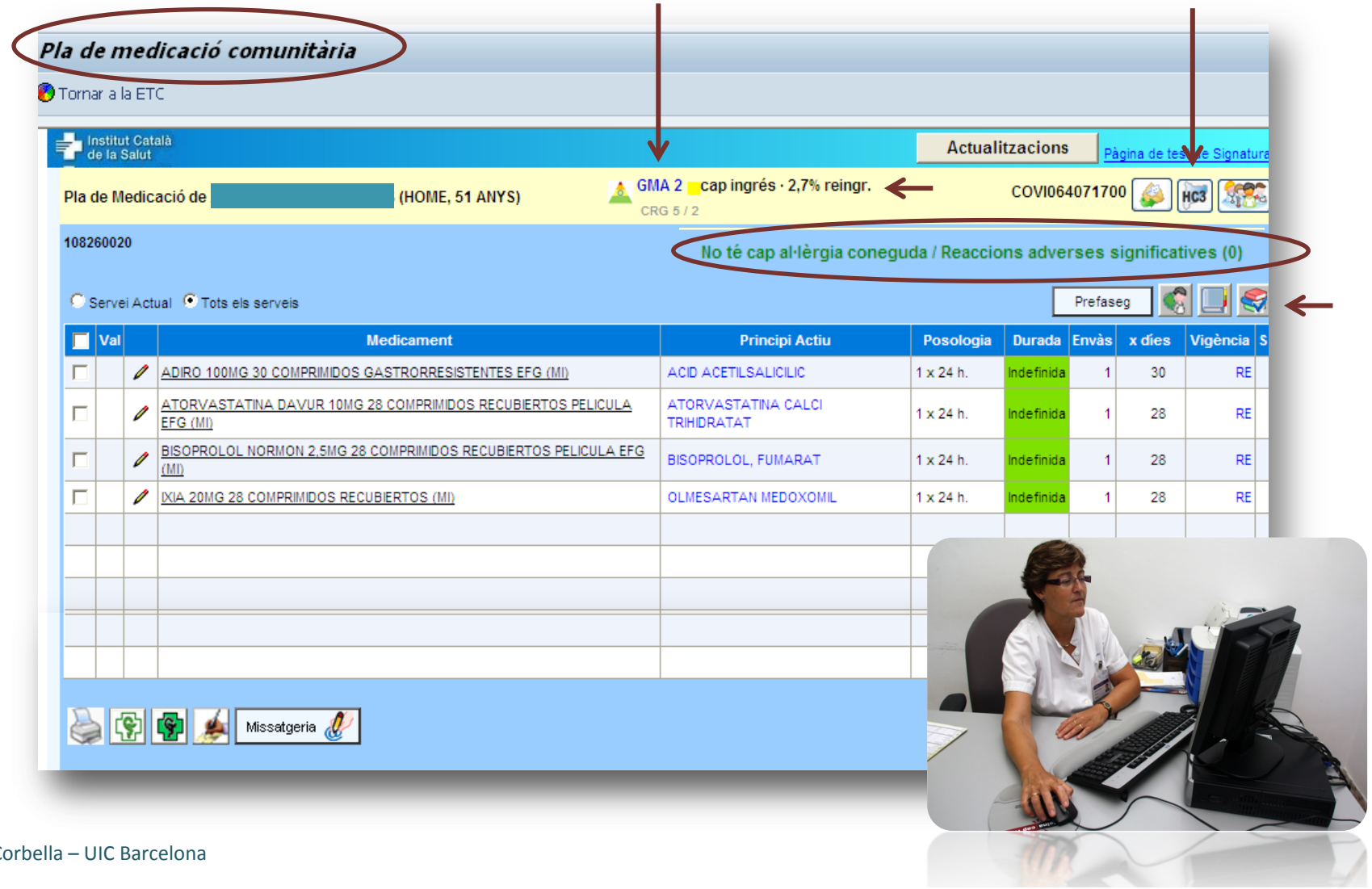
E-prescribing increases health care quality and efficiency, through the reduction of prescription errors, adverse drug events, and economic costs.

E-prescribing improves patient safety and quality of care through a variety of mechanisms including:

- eliminating illegible prescriptions,
- reducing oral miscommunications,
- implementing warning and alert systems
- integrating the patient's medication history

Electronic Prescription

bridging hospital and primary care settings…



Electronic Prescription

Review Paper ■

The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review

ELSKE AMMENWERTH, PHD, PETRA SCHNELL-INDERST, PHD, CHRISTOF MACHAN, MSC, UWE SIEBERT, PHD

Abstract The objective of this systematic review is to analyse the relative risk reduction on medication error and adverse drug events (ADE) by computerized physician order entry systems (CPOE). We included controlled field studies and pretest-posttest studies, evaluating all types of CPOE systems, drugs and clinical settings. We present the results in evidence tables, calculate the risk ratio with 95% confidence interval and perform subgroup analyses for categorical factors, such as the level of care, patient group, type of drug, type of system, functionality of the system, comparison group type, study design, and the method for detecting errors. Of the 25 studies that analysed the effects on the medication error rate, 23 showed a significant relative risk reduction of 13% to 99%. Six of the nine studies that analysed the effects on potential ADEs showed a significant relative risk reduction of 35% to 98%. Four of the seven studies that analysed the effect on ADEs showed a significant relative risk reduction of 30% to 84%. Reporting quality and study quality was often insufficient to exclude major sources of bias. Studies on home-grown systems, studies comparing electronic prescribing to handwriting prescribing, and studies using manual chart review to detect errors seem to show a higher relative risk reduction than other studies. Concluding, it seems that electronic prescribing can reduce the risk for medication errors and ADE. However, studies differ substantially in their setting, design, quality, and results. To further improve the evidence-base of health informatics, more randomized controlled trials (RCTs) are needed, especially to cover a wider range of clinical and geographic settings. In addition, reporting quality of health informatics evaluation studies has to be substantially improved.

■ **J Am Med Inform Assoc.** 2008;15:585–600. DOI 10.1197/jamia.M2667.

Electronic Prescription

Medical errors relative risk reduction

Review Paper ■

The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review

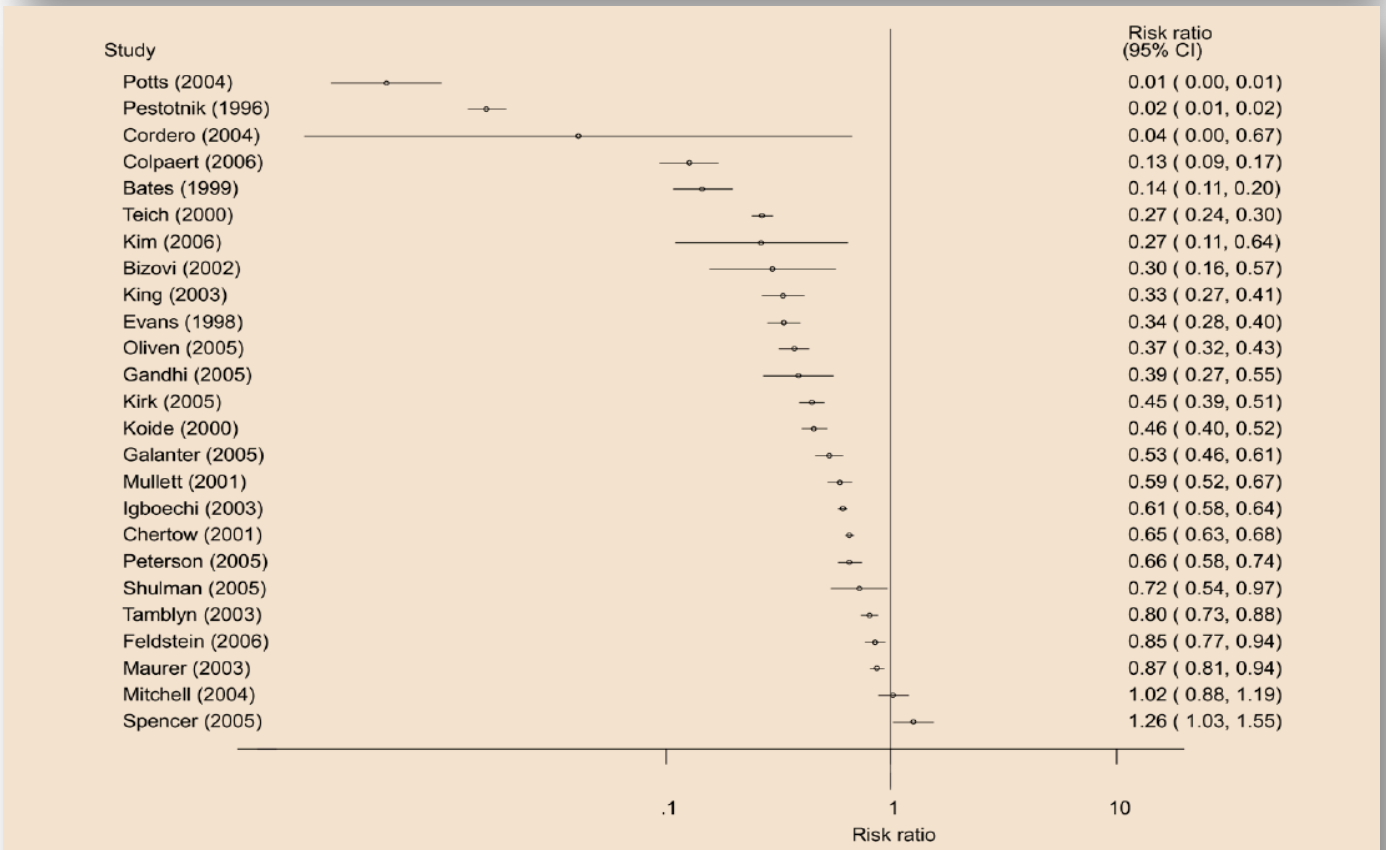


Figure 2. Risk ratios of 25 studies analyzing the effect of electronic prescribing on medication errors.

Electronic Prescription

Review Paper ■

The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review

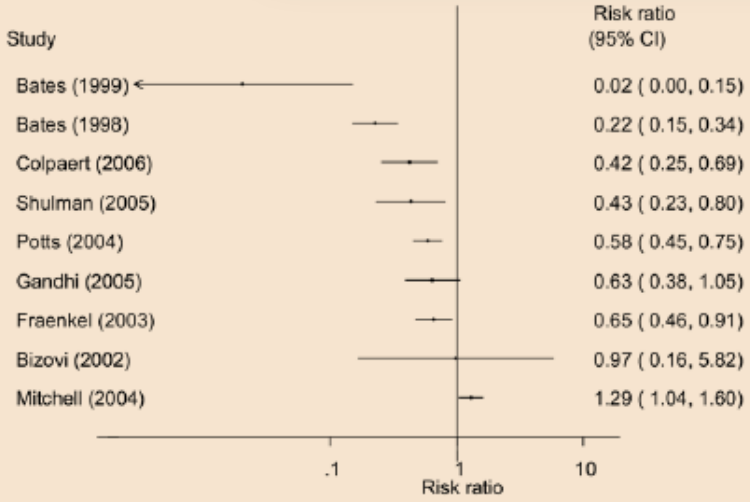


Figure 3. Risk ratios of nine studies analyzing the effect of electronic prescribing on potential ADEs.

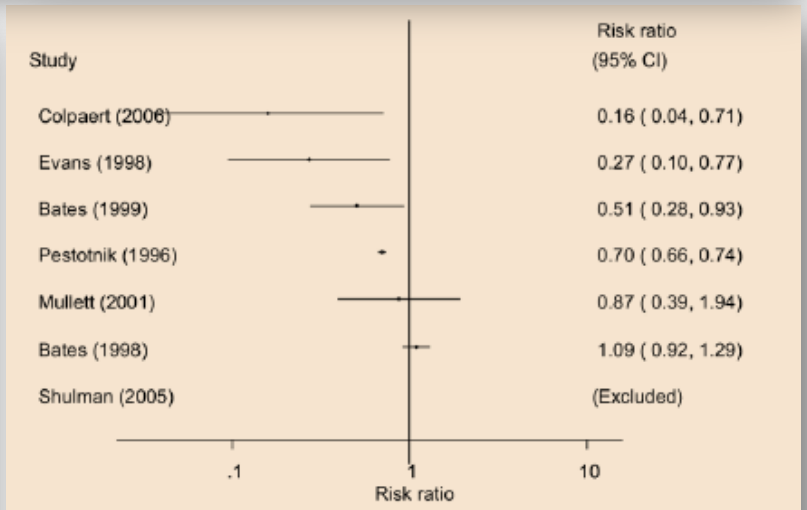


Figure 4. Risk ratios of seven studies analyzing the effect of electronic prescribing on ADEs. Shulman was excluded, because there was no event in either the intervention group or the comparision group.

ADRs relative risk reduction

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Conclusions and Relevance

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❖ In our hospital, **one out of every 30 urgent admissions** of patients aged ≥65 years is, and their mortality rate is similar to that documented in acute patients urgently admitted for other causes.

❖ Most cases involve patients exposed to **polypharmacy** (≥5 drugs) and result from well-known reactions of **commonly used drugs** such as RAS inhibitors and anticoagulants.

❖ Updated information provided by an institutional **Pharmacovigilance Program** should assist clinicians and healthcare administrators, in collaboration, to address the problem of drug toxicity in the elderly and design preventive actions.

❖ Preventive strategies should be mainly focused on **reducing polypharmacy** and should **involve both hospital and primary care settings**

❖ **Electronic medical records and e-prescription,** could integrate the patient's medication history, reducing medical errors, adverse drug events, and economic costs.

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