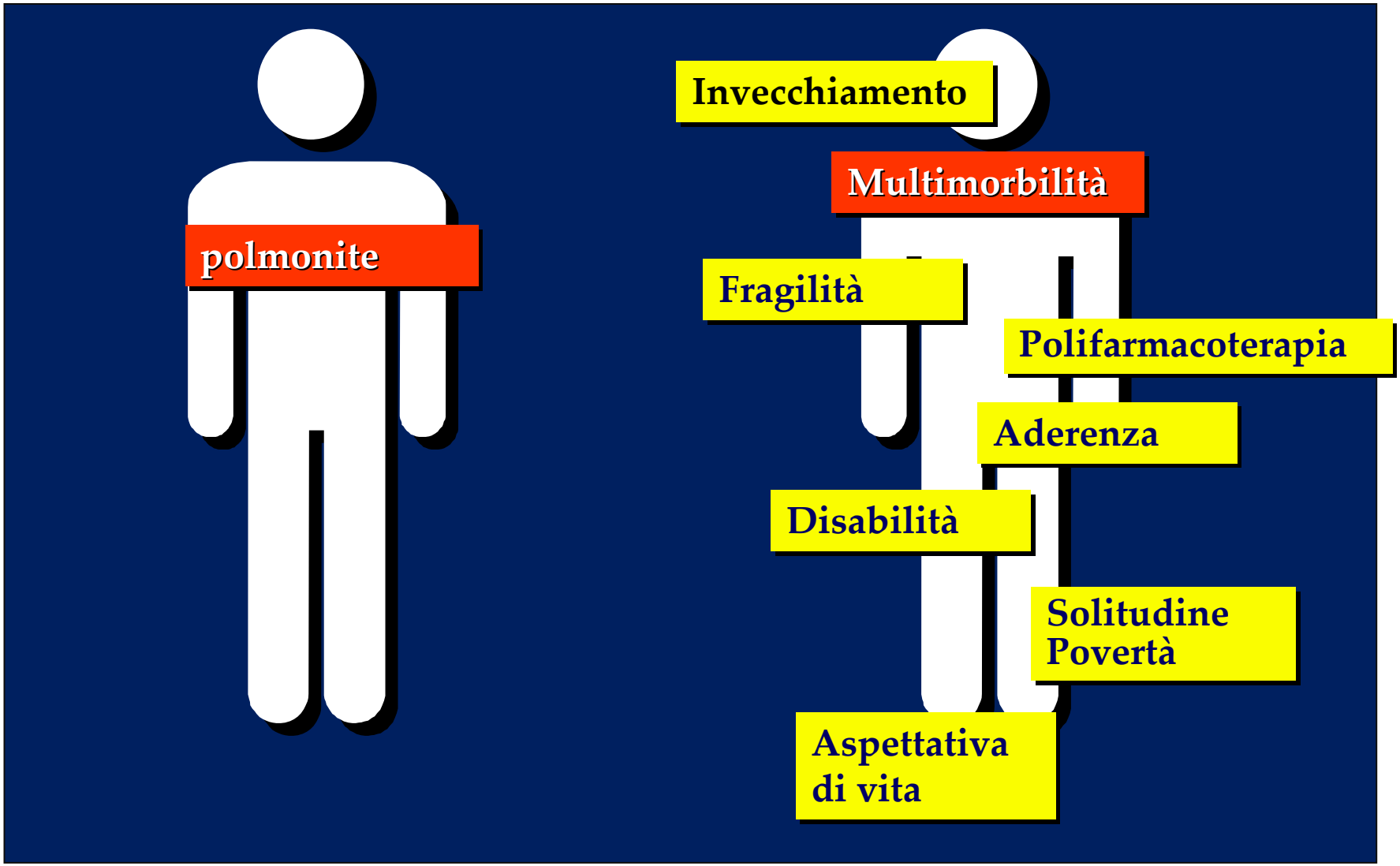
Appropriatezza prescrittiva nella popolazione anziana

Antonio Cherubini
Geriatria ed Accettazione Geriatrica d'Urgenza
IRCCS-INRCA



Soggetto giovane-adulto

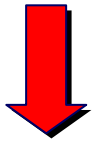
Soggetto anziano

SPECIAL ARTICLES

The End of the Disease Era

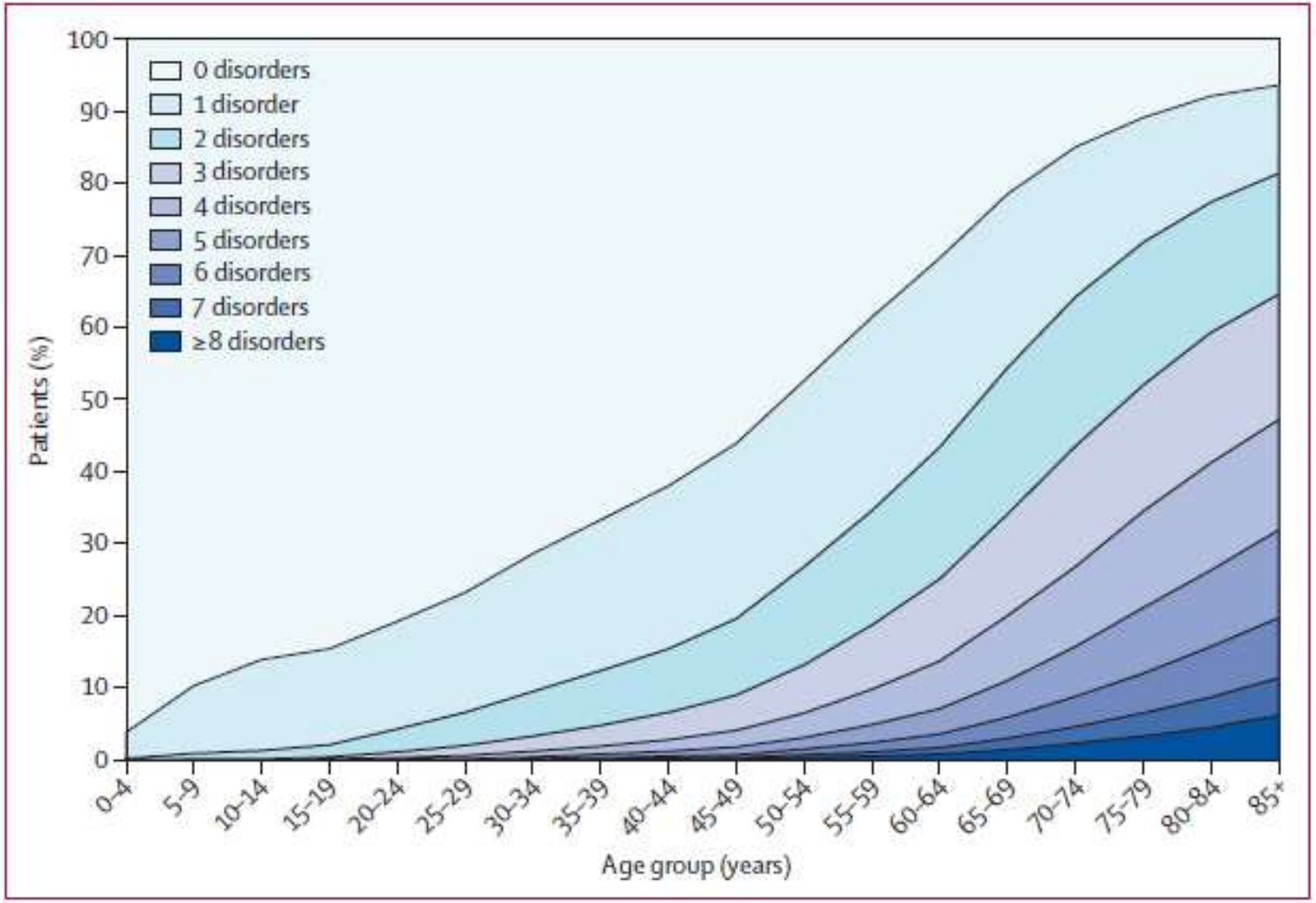
Tinetti M.E., Fried T., Am J Med, 2004

It 's time to leave the concept of disease as a central moment of the medical intervention because, due to the aging of the population, health problems are increasingly less identified as a single disease, and the biological and non-biological factors tend to not interact with each other



The focus on the of the single disease treatment is therefore misleading and harmful

Multimorbilità (UK)

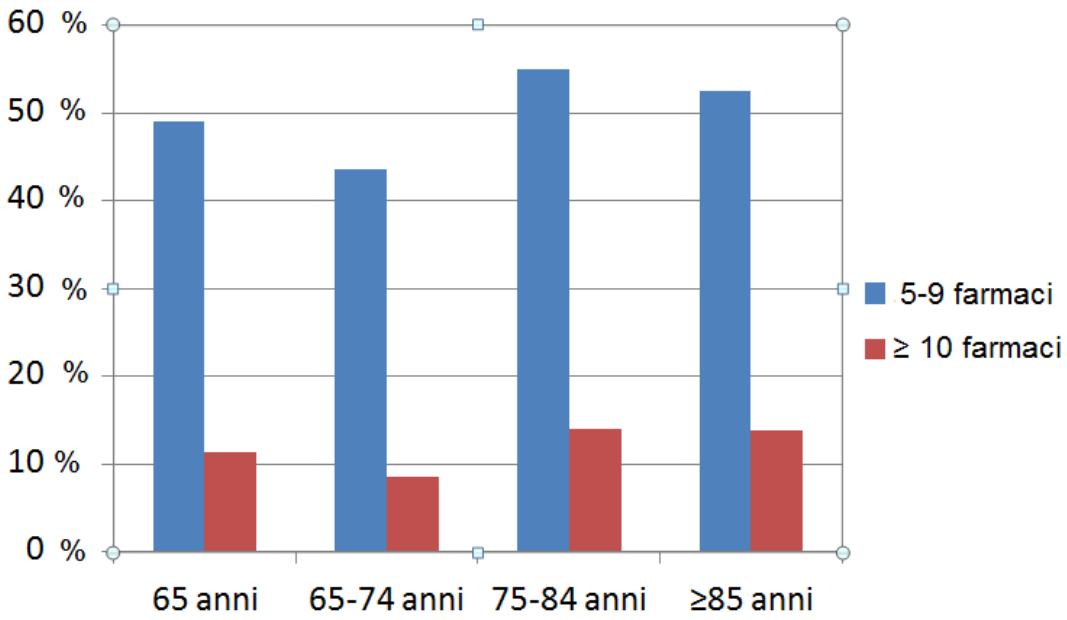


Numero di malattie croniche per gruppi di età

Barnett K. Et al. Lancet 2012; 380

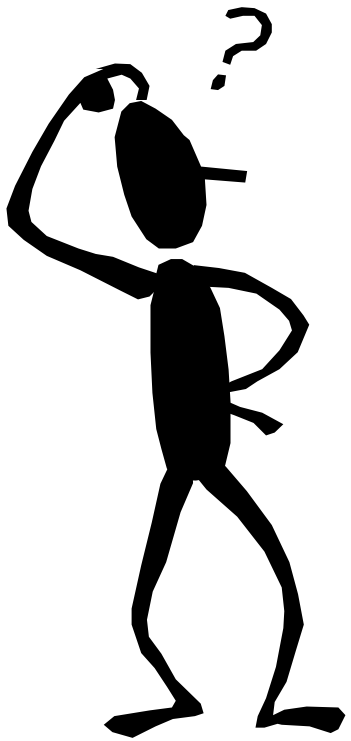
Prescribed drugs to older patients in Italy

	Anziani (≥ 65 aa) n=12.301.537	**65-74 aa n=6.154.421**	**75-84 aa n=4.474.887**	**≥85 aa n= 1.672.229**
Farmaci				
5-9	6.024.383 (49.0%)	2.681.639 (43.6%)	2.462.378 (55.0%)	880.366 (52.6%)
≥10	**1.389.591 (11.3%)**	529.506 (8.6%)	629.043 (14.1%)	231.042 (13.8%)



Onder, J Gerontol, 2014

Trattamento in base alle linee guida di una paziente di 79 anni con ipertensione, diabete mellito, osteoporosi, osteoartrosi e BPCO



Time	Medications†	Other
7:00 AM	Ipratropium metered dose inhaler 70 mg/wk of alendronate	Check feet Sit upright for 30 min on day when alendronate is taken Check blood sugar
8:00 AM	500 mg of calcium and 200 IU of vitamin D 12.5 mg of hydrochlorothiazide 40 mg of lisinopril 10 mg of glyburide 81 mg of aspirin 850 mg of metformin 250 mg of naproxen 20 mg of omeprazole	Eat breakfast 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
12:00 PM		Eat lunch 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
1:00 PM	Ipratropium metered dose inhaler 500 mg of calcium and 200 IU of vitamin D	
7:00 PM	Ipratropium metered dose inhaler 850 mg of metformin 500 mg of calcium and 200 IU of vitamin D 40 mg of lovastatin 250 mg of naproxen	Eat dinner 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
11:00 PM	Ipratropium metered dose inhaler	
As needed	Albuterol metered dose inhaler	

Boyd, C. M. et al. JAMA 2005;294:716-724.

JAMA

Potenziali interazioni farmacologiche

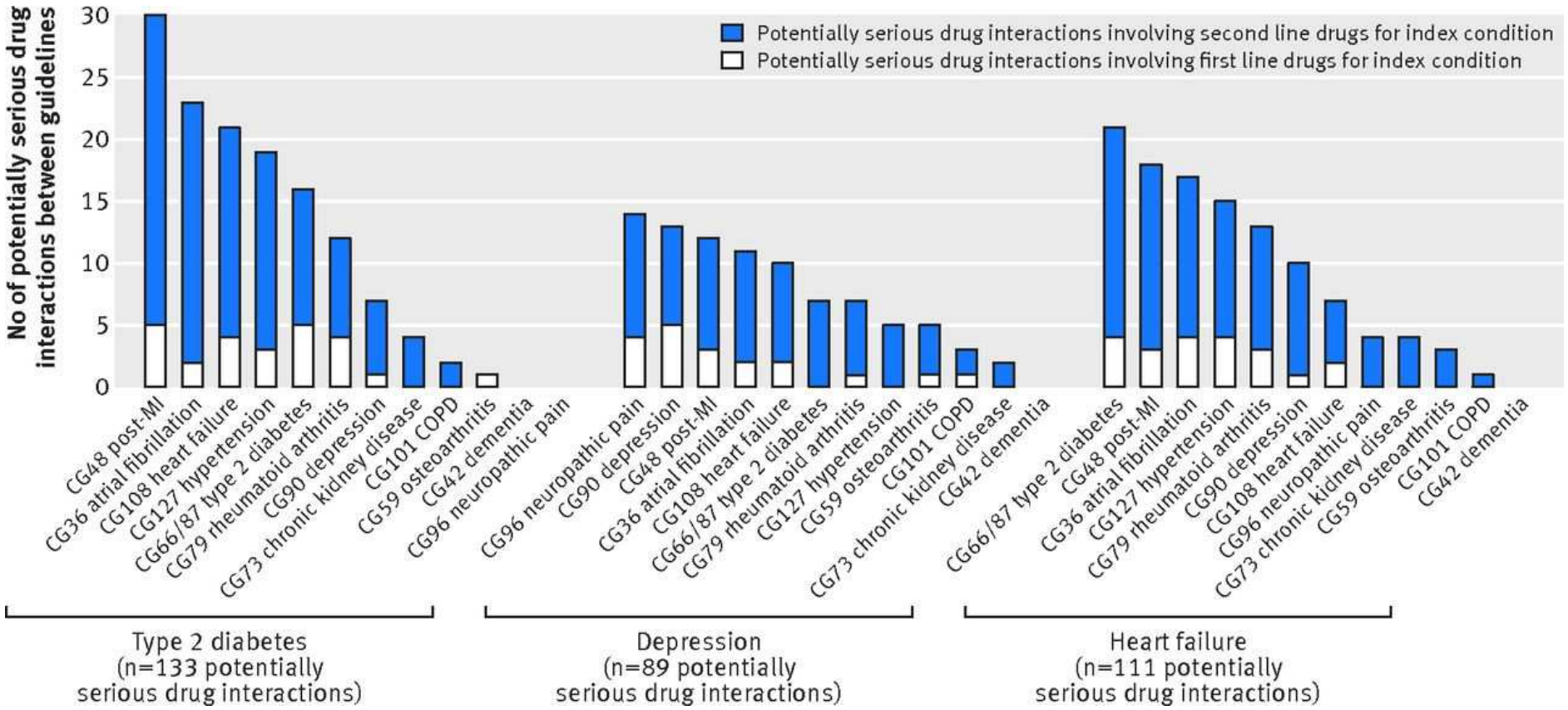
Type of Disease	Medications With Potential Interactions	Type of Interaction: Medication and Other Disease	Type of Interaction: Medications for Different Diseases	Type of Interaction: Medication and Food
Hypertension	Hydrochlorothiazide, lisinopril	Diabetes: diuretics increase serum glucose and lipids*	Diabetes medications: hydrochlorothiazide may decrease effectiveness of glyburide	NA
Diabetes	Glyburide, metformin, aspirin, and atorvastatin	NA	Osteoarthritis medications: NSAIDs plus aspirin increase risk of bleeding Diabetes medications: glyburide plus aspirin may increase the risk of hypoglycemia; aspirin may decrease effectiveness of lisinopril	Aspirin plus alcohol: increased risk of gastrointestinal tract bleeding Atorvastatin plus grapefruit juice: muscle pain, weakness Glyburide plus alcohol: low blood sugar, flushing, rapid breathing, tachycardia Metformin plus alcohol: extreme weakness and heavy breathing Metformin plus any type of food: medication absorption decreased
Osteoarthritis	NSAIDs	Hypertension: NSAIDs: raise blood pressure†; NSAIDs plus hypertension increase risk of renal failure	Diabetes medications: NSAIDs in combination with aspirin increase risk of bleeding Hypertension medications: NSAIDs decrease efficacy of diuretics	NA
Osteoporosis	Calcium, alendronate	NA	Diabetes medications: calcium may decrease efficacy of aspirin; asprin plus alendronate can cause upset stomach Osteoporosis medications: calcium may lower serum alendronate level	Alendronate plus calcium: take on empty stomach (>2 h from last meal) Alendronate: avoid orange juice Calcium plus oxalic acid (spinach and rhubarb) or phytic (bran and whole cereals): eating these foods may decrease amount of calcium absorbed (>2 h from last meal)
Chronic obstructive pulmonary disease	Short-acting β-agonists	NA	NA	NA

Abbreviations: NA, no interaction is known; NSAIDs, nonsteroidal anti-inflammatory drugs.
*Thiazide-type diuretics may worsen hyperglycemia, but effect thought to be small and not associated with increased incidence of cardiovascular events.
†This interaction is noted to be particularly relevant for individuals with diabetes; no recommendation for treatment is given.

Boyd, C. M. et al. JAMA 2005;294:716-724.

JAMA

Potentially serious drug-drug interactions between drugs recommended by clinical guidelines for 3 index conditions and drugs recommended by each of other 11 other guidelines



Dumbreck et al BMJ 2015

Condizioni geriatriche ed appropriatezza prescrittiva:

1. Deficit cognitivi e funzionali

Treatment of non dementia illness in patients with dementia

Problems	Consequences	Responses
Cognition and language	Decreased decision-making capacity Increased caregiver burden Increased risk of diagnostic procedures Adherence problems Difficulty reporting adverse effects Difficulty titrating medicines based on reporting by patient	Consider altered risk-benefit ratio balancing safety and autonomy Adjust communication strategies
Decreased life expectancy	Decreased potential benefit	Consider altered risk-benefit ratio Reserve therapy/screening for those with sufficient life expectancy to realize benefit
Exclusion from studies	Increased uncertainty about effects of therapy in this group	Policy changes to include patients with dementia in appropriate studies

Brauner et al. JAMA 2000

Concerns about older persons' ability to adhere to complex medication regimens

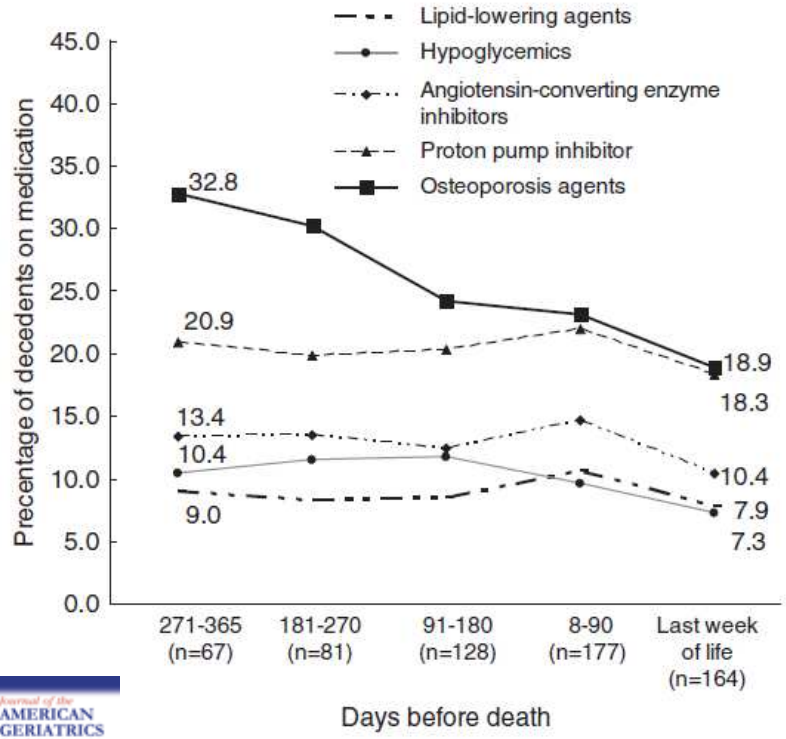
Concern	Representative Quotation
Historical evidence of inability to adhere	Also I factor in adherence to even a basic treatment. If they cannot manage a basic treatment, the one I am giving them, I am not going to complicate it further by adding something to get to the goal range.
Difficulty understanding medications	Whenever [patients] are confused about what medications they are on that suggests a problem. When they can not tell you what the medications either by name or description, and they are confused about when they are supposed to take them
Availability of social support	Often what you are doing is assessing someone's personality and their abilities to integrate complicated information and goals and if you have a patient who is limited you are obviously not going to push the meds nearly as hard unless there is somebody else in the picture who can administer them.
	I look at their functioning as a whole and also whether or not they live alone, their support system, have help.

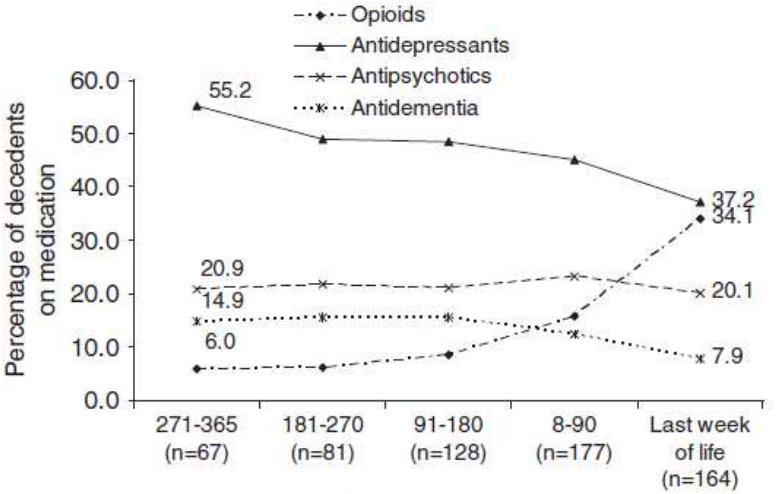
Fried, T. R. et al. Arch Intern Med 2010 ARCHIVES OF INTERNAL MEDICINE

Condizioni geriatriche ed appropriatezza prescrittiva:

1. Deficit cognitivi e funzionali
2. Limitata aspettativa di vita

Daily Medication Use in Nursing Home Residents with Advanced Dementia





Tija et al, J Am Geriatr Soc 2010

This prospective study demonstrates that daily medications for chronic conditions are commonly and persistently prescribed to NH residents with advanced dementia. Although some medications of questionable benefit were discontinued toward the end of life (e.g., antidementia drugs), reductions often occurred only when death was imminent, and some drugs with unclear benefits (e.g., lipid-lowering agents) or potential harmful side effects (e.g., antipsychotics) did not decline. In addition, although the stated primary goal of care was comfort for 90% of residents, up to 40% were prescribed drugs deemed inappropriate in end-stage dementia when palliation is the goal of care. These findings raise concerns not only about the burden of medication use in advanced dementia, but also about how decisions regarding drug treatment are made for these residents.

Condizioni geriatriche ed appropriatezza prescrittiva:

1. Deficit cognitivi e funzionali
2. Limitata aspettativa di vita
3. Sindromi geriatriche

Cadute

Table 2. Recommended Components of Clinical Assessment and Management for Older Persons Living in the Community Who Are at Risk for Falling.

Assessment and Risk Factor	Management
Circumstances of previous falls*	Changes in environment and activity to reduce the likelihood of recurrent falls
Medication use High-risk medications (e.g., benzodiazepines, other sleeping medications, neuroleptics, antidepressants, anticonvulsants, or class IA antiarrhythmics)*†‡ Four or more medications‡	Review and reduction of medications
Vision* Acuity <20/60 Decreased depth perception Decreased contrast sensitivity Cataracts	Ample lighting without glare; avoidance of multifocal glasses while walking; referral to an ophthalmologist
Postural blood pressure (after ≥5 min in a supine position, immediately after standing, and 2 min after standing)‡ ≥20 mm Hg (or ≥20%) drop in systolic pressure, with or without symptoms, either immediately or after 2 min of standing	Diagnosis and treatment of underlying cause, if possible; review and reduction of medications; modification of salt restriction; adequate hydration[46]; compensatory strategies (e.g., elevation of head of bed, rising slowly, or dorsiflexion exercises); pressure stockings; pharmacologic therapy if the above strategies fail

N Engl J Med. 2003;348:42-9. The NEW ENGLAND JOURNAL of MEDICINE

Condizioni geriatriche ed appropriatezza prescrittiva:

1. Deficit cognitivi e funzionali
2. Limitata aspettativa di vita
3. Sindromi geriatriche
4. Esclusione trial clinici

SPECIAL ARTICLE

Fighting Against Age Discrimination in Clinical Trials

Antonio Cherubini, MD, PhD, Susanna Del Signore, MD,† Joe Ouslander, MD,‡ Todd Semla, MS, PharmD,§‖ and Jean-Pierre Michel, MD#*

SEPTEMBER 2010–VOL. 58, NO. 9 JAGS

ORIGINAL INVESTIGATION

The Persistent Exclusion of Older Patients From Ongoing Clinical Trials Regarding Heart Failure

Antonio Cherubini, MD, PhD; Joaquim Oristrell, MD, PhD; Xavier Pla, MD; Carmelinda Ruggiero, MD, PhD; Roberta Ferretti, MD; Germán Diestre, MD; A. Mark Clarfield, MD, FRCPC; Peter Crome, MD, DSc; Cees Hertogh, MD, PhD; Vita Lesauskaite, MD, PhD; Gabriel-Ioan Prada, MD, PhD; Katarzyna Szczerbinska, MD, PhD; Eva Topinkova, MD, PhD; Judith Sinclair-Cohen, BSD; David Edbrooke, MD, FRCA; Gary H. Mills, MD, PhD

Background: Much clinical research of relevance to elderly patients examines individuals who are younger than those who have the disease in question. A good example is heart failure. Therefore, we investigated the extent of exclusion of older individuals in ongoing clinical trials regarding heart failure.

Methods: In the context of the Increasing the PaRticipation of the ElDerly in Clinical Trials (PREDICT) study, data from ongoing clinical trials regarding heart failure were extracted from the World Health Organization Clinical Trials Registry Platform on December 1, 2008. Main outcome measures were the proportion of trials excluding patients by an arbitrary upper age limit or by other exclusion criteria that might indirectly cause limited recruitment of older individuals. We classified exclusion criteria into 2 categories: justified or poorly justified.

Results: Among 251 trials investigating treatments for heart failure, 64 (25.5%) excluded patients by an arbitrary upper age limit. Such exclusion was significantly more common in trials conducted in the European Union than in the United States (31/96 [32.3%] vs 17/105 [16.2%]; $P = .007$) and in drug trials sponsored by public institutions vs those by private entities (21/59 [35.6%] vs 5/36 [13.9%]; $P = .02$). Overall, 109 trials (43.4%) on heart failure had 1 or more poorly justified exclusion criteria that could limit the inclusion of older individuals. A similar proportion of clinical trials with poorly justified exclusion criteria was found in pharmacologic and nonpharmacologic trials.

Conclusion: Despite the recommendations of national and international regulatory agencies, exclusion of older individuals from ongoing trials regarding heart failure continues to be widespread.

Arch Intern Med. 2011;171(6):550-556

Adverse Drug Events (ADE)

- **REAZIONI AVVERSE DA FARMACI**
- **EVENTI NOCIVI CONSEGUENTI ALL'UTILIZZO DEI FARMACI LEGATI AD ERRORI:**
  - **NELLA PRESCRIZIONE**
  - **DISPENSAZIONE**
  - **ADERENZA ALLA TERAPIA**
  - **MONITORAGGIO**

Adverse drug events as a cause of hospitalization in older adults.

Salvi F[1], Marchetti A, D'Angelo F, Boemi M, Lattanzio F, Cherubini A.

Drug. Saf. 2012

Gli anziani tendono a sviluppare ADEs con una probabilità 7 volte maggiore rispetto ai giovani. Le ADE possono determinare ospedalizzazioni in particolare nelle donne e in chi assume più farmaci.

La prevalenza delle ospedalizzazioni relative all'assunzione di farmaci presenta larga eterogeneità tra i diversi studi (in media 5-10% con punte fino al 31%), in relazione al setting di studio (tutte le ammissioni in ospedali o solo ammissioni acute), alla popolazione in esame (ospedale intero, specifici reparti, popolazione selezionata o certi gruppi di età), al tipo di problemi relativi al farmaco che vengono misurati (ADR o ADE), al tipo di metodo di raccolta di dati (revisione delle cartelle, segnalazioni spontanee o ricerca nei database), al metodo e definizione utilizzato per rilevare ADEs.

BMJ 2016;353:i2139 doi: 10.1136/bmj.i2139 (Published 3 May 2016)

ANALYSIS

Medical error—the third leading cause of death in the US

Medical error is not included on death certificates or in rankings of cause of death. **Martin Makary** and **Michael Daniel** assess its contribution to mortality and call for better reporting

Martin A Makary *professor*, Michael Daniel *research fellow*

Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

The annual list of the most common causes of death in the United States, compiled by the Centers for Disease Control and

How big is the problem?

Adverse medication events are the leading cause of iatrogenic death; 70% of deaths occurred in patients aged > 75 years.

Interventi

CATEGORIE DI INTERVENTI

- Valutazione multidimensionale geriatrica
- Applicazione Criteri PI
- Formazione
- Sistemi informatizzati di supporto
- Farmacista
- Team multidisciplinare
- Politiche regolatorie
- Multifattoriali

Effects of geriatric evaluation and management on ADE and suboptimal prescribing in the frail elderly

- METHODS: inpatient geriatric unit and outpatient geriatric clinic teams evaluated and managed patients according to published guidelines and VA standards. Patients were followed for 12 months.. Suboptimal prescribing measures included unnecessary and inappropriate drug use (MAI), inappropriate drug use (Beers criteria), and underuse.

- RESULTS: Inpatient geriatric unit care reduced unnecessary and inappropriate drug use and underuse significantly during the inpatient period ($P < 0.05$). Outpatient geriatric clinic care reduced the number of conditions with omitted drugs significantly during the outpatient period ($P < 0.05$) and resulted in a 35% reduction in the risk of a serious adverse drug reaction compared with usual care (adjusted relative risk 0.65; 95% confidence interval: 0.45 to 0.93).

Schmader Am J Med. 2004

Suboptimal Prescribing in Older Inpatients and Outpatients

Hanlon J.T., JAGS, 2001

Ci sono tre categorie di *Prescrizione 'subottimale':*

- ***Sovrautilizzazione***
- ***Uso inappropriato***
- ***Sottoutilizzazione***

Prescrizione Potenzialmente Inappropriata

'Prescrizione di un farmaco che ha più rischi che benefici o in cui le cui dosi prescritte non sono in accordo con gli standard medici accettati'

Hanlon J.T. et al. JAGS 2001

Prescrizione Potenzialmente Inappropriata

1) L'uso di un farmaco

- che non ha l'indicazione
- che ha l'indicazione sbagliata
- che ha un alto rischio di evento avverso (ADE)
- che non è indispensabile
- per un periodo troppo lungo o troppo breve

2) La mancanza della prescrizione appropriata di una terapia farmacologica

O'Mahony D., 2011

Prescrizione Potenzialmente Inappropriata

Ci sono due principali approcci metodologici per valutare l'inappropriatezza prescrittiva :

Prescrizione Potenzialmente Inappropriata

1) Criteri impliciti: Indice di Appropriatezza Prescrittiva

MAI basato su 10 criteri

- **Indicazioni**
- **Efficacia**
- **Formazione del paziente**
- **Possibilità di utilizzare il farmaco nel singolo paziente**
- **Interazioni tra Farmaci**
- **Interazioni Farmaco/Malattia**
- **Duplicazione non necessaria**
- **Durata**
- **Costo**

Hanlon J.T. et al. J Clin. Epid. 1992

Prescrizione Potenzialmente Inappropriata

2) CRITERI ESPLICITI, es LISTE DI FARMACI INAPPROPRIATI

- Beers 1991/1997/2003/2012/2015
- Mc Leod 1997
- STOPP-START 2008/2014
- FORTA LIST

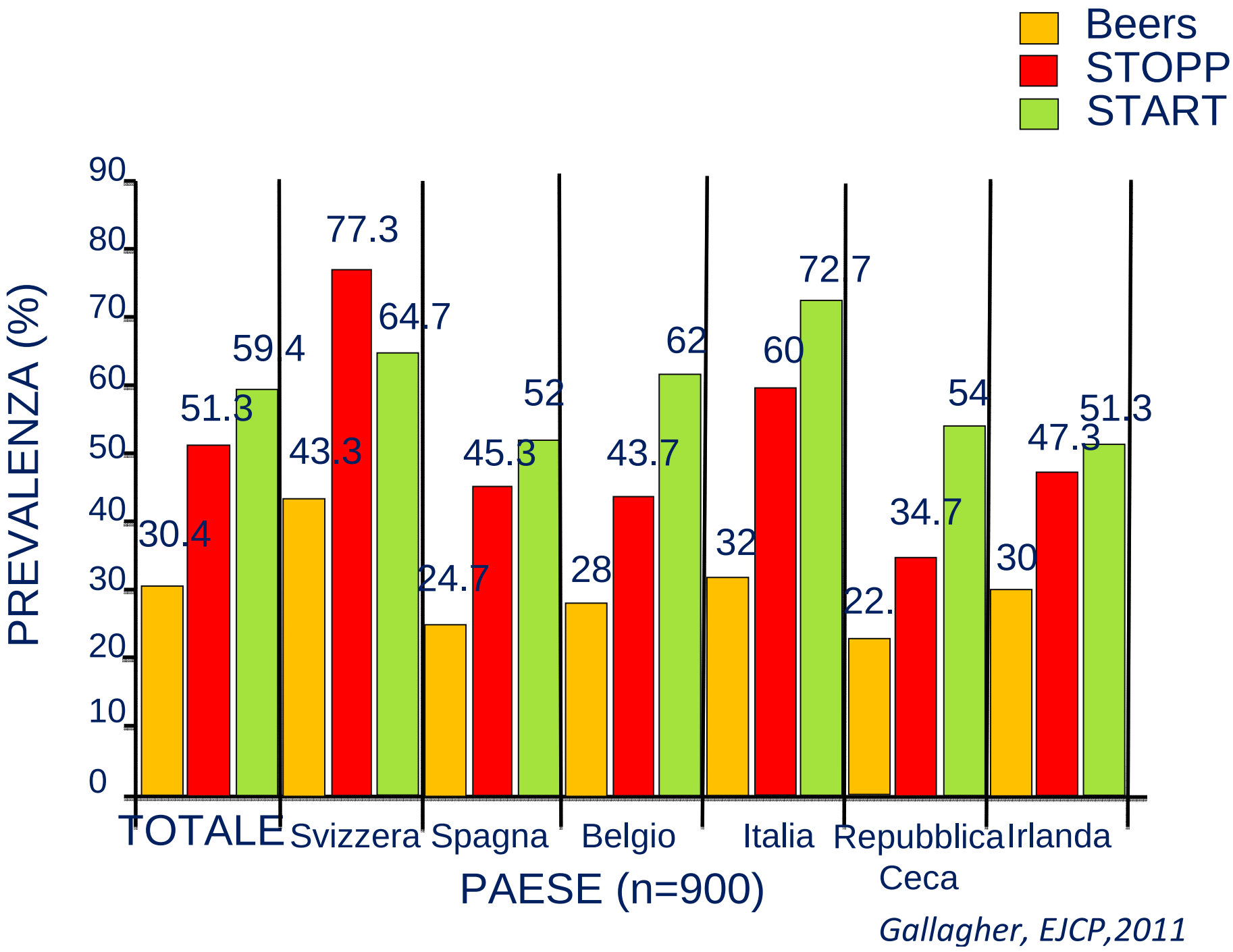
Age and Ageing 2014; **0:** 1–6
doi: 10.1093/ageing/afu145

STOPP/START criteria for potentially inappropriate prescribing in older people: version 2

Denis O'Mahony[1,2], David O'Sullivan[3], Stephen Byrne[3], Marie Noelle O'Connor[2], Cristin Ryan[4], Paul Gallagher[2]

Risultati:

- La lista finale ha raggiunto 114 criteri (80 criteri STOPP e 34 START)
- Rispetto alla prima versione c'è stato un aumento del numero di criteri del 31%.
- Sono state create nuove categorie di criteri ("farmaci antipiastrinici/anticoagulanti, farmaci che influenzano o che sono influenzati dalla funzione renale).
- Le nuove categorie includono anche farmaci per il sistema urogenitale, analgesici e vaccini.



Gallagher, EJCP,2011

Prevention of Potentially Inappropriate Prescribing for Elderly Patients: A Randomized Controlled Trial Using STOPP/START Criteria

PF Gallagher[1], MN O'Connor[1] and D O'Mahony[1,2]

Clin Pharmacol Ther. 2011 Jun;89(6):845-54.

Intervention with the Screening Tool of Older Persons Potentially Inappropriate Prescriptions/Screening Tool to Alert Doctors to Right Treatment Criteria in Elderly Residents of a Chronic Geriatric Facility: A Randomized Clinical Trial

Dvora Frankenthal, MSc, Yaffa Lerman, MD,*† Edward Kalendaryev, MD,‡ and Yehuda Lerman, MD**

J Am Geriatr Soc. 2014 Sep;62(9):1658-65.

Reduction of Potentially Inappropriate Medications Using the STOPP Criteria in Frail Older Inpatients: A Randomised Controlled Study

O. Dalleur · B. Boland · C. Losseau · S. Henrard · D. Wouters · N. Speybroeck · J. M. Degryse · A. Spinewine

Drugs Aging. 2014 Apr;31(4):291-8.

Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial

Marie N. O'Connor, MD, David O'Sullivan, PhD,† Paul F. Gallagher, PhD,*‡ Joseph Eustace, MD,§ Stephen Byrne, PhD,† and Denis O'Mahony, MD*‡*

J Am Geriatr Soc. 2016 Aug;64(8):1558-66.

RCT 4: Incident ADRs

Study Arm	Number (%) of patients with at least one instance of IP according to STOPP/START criteria at randomization	Number (%) of ADRs attributable to medications listed in STOPP/START criteria	Number (%) of ADRs *not* attributable to medications listed in STOPP/START	Total number of ADRs	Total numbers of patients with ADRs
Control (n = 372)	158 (42.5%)	51 (57%)	38 (43%)	89	78 (23.9%)
Intervention (n = 360)	176 (48.9%)	15 (33%)	30 (67%)	45	42 (12.5%)

ADR rate in Intervention Group = 12.5%
vs. ADR rate in control Group = 23.9%
Absolute Risk Reduction = 11.4%; NNT = 9

Adjusting for number of drugs, PIMs, renal failure, liver disease, heart failure, age, dementia and falls…….
ADR risk Odds Ratio = 0.43 (CI: 0.28 - 0.67)

O'Connor MN et al., *J Am Geriatr Soc* 2016; 64(8):1558-66.

Development and clinical trials of a new Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons

FP7 project, funded by EC under Grant Agreement no. 305930

CATEGORIE DI INTERVENTI

- Valutazione multidimensionale geriatrica
- Applicazione Criteri PI
- Formazione
- Sistemi informatizzati di supporto
- Farmacista
- Team multidisciplinare
- Politiche regolatorie
- Multifattoriali

CONCLUSIONI

- La prescrizione appropriata è un obiettivo prioritario nel paziente anziano
- Numerosi studi hanno valutato differenti interventi per ridurre la prescrizione inappropriata, con frequente riduzione di tale fenomeno, ed in alcuni casi una riduzione delle ADE, ma la loro efficacia in termini di beneficio clinico è tuttora non dimostrata

- La prescrizione farmacologica nel paziente anziano è un'attività complessa, che richiede una accurata valutazione del paziente ed un costante monitoraggio con eventuale rivalutazione della terapia